The Lancet International Commission on Dementia Prevention and Care

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Executive Summary

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

Dementia is the greatest global challenge for health and social care in the 21st century. It occurs mainly in older people so increases in numbers and costs are driven, worldwide, by increased longevity resulting from the welcome reduction in people dying prematurely. The Lancet International Commission on Dementia 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.

There were around 47 million people living with dementia globally in 2015, and this is projected to increase to 66 million by 2030 and 115 million by 2050. Dementia affects the individual living with it, who gradually loses 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. In addition, it affects wider society as people also require health and social care. The 2015 global cost of dementia was estimated to be US$818 billion and this will continue to increase as the numbers of people with dementia rise. Nearly 85% of costs are related to family and social, rather than medical, care. It may be that future new medical care, including public health measures, may 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 decade. There are lifestyle factors that may reduce, or increase, an individual's risk of developing dementia. In some populations dementia is already being delayed for years; while in others the numbers of people living with it has increased. In this commission, we have extended current models of risk by including hearing loss, derived from a new review and meta-analysis performed for this report, and social isolation. 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 have been derived to demonstrate the possible impact on future incidence of successful elimination of the most potent factors. We have brought together all this evidence and have calculated that around one third of dementia may theoretically be preventable. More childhood education, exercise, maintaining social engagement, reducing or stopping smoking, 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 impact on the brain.

Of course not everyone will be able to make changes, some changes will not make a difference and some dementia risk is genetic and not currently modifiable. Nonetheless delaying dementia for some years for even a small percentage of people would be an enormous achievement and enable many more people to reach the end-of-life without developing dementia. Many people present to services with Mild Cognitive Impairment (MCI) a risk state for dementia, which occurs in up to a fifth of people aged over 65 and this provides an opportunity for more targeted interventions.

It is now known that many of dementia's manifestations are manageable and while the underlying dementing illnesses are generally not curable, they may 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 which 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 are implemented, people with dementia will have their cognition optimised and 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 an agent who can enact pre-specified wishes or make choices consistent with their values.

People with dementia are usually older, often have co-morbidities and may 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 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. As there are limited resources, 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 under-served, growing population. Effective dementia prevention 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.

Key Messages

1 There are increasing numbers of people with dementia globally although incidence in some countries has decreased.

2 Be ambitious about prevention: We recommend energetically treating hypertension in middle aged and older people 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; may have the potential of delaying or preventing a third of dementias.

3 Treat cognitive symptoms: To maximise cognition, people with Alzheimer's dementia or Dementia with Lewy Bodies should be offered Cholinesterase Inhibitors (ChEIs)at all stages, or memantine for severe dementia. ChEIs are not effective in Mild Cognitive Impairment.

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

5 Care for family carers. Family carers are at high risk of depression. Effective interventions reduce the risk and treat the symptoms, include START (Strategies for Relatives) or REACH (Resources for Enhancing Alzheimer's Caregiver Health intervention) 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 persons' 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 those 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 as they may 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.

Introduction

As the world's population ages, increasing numbers of people are living with dementia and this is projected to continue to rise, especially in low- and middle-income countries (*figure 1*) (1). There were around 47 million people 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, may replace and reduce some of this cost (3).The number of people with dementia is expected to increase to 66 million by 2030 and 115 million by 2050 (4), driven by rising numbers of older adults (5;6). However, some recent population studies have found a lower incidence of people with dementia than predicted from previous projections, and therefore while the rate of increase and crisis related to providing care continues, this may not be quite as large as previously expected (7;8).

Dementia was long considered to be neither preventable nor treatable, but encouraging progress has been made. The Lancet International Commission on Dementia Prevention and Care has therefore met to consolidate emerging knowledge as to what can work and what individuals should do to prevent and manage dementia particularly with the health systems in high income countries. It is now known that many of dementia's manifestations are manageable and while the underlying illnesses are not curable, the course may be modifiable with good dementia care. Current 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 (MCI) are characterised by decline from a previously attained cognitive level but in dementia, in contrast to MCI, the decline impacts on activities of daily living or social functioning (9). In MCI, although the patient can still engage in complex activities, for example, paying bills or taking medication, greater effort or new strategies may be required. Dementia is usually preceded by MCI, and the boundary between two is grey, and many people present to dementia services with MCI.

There are many different causes of dementia, with Alzheimer's disease (AD) the most common. Vascular dementia is the next most common, followed by dementia associated with Lewy bodies (DLB). Mixed dementia with features of more than one aetiology are also common. Frontotemporal degeneration and dementias associated with brain injury, infections, and alcohol abuse are less common causes (10). 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 '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 (11). This may lead to people avoiding diagnosis as they may feel stigmatised by others or in their own mind. Diagnostic and Statistical Manual of Mental Disorders (DSM 5) has stopped using the word dementia and instead uses the phrase "major neurocognitive disorders" (12). These are illnesses with demonstrable neural substrate abnormalities together with cognitive symptoms, which occur in people who have had normal brain development (13). Mild neurocognitive disorder has also been added to DSM 5, equating to World Health Organisation International Classification of Diseases (ICD-10) classification of mild cognitive disorder (9).

The evaluation of the needs of a person with dementia has to consider other illnesses and medications that impact and interact with the dementia, and their social and physical living

environment. Dementia usually occurs in people aged > 65 years old (14) when comorbidity is common. Age-related physical health problems and dementia co-occur more often than by chance. This 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; 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 (15). Impaired mental and physical function also interfere with exercise or social activities (16). These health and social challenges influence diagnosis, prognosis, response to treatment and need for health and social care. Yet people with complex needs are generally under-represented in trials; those who are eligible for and participate in research tend to be fitter, younger, male and more highly educated (17).

In this commission we have used the best current evidence to make recommendations. When current evidence is incomplete we have summarised the balance of evidence and explained its strengths and limitations. An overall limitation is that this is generally focussed on and from high income countries and we have less evidence from middle and low income countries.

Preventing

Demographics and dementia

The number of people with dementia is rising rapidly (*figure 1*), primarily due to worldwide ageing populations, particularly in low- and middle-income countries (1;4). This trend is expected and widely reported (18;19). There are increasing numbers of people with dementia everywhere.

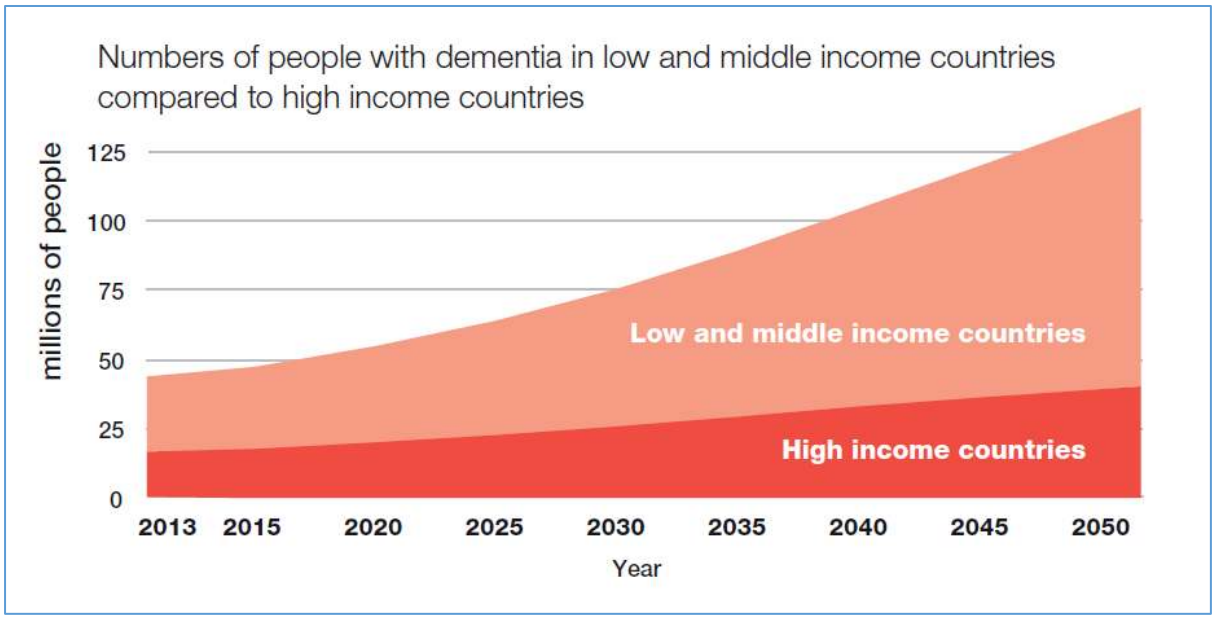

Figure 1. The growth in numbers of people with dementia in high-income and low- and middle-income countries

Figure reproduced from 'The Global Impact of Dementia 2013-2050' (1) by permission of *Alzheimer's Disease International*

While there is no current disease-modifying treatment for any common dementia, delaying dementia's onset would benefit even the oldest adults (20). There has been an unexpected observed decline in age-specific dementia incidence or prevalence rates in some countries, such as the United States (US), the United Kingdom (UK), Sweden, the Netherlands, and Canada (7;8;21-26). Conversely, there have been reports of an increase in incidence rates in China (27) and prevalence rates in Japan (28;29) while rates in Nigeria are stable (30).Both US studies found the decrease in age specific prevalence (despite an increase in the absolute number of people with dementia) was associated with increasing education (25;26).

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 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. However, the increasing midlife rates of obesity and associated ill-health are projected to lead to a 19% increase in dementia rates in China and 9% in US (31).

The complexity of dementia neuropathology complicates prevention

Some dementia risk factors, including cardiovascular, cerebrovascular, metabolic and psychiatric factors, diet, lifestyle and education, are potentially changeable (32). Dementia is heterogeneous and risk factors vary, and also co-exist, for different types of dementia. Vascular brain injury including strokes and microvascular infarcts not only lead to vascular dementia but occur more commonly in older people with AD (33-35), and are present in some people who do not have dementia. In those with both neuropathological AD and lacunar infarcts, the cognitive impairment is more severe than those without such infarcts (36). These patients are sometimes diagnosed as having "mixed dementia" (37), AD in which plaques and tangles are seen alongside microvascular infarcts or less commonly Lewy bodies, all of which likely contribute to cognitive decline (38-42).

It is possible, as we have done below, to model the effect of changing the potentially modifiable risk factors. Currently, the evidence for 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 (43).

The EU Joint Programme on Neurodegenerative Disease Research called in 2014 for population- and disease-based cohorts to be exploited to obtain the high quality evidence necessary to capture the range of potential health influences and confounding factors starting in midlife, and provide evidence on the direction of causality(44).

While modifying 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 over the age of 65. Overall about 80% of dementias are in people aged ≥75

years (14;45) and there may be an interaction between age, neuropathology, comorbidity and the clinical presentation. It is likely that age on its own would 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 AD do not have dementia (40), indicating resilience. *Figure 2* illustrates how some cognitively normal individuals in community-based U.S. studies tolerate a large and mixed burden of vascular, Lewy body and Alzheimer's neuropathology (40). 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, therefore develop dementia more slowly (46). This reserve is related to either the brain anatomical substrate or adaptability of cognition, due to factors discussed in more detail below (47;48).

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, as the resultant neuropathology reduces the cognitive reserve buffer. As predicted, those with less cognitive reserve due to intellectual disability develop dementia at a younger age (49). Additionally, people of African origin in the UK and US who have high rates of hypertension, have increased rates of dementia at younger age (50-52).

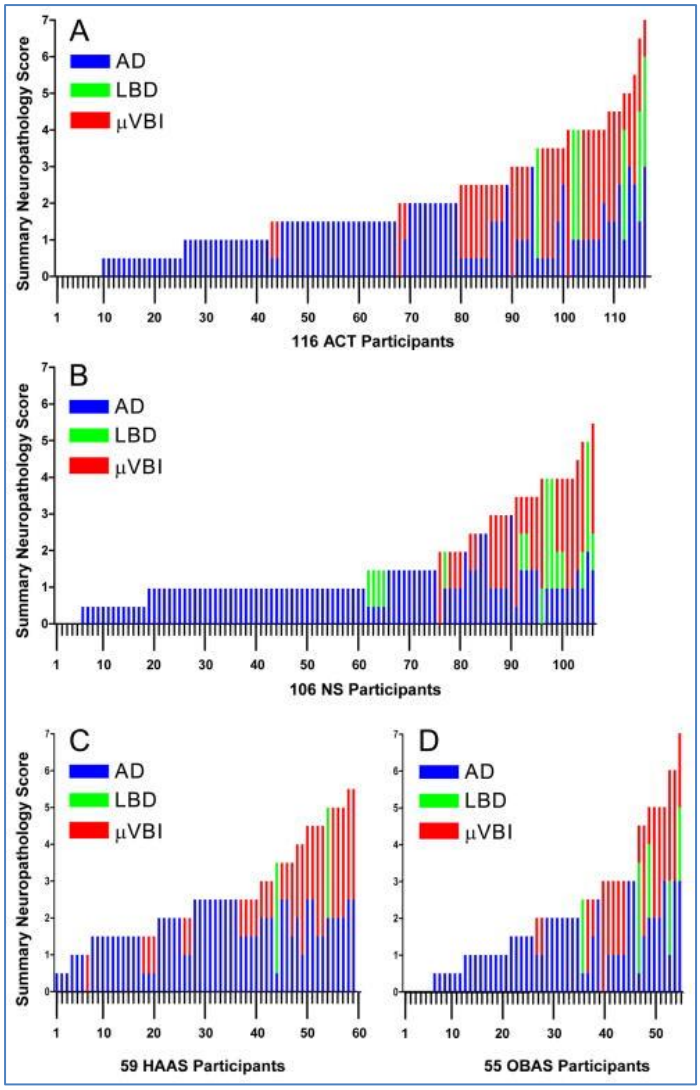

Figure 2. Brain autopsy results from cognitively normal individuals expressed as Summary Neuropathology Score (potentially range 0 to 9) ranked from lowest to highest.

*Key: Each stacked bar shows an individual's burden of AD (blue), LBD (green), and μVBI (red). (**A**) 116 Adult Changes in Thought (ACT) participants, (**B**) 106 Nun Study (NS) participants, (**C**) 59 Honolulu Asian Aging Study (HAAS) participants, (**D**) 55 Oregon Brain Health & Science (OBAS) participants.*

Figure reproduced from Sonnen *et al* (40) by permission of the American Medical Association

A broader approach to dementia prevention including promoting resilience makes sense in our ageing societies. Strategies for promoting resilience to prevent or delay dementia's onset are extrapolated from studies on declining dementia incidence rates which report healthier lifestyles are associated with declining prevalence of cognitive impairment and dementia (23;24). Cognitive resilience in late life is likely to be enhanced by building reserve earlier in life through education and other intellectual stimulation (53;54). Through neuronal branching and plasticity such changes may subsequently be translated into brain reserve. Lower rates of late-life dementia are found with higher education levels (25). Improved socio-economic status during gestation and early childhood has a protective association with late-life dementia risk (55). These findings indicate that improving

brain reserve (53;54;56) 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 effective prevention of dementia. In the risk literature, midlife has been defined as aged 45-65 years and late life as aged > 65. 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 (32).

Newly calculated population attributable fraction for modifiable risk factors

Which modifiable risk factors?

We sought to calculate a combined PAF for known modifiable risk factors for dementia. We decided which risk factors to include by identifying those listed in the UK National Institute of Health and Care Excellence (NICE) (57) and US National Institute of Health (NIH) (58) guidelines. For risk factors included in recent papers reporting dementia PAF – vascular risk factors, not continuing in education beyond primary school and depression (32;59) – we used their data on relative risk and prevalence. For the additional risk factors included in our calculations, we sought systematic reviews of their relative risk and prevalence and, in the absence of one; we asked other authors on the Lancet Commission for suitable papers and conducted our own meta-analysis. We focused on all-cause rather than cause-specific dementia as there was most data for this outcome. As far as possible, we used prevalence and relative risk data from international studies to make our figures relevant to global dementia risk (see *Table 1*).

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 (60). This paper 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 have used the figures for social contact as we judged this the most accurate measure of actual contact time. The weighted relative risk (RR) for incident dementia associated with less frequent social contact was 1.57 (95% CI [1.32-1.85]). PAF calculations require knowing the prevalence of the risk factor but this was not given in any of these papers. There was also heterogeneity in individual papers' definition of infrequent social contact. We therefore used results from a representative sample of older people in the UK (61) to estimate prevalence and incorporated the prevalence of reporting social contact less than monthly, which is probably a conservative definition.

There were no systematic reviews for hearing loss and incident dementia. We therefore consulted experts to generate a list of relevant papers and used the quality checklist for prognosis studies (62) 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), incident dementia as an outcome, and adjusted for age and cardiovascular risk factors as potential confounding factors. Three studies met these criteria (63-65), with follow-up over 9, 12 and 17 years. Each found that peripheral hearing loss was a significant risk factor for dementia. We meta-analysed this data and calculated a pooled RR of 1.94 (95% CI [1.38-2.73]) (*figure 3*).

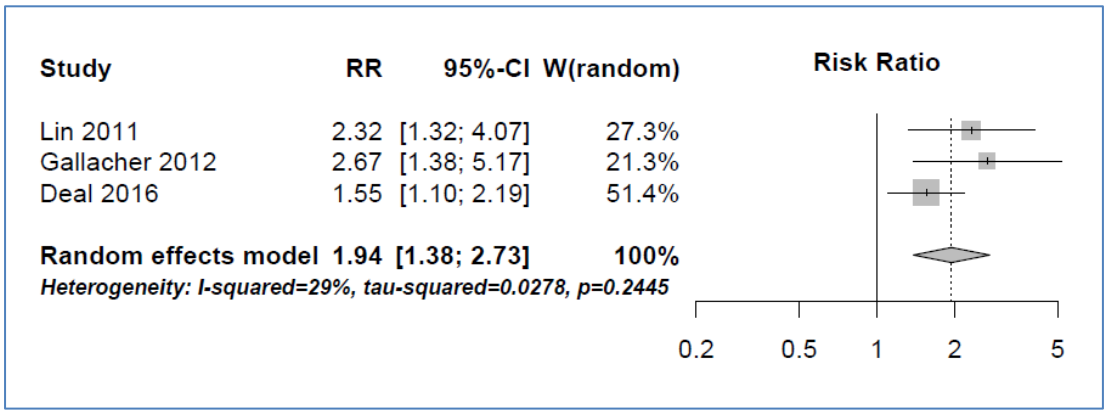

Figure 3. Forest plot of effect of hearing loss, measured by pure tone audiometry, on incident dementia rates 9-17 years later in cognitively healthy people

PAF for modifiable risk factors

The attributable risk in a population depends on the prevalence of the risk factor and the strength of its association (relative risk) with the disease. In our calculations, we have used relative risks from systematic reviews and, while these were adjusted for many confounders, they could not have been adjusted for all the risk factors in our total PAF calculation. Therefore using the formula for calculation of individual risk factor PAF for circumstances in which all confounding risk factors have been adjusted for would be inappropriate (66). We therefore used a version of the formula which was used in a previous paper and which is more appropriate when confounding has not been fully accounted for (32;59).

Formula for individual Population Attributable Fraction (PAF)

PAF = Pe (RRe-1) / [1 + Pe (RRe-1)]

Pe = prevalence of the exposure

RRe = relative risk of disease due to that exposure

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 data points 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 (i.e. how much each unobserved component explained each measured variable).

Calculation of overall Population Attributable Fraction (PAF)

We then calculated overall PAF: $PAF = 1-[(1-PAF_1)(1-PAF_2)(1-PAF_3)\ldots]$

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:

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

Box 1. Method for calculation of population attributable fraction and communality

Communality of risk factors

We used figures from the 2014 Health Survey for England (HSE), a representative sample of over 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 (32;67;68). HSE data has 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 there were three principal components which explained 53% of the total variance between the nine risk factors, suggesting substantial overlap. The prevalence, communality and relative risk with the PAF adjusted for communality of each included risk factor is in *table 1.* We then calculated overall PAF (*table 1*) using the same formula as others had but incorporating the additional variables of hearing loss and social isolation (*box 1*). We present the new model of life course risk factors in *figure 4.*

Total potentially modifiable risk factors for dementia

Risk Factor	Relative risk for dementia	Prevalence (%)	Communality (%)	PAF (%)	Weighted PAF* (%)
Early life					
Less education (none or primary school only)	1.6	40.0	64.6	19.1	**7.5**
Midlife (age 45-65)					
Hypertension	1.6	8.9	57.3	5.1	**2.0**
Obesity	1.6	3.4	60.4	2.0	**0.8**
Hearing loss	1.9	31.7	46.1	23.0	**9.1**
Later life (age >65)					
Smoking	1.6	27.4	51.1	13.9	**5.5**
Depression	1.9	13.2	58.6	10.1	**4.0**
Physical inactivity	1.4	17.7	26.6	6.5	**2.6**
Low social contact	1.6	11.0	45.9	5.9	**2.3**
Diabetes	1.5	6.4	70.3	3.2	**1.2**
Total adjusted for communality					**35.0**

Table 1. Risk factors for dementia; relative risk for dementia, prevalence, communality and Population Attributable Fraction (PAF) for dementia

*Notes: *Weighted PAF is the relative contribution of each risk factor to the overall PAF when adjusted for communality*

Our results suggest that around 35% of dementia is attributable to a combination of these nine risk factors; namely education to a maximum of age 11 or 12, midlife hypertension, midlife obesity, hearing loss and later-life depression, diabetes, physical inactivity, smoking and social isolation. In comparison, completely eliminating the Apolipoprotein E (ApoE) Ɛ4 allele as the major genetic risk factor is calculated to produce a 7% reduction in incidence, using the PAF calculation methods (69).

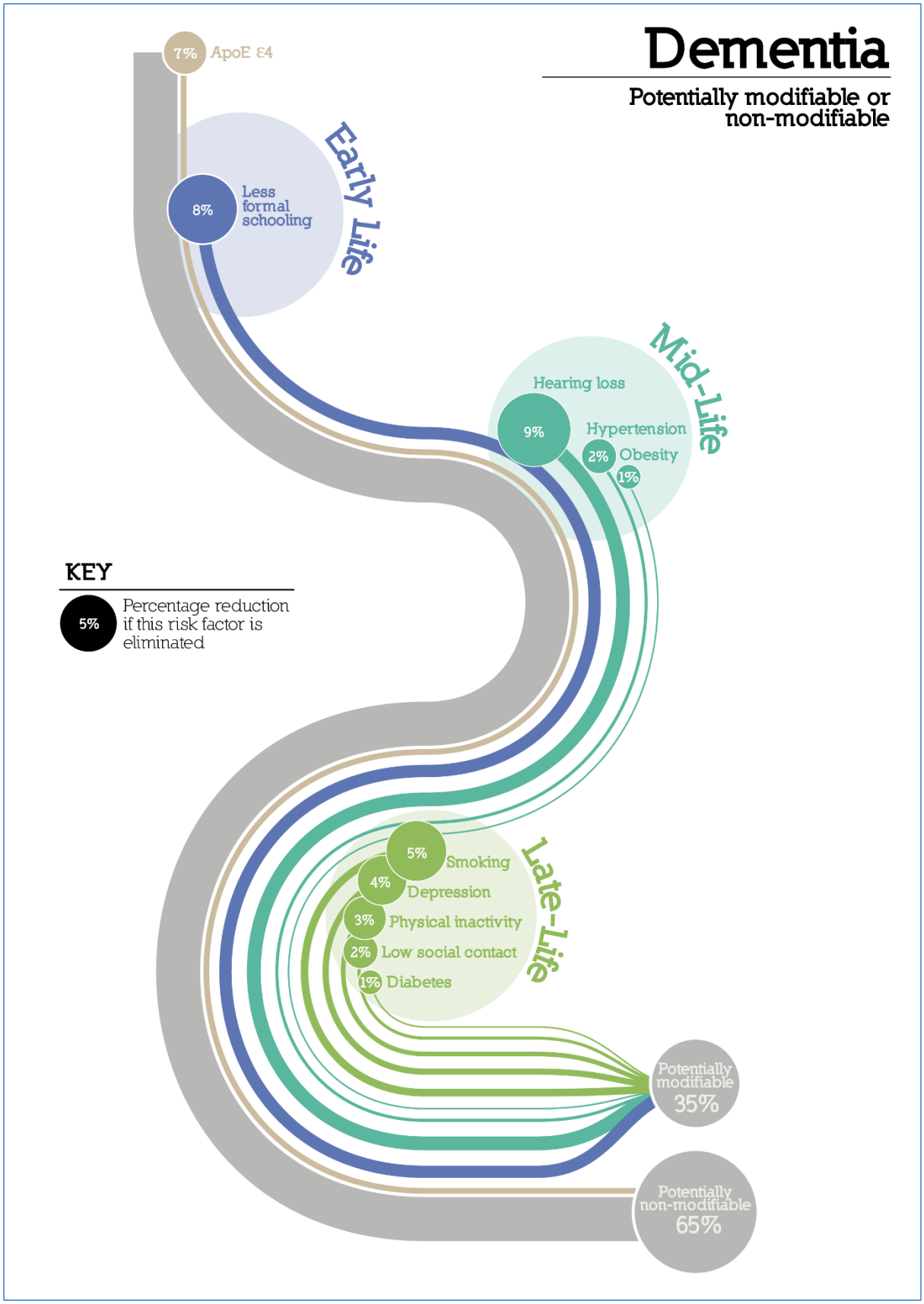

Figure 4. Life course model of contribution of modifiable risk factors to dementia

Notes: Numbers are rounded to nearest integer.

Effects of potentially modifiable risk factors on the brain

A summary of the suggested mechanisms linking these risk factors to dementia are shown in *figure 5*. Vascular damage to the brain not only increases risk of microvascular and macrovascular lesions but also of atrophy and neurodegeneration. Oxidative stress and inflammation is associated with deposition of amyloid-beta (70). Diabetes and metabolic syndrome are associated with atherosclerosis and brain infarcts, and glucose-mediated toxicity causes microvascular abnormalities and neurodegeneration (71). Evidence of impaired insulin receptor activation in AD (72) has led to suggestions that it may represent 'an insulin resistant brain state' (73). Exercising more in midlife is associated with a reduced risk of dementia (74). Exercise is postulated to have a neuroprotective effect, potentially through promoting release of Brain Derived Neurotrophic Factor (75) (76), reducing cortisol and reducing vascular risk. Exercise alone, as discussed below, does not appear to improve cognition in healthy older adults (77).

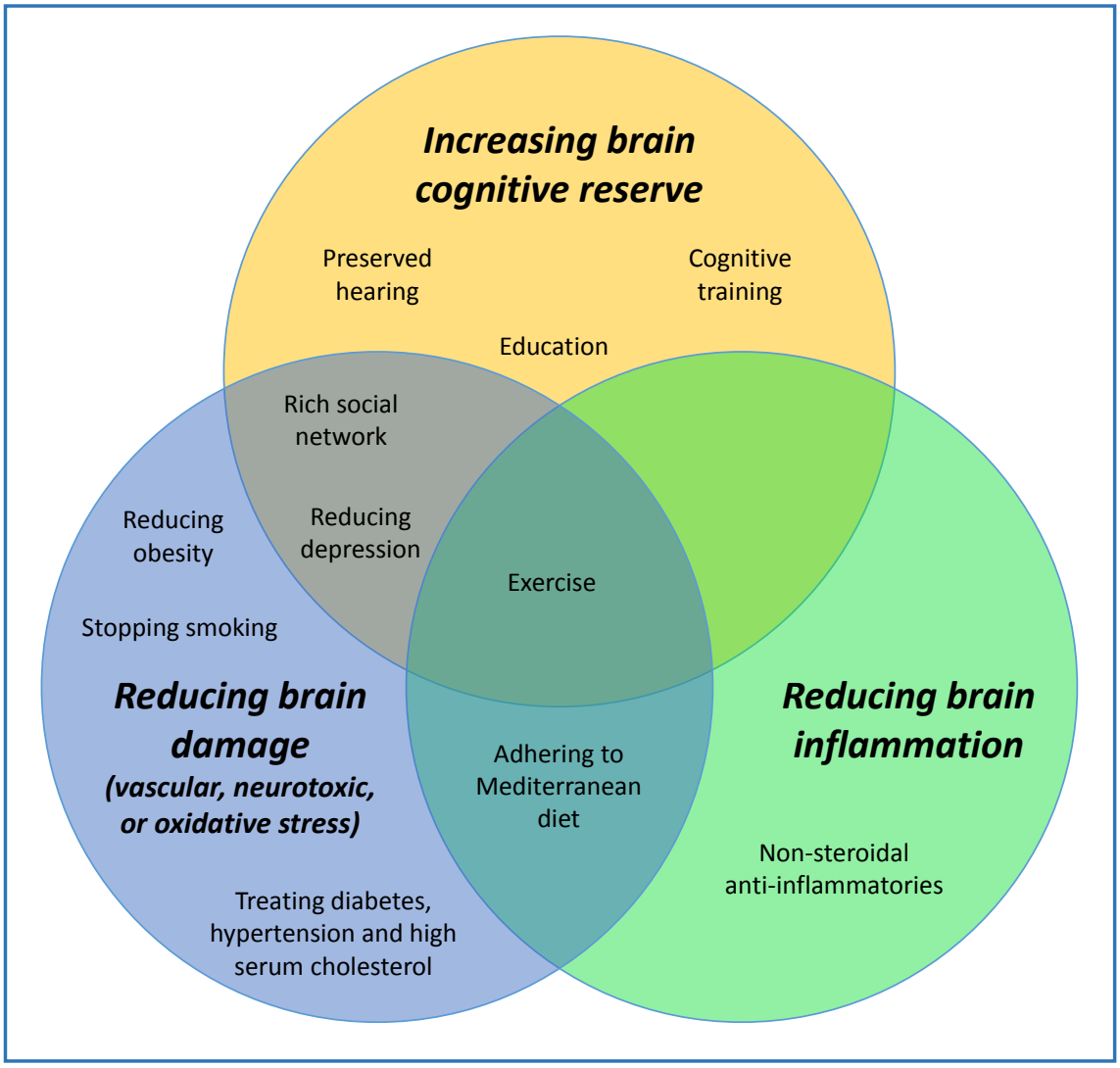

Figure 5. Potential brain mechanisms for preventative strategies in dementia

Specific risk factors and mechanisms

We discuss the specific risk factors and their effect below and they are summarised in figure 5.

Education

Less formal schooling is associated with a relative risk of dementia of 1·59 (95% CI [1·35-1·86]) and the high PAF is because of the large worldwide estimated prevalence of 40%. Less time in education, which we defined as lack of secondary school education, has the second highest PAF in our model. Low educational level is thought to result in vulnerability to cognitive decline due to lack of cognitive reserve (56) which enables people to maintain function despite brain pathology (78). We do not yet know whether education post-secondary school is additionally protective.

Hearing

Recognition of hearing loss as a risk factor for dementia is relatively new and it 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. Cohort studies that have investigated hearing have usually found that even mild levels of hearing loss increase the long-term risk of cognitive decline and dementia in those who are cognitively-intact but hearing-impaired at baseline (63;65;79-87). However, while there are 11 positive studies, two found the increased risk was no longer significant in adjusted analyses (88;89).

The risk of hearing loss for dementia in the meta-analysis of three studies which we performed for this paper (*figure 3*, pooled relative risk =1.94; 95% CI [1.38-2.73]) is not only higher than the risk from other individual risk factors; but it is also pertinent to many people as it is highly prevalent, occurring in 32% of those aged > 55 (90). Its high relative risk and prevalence explains the high PAF. We have used the prevalence of hearing loss in those over 55 to calculate PAF as this was the youngest mean age in which presence of hearing loss was shown to increase dementia risk (65). Hearing loss is therefore grouped with the midlife risk factors but evidence suggests it continues to increase dementia risk in later life.

The mechanism underlying peripheral hearing loss associated cognitive decline is not yet clear, nor is it established whether correction, such as hearing aids, can prevent or delay dementia's onset. Older age and microvascular pathology increase the risk of both dementia and peripheral hearing loss, and may therefore confound the association. Hearing loss may either add to the cognitive load of a vulnerable brain leading to changes in the brain (91), or lead to social disengagement or depression (92;93) and accelerated atrophy (94), all of which could contribute to accelerated cognitive decline (95).

While impaired hearing may detrimentally influence performance on formal cognitive assessments, those with impaired baseline hearing had normal baseline cognition so this cannot, however, account for the findings.

We lack experimental evidence on whether some of these negative effects may be alleviated by hearing aid use. Any intervention would require greater complexity than merely suggesting to people that they use a hearing aid. This is because only a minority of people with hearing loss are either diagnosed or treated (96), and when prescribed, many people do not use hearing aids (97).

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) (98). 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 (99). This is consistent with the fact that central auditory areas are affected by Alzheimer's disease pathology (100). 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 (99) while the prevalence of peripheral hearing loss in the studies included in the meta-analysis in a similar middle aged and older population is much larger (28%, 43% and 58%, depending on the specific study). Milder levels of central hearing loss might be more prevalent but they have not been linked to increased risk of dementia (101).

A recent small pilot intervention, Hearing Equality through Accessible Research & Solutions (HEARS), used visual materials and training for the participant and a family member, to increase listening devices usage in cognitively healthy older adults and indicated that it may be possible to increase their use(102).

Exercise and physical activity

Older adults who exercise are more likely to maintain cognition, but like cognitive interventions, there is no current evidence that this prevents cognitive decline or dementia. One meta-analysis of 15 prospective cohort studies following 33,816 individuals without dementia for 1-12 years, found that physical activity had a significant protective effect against cognitive decline, with high levels of exercise being the most protective: hazard ratio 0.62 (95% CI 0.54-0.70) (103). Another meta-analysis included 16 studies with 163,797 participants without dementia and found that the relative risk of dementia in the highest physical activity groups compared to the lowest was 0.72 (95% CI 0.60-0.86) and the relative risk of AD was 0.55 (95% CI 0.36, 0.84) (104). Physical exercise leads to benefits in older people without dementia, including improving balance and reducing falls (105), improving mood (106), reducing mortality and improving function (107).

Diabetes, hypertension and obesity

Hypertension had the highest PAF amongst this group of risk factors, linked by their status as vascular risk factors, but they all had PAFs below 5% (108). Obesity is linked with pre-diabetes and metabolic syndrome which is characterised by insulin resistance and high levels of peripheral insulin. This is thought to cause a decrease in brain insulin production which can impair amyloid clearance (109). Increasing inflammation and high blood glucose concentrations may also be mechanisms by which diabetes impairs cognition (110).

Smoking

Smoking had the third highest PAF, in keeping with previous analyses (32). The association with cognitive impairment may be due to the link between smoking and cardiovascular pathology but cigarette smoke also contains neurotoxins which heighten the risk (111). Again, its high prevalence contributes to increasing the PAF and population level. Interventions are currently being used to reduce cigarette smoking and it has and is declining in most countries, although in 2015 it appeared to be increasing in the Eastern Mediterranean and Africa (112).

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 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 (113). The mechanism is likely to be multifactorial, as depression is linked to cerebrovascular pathology, and affects stress hormones, neuronal growth factors and hippocampal volume (114). In the past three decades there has been increased antidepressant prescription and this is hypothesised to impact on dementia incidence as animal data suggests that some antidepressants, including citalopram, decrease amyloid production (115-117).

Social contact

The PAF for social contact was similar to that of hypertension or physical inactivity. As with depression, social isolation may be a prodrome or a part of the dementia syndrome. However, there is a growing body of evidence that social isolation is a risk factor for dementia and it increases the risk of hypertension (118), coronary heart disease (119) and depression (120). Social isolation may also result in cognitive inactivity, linked to faster cognitive decline and low mood (60). All of these are risk factors for dementia themselves. This highlights the importance of considering the social engagement of older people and not only their physical and mental health.

Lifestyle factors- Mediterranean diet and alcohol use

Those who adhere to the Mediterranean diet (low meat and dairy, high fruit, vegetables and fish) have fewer vascular risk factors, and reduced plasma glucose and serum insulin levels, insulin resistance and markers of oxidative stress and inflammation (121). Not smoking, exercising regularly, eating fruit and vegetables daily and drinking only a moderate amount of alcohol increase life expectancy and health in ageing (122) so there is growing interest in these factors' impact on cognition. We do not have data to include dietary factors and alcohol in our calculations but they may be important.

Head injury

Most head injuries are mild and the commonest head injury is a non-repetitive traumatic brain injury (TBI). The largest study of TBI found that 12% of 7,130 participants in a 20 year longitudinal cohort study had a history of TBI (defined as > 1 hour loss of consciousness). This was neither associated with a greater risk of development of dementia nor AD, nor increased plaques and tangles in the 1,589 participants who had an autopsy (123). TBI was associated with the development of Parkinson's disease and Lewy body pathology.

An earlier meta-analysis of seven studies, following people up at least one year after TBI, found it was not associated with increased risk of all cause dementia, but there was increased risk of AD (OR 1.40, 95% CI [1.02-1.90]) (124), and there is some evidence that this effect is modified by sex; that the risk of dementia following TBI is greater for men (125;126). The meta-analysis also found there was no difference in risk between single and repetitive TBI. It concluded there were limitations in and heterogeneity of studies.

It is unclear what short-term brain pathology is typically caused by a single blast related head injury (127). Repetitive mild head injury in athletes or war is associated with chronic traumatic encephalopathy, a progressive tauopathy, which can eventually manifest as dementia (128). The Institute of Medicine has concluded that moderate or severe TBI, such as in war, is a risk factor for AD (129) but overall the evidence appears to be that non-repetitive TBI does not predispose to all cause dementia.

Other factors

Visual impairment and sleep disorders have received some attention for their role in the development of cognitive impairment (57). Sleep might promote repair of damage caused by other factors but given the lack of systematic reviews or enough consistent, high quality evidence we have not been able to include it in our calculations of PAF. Bilingualism may also be protective, as a cognitive activity (130) but results from prospective cohort studies regarding its protection against cognitive decline have been mixed (131;132). One longitudinal study has found that living near major roads increases the chance of having a recorded diagnosis of dementia (133).

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 of causality would be randomised controlled trials in humans. This is 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 (134).

The emergent risk factors in our publication, including hearing loss and low social engagement, meet these criteria, suggesting plausible causal relationships. For hearing loss, for example – (1) *Strength of association*: Our meta-analysis showed effect size of 1.94 (95% CI [1.38-2.73]); (2) *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% confidence intervals; (3) *Temporality*: the studies measured hearing loss, then followed non-demented people for at least 9 years, identifying incident dementia cases during this follow-up; (4) *Biological gradient*: There is a dose-response whereby mild, moderate or severe hearing loss lead to increased relative risk of dementia of 1.89, 3.00 and 4.94, respectively(135); (5) *Plausibility*: In animal models, hearing loss precedes changes in brain structures (136), volume (137) and networks(138). Improving hearing (and social and exercise interventions) might improve cognition by environmental enrichment, associated with reduced amyloid deposition in mice models (139). There are likely additional human-specific mechanistic pathways because of the importance of language relative to other species; language is a key element of the co-evolution of larger brain size, social interaction and larger-scale group cooperation in humans (140). Hearing loss in humans may 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 current evidence suggests would not occur if risk factors were eliminated. This figure should be interpreted with caution as 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 effect of potentially modifiable risk factors is higher than previous estimates reported but 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 used data to calculate communality from the Health Survey for England from 2014, whereas previous estimates used data from 2006. We have made our estimates as conservative as possible by calculating communalities for adults > 65 years of age, as this is the age-group most vulnerable to dementia, and correlation between risk factors is likely to be more relevant in this age-group rather than in all adults.

When in the life course is a risk factor important?
While we have presented the current evidence about specific times when a risk factors has been shown to be important during the life course, they may be relevant at other times. It may be that ongoing education continues to increase cognitive reserve. Similarly, diabetes, hypertension, depression, being sedentary and smoking are probably important 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 factors, such as diet, alcohol, traffic or sleep which may be relevant. It is therefore possible that the potentially preventable fraction of dementia is underestimated in our figures.

Reverse causality
The direction of causality is sometimes unclear and may sometimes be bidirectional. For example, reduced socialisation or increased depressive symptoms may be caused by, and cause, cognitive decline and thus our figures may be an overestimate. When considering some risk factors which occur not long before the onset of impairment, it is difficult to be sure of direction of causation; e.g., whether depression increases the risk of dementia or dementia increases the risk of depression or if the relationship 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 may 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. We have also used conservative estimates of prevalence for social isolation or hearing loss aged over 55, to produce as accurate an estimate of PAF as possible.

Data quality

Finally, there are differences in the quantity of data so that the estimates for hearing loss are less stable than those for hypertension, smoking or diabetes, for example, since there are fewer studies that that have been used to contribute to the estimates presented.

Importance of PAF findings

The general principle is that there is an important proportion of modifiable risk factors in dementia, whether we assume the true PAF to be lower or higher than our estimate. This could translate into a large impact on the global burden of dementia which would then have huge implications for social and healthcare 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 may push back the onset of many cases for some years. Dementia prevalence would be halved if its onset were delayed by five years (141). Estimates are that worldwide dementia prevalence would be reduced by over a million cases, with a 10% reduction in the prevalence of the seven principal health and life-style factors; or an intervention that delayed dementia by a year, might decrease the number of people living with dementia globally by 9 million in 2050 (32;59). While we might not expect risk factor modification to have this magnitude of impact in reality, any reduction in dementia risk would be a significant achievement.

Interventions to prevent dementia

Single agent trials 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. There have been intervention studies building on the evidence of modifiable dementia risk factors to reduce dementia incidence, testing the effects of physical activity, cognitive training, and medication including antihypertensives (142;143). The low dementia incidence rates meaning that trials have to be large to and long to show a reduction in dementia cases and with the multiple risk factors contributing to dementia may explain why most prevention trials have been inconclusive (144), leading to the development of multi-modal preventative strategies.

Antihypertensives

While most interventions trials have been ineffective, the exception is antihypertensives. A trial in non-demented but hypertensive(defined as 160-200/<110mmHg) people aged >80 years, of the antihypertensive indapamide, with the option of perindopril, 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% confidence intervals overlapped between treatment and placebo groups (hazard ratio [HR] 0.86, 95% CI [0.67-1.09]). However, when these data were combined in a meta-analysis 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]) (145). Similarly, a meta-analysis showed there was a reduction in cognitive decline in the treatment groups (weighted mean difference = 0.42; 95% CI [0.30-0.53]) (146). This was consistent with an RCT, aiming to reduce systolic blood pressure to <150mm Hg in people aged > 60 without dementia using nitrendipine (10-40 mg/day) with the possible addition of enalapril (5-20 mg/day) or hydrochlorothiazide (12.5-25 mg/day) which reduced dementia's incidence rate (147). In

the pre-Diva trial discussed below, the treatment of hypertension also appeared to be important (148). The benefits of strictly managing hypertension must be balanced with risks and target blood pressure for people aged >80 years should be below 150/90mmHg (149).

Non-steroidal anti-inflammatory drugs, hypoglycaemic agents, vitamins, hormone replacement, ginkgo, statins

By contrast, trials of non-steroidal anti-inflammatory drugs (NSAID) (150), a 24 week RCT of an 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 that statins do not prevent (or increase) cognitive impairment or dementia from two negative trials with 26,340 participants aged 40 to 82 years of whom 11,610 were aged 70 or older with risk factors for vascular disease (152).

While several meta-analyses have shown HRT to have a 29-44% protective effect against dementia, a US study observed negative effects (153). The latter study was, however, on women many years after the menopause and at high cardiovascular risk. More recent reviews of both observational and intervention studies conclude there are overall neither harmful nor beneficial effects in relation to dementia, with negative effects being more likely in women in poor health, especially those with cardiovascular disease and diabetes (154). HRT cannot presently be recommended to prevent dementia; however, it is possible that there may be beneficial effects for a sub-group of healthy women receiving treatment in the peri-menopausal 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

Four hundred and forty seven healthy participants, with a mean age of 67 years, at high cardiovascular risk but with no cardiovascular disease or significant cognitive impairment were randomly assigned to one of three dietary groups (155). These were a Mediterranean diet supplemented with extra virgin olive oil (1 L/week), a Mediterranean diet supplemented with mixed nuts (30 g/d), or a control diet (advice to reduce dietary fat) and adherence to the supplements was measured by urine testing. In the primary analysis of composite cognitive change over 4 years, those in intervention groups did better than the control group. Secondary analysis of the numbers developing MCI found no significant difference, and no participants developed dementia, suggesting that this intervention may have effect on cognitive aging 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 there were more dropouts in the control group, which suggests that the intervention's benefits may have been underestimated.

Cognitive interventions

Initial evidence that engaging in cognitively stimulating activities may benefit cognition and reduce dementia risk came from epidemiological studies. One study assessed the frequency of participation in seven common mentally-stimulating activities at baseline and followed up 801 older adults without dementia for 4.5 years (108). A 1-point increase in the cognitive activity score was

associated with a 33% reduction in the risk of AD. A meta-analysis of 29,279 individuals from 22 longitudinal cohort studies with a median follow up of 7.1 years calculated a summary odds ratio (OR) of incident dementia for high vs low engagement in mentally-stimulating activities of 0.5 (95% CI [0.42-0.61]), after controlling for other dementia predictors such as age, sex, general health, cerebrovascular disease, education, occupation and baseline cognition (56). This suggests that cognitive reserve is not a static property, but may 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 currently of prevention of cognitive decline or dementia. When 2,802 healthy older people were randomised to receive ten group sessions focusing on attention, memory or reasoning, there were improvements within the trained domains (156), with functional benefits at 10 year follow up (157). A recent online study compared reasoning training with general cognitive training and an active control in 6,742 participants, of whom 2,912 were aged > 60 years. Although there was significant dropout over the six month study, reasoning training demonstrated generalised benefits in both trained and untrained measures of executive function (d = 0.42), on activities of daily living (effect size d = 0.15) and verbal learning (d = 0.18) (158). The combination of cognitive training with other lifestyle interventions in the FINGER trial is described below (159). The commercial brain training tools that are widely promoted often have efficacy claims that are not substantiated by real evidence that they can prevent cognitive decline.

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. Recent meta-analyses have either reported no overall evidence that exercise improves cognition in healthy older adults (77), or that benefits are limited to specific cognitive domains. A recent meta-analysis reviewed 25 studies of aerobic exercise, resistance training or Tai Chi (160). Fifteen of these reported significant improvements for exercise vs controls on measures of executive function, memory or composite measures of cognition. However, the only significant results from the meta-analysis were for resistance training improving reasoning vs controls (two studies, mean difference = 3.16 (95% CI [1.07-5.24] 135 participants) and Tai Chi improving processing speed and attention vs no exercise control (two studies, 156 participants). Conversely, a meta-analysis of 29 studies of aerobic exercise in healthy adults, including three studies of participants with MCI, found overall exercise related improvements in people with MCI's memory (Hedges' g = 0.237, p = 0.05) (161). A recent RCT of 100 adults with MCI, randomised to resistance training or cognitive training, reported that resistance training significantly improved the primary cognitive outcome, ADAS-Cog (effect size = - 0.33 (95% CI [- 0.73-0.06])) at 6 months and executive function at 18 months (162). 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 direct neurological effects such as increased neurogenesis, cerebral blood flow, and levels of Brain Derived Neurotrophic Factor(76;163;164). It is suggested that some inter-individual variability in response contributing to the conflicting RCT findings may be related to individual differences in exercise-related neuroplasticity (165). It may also be that protective effects in long-term studies accumulate over years rather than over a short time and that people who exercise are different in several ways to those who do not. One RCT of 40 minutes walking three

times weekly for a year (versus stretching and conditioning) showed exercise training increased hippocampal size and improved memory in healthy adults aged 55-80 (166). Overall there is not sufficient scientific evidence that physical activity reduces dementia risk (167).

Social engagement

Longitudinal studies suggest that social interaction may prevent or delay dementia but there is a lack of intervention study evidence 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 (168). A recent meta-analysis of social activity found that incident dementia risk was elevated for people with more limited social activity participation (RR: 1.41, 95% CI [1.13-1.75]) and less frequent social contact (RR: 1.57, 95% CI [1.32-1.85]) (60) but not those who had low satisfaction with social contact. The relatively short follow-up period in some studies precludes strong conclusions about the direction of causation.

People with dementia may be less motivated to engage socially or find more difficulties in organising activities, be embarrassed by their difficulties or worried they may be unable to manage previous activities or may 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 (169). While many family members may increase contact as the person with dementia requires more support, visits by family members tend to decrease as the dementia becomes more severe, as relatives may find it distressing or be unsure that their relative gains from their visits. People with more severe dementia may move homes for support further from their previous social support network.

There is little knowledge about the effect of social activity interventions on cognition. One pilot RCT for older adults with social activity as an intervention component found adults with impaired executive function showed significant improvements (170). Another pilot RCT compared cognitive training, health promotion course, and a book-club as interventions for people with subjective memory problems but not dementia and found no between group difference (171)

Studies using combination strategies to prevent dementia

The FINGER study

The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) (159;172) provided four intensive lifestyle-based strategies (diet, exercise, cognitive training and vascular management) to over 600 people, aged over 60, who were at high risk of dementia according to their age, sex, education, systolic blood pressure, total cholesterol and physical activity (173). It compared cognition in the intervention group to controls who received general health advice. This highly intensive intervention consisted of about 200 meetings (300 hours) with health professionals and trainers over two years.

Participants in the intervention group showed a mean improvement versus the control group in a composite measure of cognition (Cohen's d =0.13) on executive function and processing speed, but not memory. Despite the intervention's intensity, the effect was small, although this demonstrates potential for lifestyle modification to improve cognition function in people at risk of dementia. Pragmatic multi-modal models for dementia prevention should be tested in other populations and

settings (159). Earlier intervention and longer follow-up will determine whether these approaches reduce dementia risk.

The pre-DIVA study

The Prevention of Dementia by Intensive Vascular Care (preDIVA) study in the Netherlands (174) also aimed to reduce vascular risk factors to prevent dementia in a six-year multi-domain, nurse-administered vascular care intervention open-label, cluster-randomised controlled trial (RCT) with a total of 3,526 participants 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 interviewing. Blood glucose and lipid concentrations were assessed every two years in both groups and when indicated otherwise. If indicated, medication was given for hypertension, diabetes or dyslipidaemia. There was no significant difference in dementia incidence between the intervention and usual care group over 6.7 years (hazard ratio [HR] 0·92, 95% CI [0·71-1·19]) (148). The authors thought the negative findings may have been related to the relative lack of cardiovascular risk factors in the study population, reducing the possibility of risk reduction. An accompanying editorial noted that, in the intervention group, 10% more of the participants who were not using antihypertensives at baseline were subsequently treated, and in those participants, there was reduced risk of dementia (22 [4%] of 512 intervention developed dementia vs 35 [7%] of 471 control; HR 0·54, 95% CI [0·32-0·92]) (175). These outcomes illustrate the importance of targeted interventions and of a clear model linking risk factors to dementia.

Other multidomain studies

The Multidomain Alzheimer Preventive Trial in France (MAPT; NCT00672685) (176) with multidomain lifestyle interventions and the Healthy Aging Through Internet Counselling in the Elderly (HATICE) (177) project have similar aims, the latter using 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. This is related to the desire for conclusive RCTs to confirm efficacy; the cost and intensity of interventions needed to change behavior; and doubts as to the underlying aetiology of dementia. There are, however, numerous examples where public health interventions have reduced disease incidence before the disease process has been understood e.g. hand-washing reducing puerperal fever, clean water eliminating cholera and condoms reducing HIV transmission. Risk reducing strategies in many countries in cardiovascular and metabolic health, cigarette smoking, depression, social and physical activity, and hearing may be implemented and might account for the decreased incidence of dementia in more recent cohorts.

Although dementia is diagnosed in late life, pathology develops years earlier (178). Increasing evidence from epidemiological, clinical, imaging and biomarker studies suggests that dementia, especially AD, may be a clinically silent disorder starting in mid-life, whose terminal phase is characterised by dementia (179;180). A fundamental question is, therefore, when in the lifespan should dementia prevention programmes be implemented and for how long? Studies to date appear to show that providing modestly enhanced care to non-targeted patients already receiving medical care does not reduce dementia (175).

Key points and recommendations

Preventing or delaying dementia onset is a public health priority with potential to reduce not only the disability of individuals but also associated societal and economic burden. In many countries dementia is already being delayed for years. Thus while trials, which by their nature are relatively short and include a smaller number of people, are disappointing, results from risk factor modification for whole populations or high risk populations have been more hopeful.
Dementia may constitute the terminal stage of disease processes beginning decades earlier, and lifestyle changes targeting these processes may sometimes prevent or delay dementia onset. There is good evidence that treating hypertension reduces dementia incidence and preliminary evidence that modifying 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: Preclinical AD

Preclinical AD occurs when there are early Alzheimer's pathogenic changes but no memory impairment *(181)*. These pathogenic changes in AD include extra-cellular deposition of, beta amyloid also known as Abeta 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 AD is to identify individuals at high risk of progression to dementia due to AD, so that they can have the opportunity to participate in treatment trials to delay or prevent cognitive decline. They can also be informed and make changes in their lifestyle which may delay dementia's onset. Some people may also find prognostic information to be useful, as it allows them to make plans and lifestyle changes for a possible future dementia.

Many or even most of those 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, e.g., amyloid scans results, is presented cautiously as it has the potential to cause harm without compensatory benefit. The potential of early detection will be realised if effective AD modifying treatments for these stages are developed, in which case detection would be essential in order 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 yet to be worked out in any detail (182).

Preclinical AD is also known as "asymptomatic at-risk state for AD" as it is uncertain what the predictive value is of this pathology. Those with rare familial AD are sometimes termed as having "presymptomatic AD" and are expected to develop AD (183). AD has an insidious onset and most

people pass through a preclinical asymptomatic phase when cerebral Aβ42 amyloid and other abnormal proteins are accumulating in the brain, followed by MCI, and ultimately progress to dementia (184). Abnormal biomarkers are common, with 10 to 30% of cognitively normal older people, depending on age, having significant brain amyloid deposits in PET scanning; these increase with age; and are more likely to be high in those with the APOE ε4 allele (185). These follow-ups have been in highly selected populations and we do not know their predictive value in more general populations of older people. Most cognitively normal older people, with significant 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 significant predictor of progression to dementia from MCI in one study, with 59% progressing to dementia within 3 years (187). Similarly, 3-year conversion from MCI to AD was predicted by low baseline CSF (equivalent to high brain) amyloid-β levels (188). A small, three year, longitudinal study of 32 cognitively normal, amyloid positive older adults, found 25% had developed MCI or dementia due to AD over three years, while only one of 73 of those with a negative amyloid scan developed MCI (189). Overall, although amyloid deposition is a risk for the development of AD (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 AD, characterised by biomarkers or the pathology of AD without signs or symptoms. For example EPAD (the European Prevention of Alzheimer's Disease program), a Horizon 2020/Innovative Medicines Initiative in collaboration with the EFPIA (European Federation of Pharmaceutical Industries and Associations) is designed to address this question by developing a platform able to deliver large pre-clinical 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 persons in the decades prior to dementia onset, then the outcome measures could be biomarkers or time to dementia diagnosis. The latter would take large populations and many years of follow-up. Any evaluation should include side effects, as these may limit long-term treatment. Further information on cognitive, imaging and biomarker is needed to establish what should be measured and to determine treatment effect size.

Cohorts of healthy older people and those at risk, such as the PREVENT study (193), Alzheimer's Disease neuroimaging initiative (ADNI) (194) and Dominantly-inherited Alzheimer's network (DIAN) (195), are currently being assembled for these purposes. There are now several clinical trials aimed at prevention in people who are cognitively well but at higher risk of Alzheimer's disease by virtue of genetics or biomarkers (196).

Key points and recommendations

Depending on their age, 10-30% of cognitively normal older individuals have abnormal brain amyloid or A*β* and tau levels in CSF. Only a minority of those adults will progress to MCI or dementia due to AD over three years. There are potential ethical concerns about identifying a population at risk of dementia, many of whom may 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 (MCI) is also sometimes called Cognitive Impairment No Dementia (CIND) (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 normal aging and early dementia, which sometimes reverts to normal cognition. MCI 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 MCI are clinically and neuropathologically heterogeneous (197). It affects many more people than dementia does, and estimates of prevalence vary from 4-19% of people aged ≥65, depending on the definition used and how it is interpreted (198;200;201). Functional loss secondary to cognitive impairment has previously been the entry point of persons with neurodegenerative disorders into the health and social care system but many people now present with MCI. Around 39% of those diagnosed with MCI in specialist settings and 22% in population studies, develop dementia over the subsequent three years(202), compared to 3% of the non-MCI population of the same age (203). MCI can be divided into amnestic MCI (aMCI) defined as those with a particular impairment of episodic memory (204) often thought to be likely to develop into AD; and non-aMCI.

Prodromal AD

People with aMCI and a positive CSF A*β* and tau biomarker, or positive A*β* PET scan, have been termed as having prodromal AD (181;183) or MCI due to AD (205) an advance over the heterogeneous term MCI. This subgroup is more likely to progress to Alzheimer's Dementia (199). In other subgroups, MCI may be caused by vascular pathology, or herald other types of dementia.

Development of future MCI interventions should recognise this heterogeneity, or direct specific interventions at homogenous sub-groups, for example, those likely to have prodromal AD. However, if disorders such as AD can be diagnosed in the preclinical or prodromal period then treatment would ideally be given then.

Risk factors for progression from MCI to dementia

There is evidence from prospective studies, summarised in a systematic review, that diabetes, pre-diabetes, metabolic syndrome, lower serum folate levels, and the presence of neuropsychiatric symptoms increase the risk of progression from MCI to dementia, but less education does not (206). Mediterranean diet decreases the risk of conversion from amnestic MCI to AD(206). A slightly different view emerged from a large but unreplicated community cohort study where people were retrospectively classified as having MCI (207). It suggested that risk factors for progression to dementia differed between men and women; and 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 MCI

have neuropsychiatric symptoms; most commonly depression, anxiety, apathy and irritability (210). Some of the symptoms may be a reaction to the experience of declining abilities. Neuropsychiatric symptoms may be indicators of people who are at higher risk of dementia as they predict conversion to dementia (206). Nonetheless, neuropsychiatric symptoms may be implicated in the aetiology of dementia, through neuroendocrine axis activation; or interact synergistically with a biological factor, such as genetic predisposition. Either of these putative relationships suggests treatment might have potential to delay dementia but it is unclear whether they are truly potentially modifiable risk factors rather than indicating individuals who are further along the path to a dementia syndrome.

PAF for Modifiable Risk Factors in MCI

In order to highlight the potential for slowing progression of MCI to dementia, we have calculated the PAF using the formula above, 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 develop dementia from MCI if that risk factor could be completely eliminated. The direction of causality of neuropsychiatric symptoms discussed above does, however, remain.

We calculated communality for these risk factors using data on people aged> 65 years from the Health Survey England using the methods described above. In the absence of data on Mediterranean diet, we used obesity as a proxy measure for not following a Mediterranean diet; and for neuropsychiatric symptoms, we used depression. We have also conservatively assumed these prevalences in people aged ≥65 years are the same as in the population with MCI. The principal component extracted using 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 MCI 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 relative risks, prevalence and communalities and the PAF are These risks are ones for which we have data but that other factors, including hearing and social interaction, may be important in MCI but there is a lack of evidence at present.

Risk Factor	Relative risk for dementia	Prevalence (%)	Communality (%)	PAF (%)	Weighted PAF* (%)
Diabetes	1.65	6.4	7.6	4.0	1.5
Neuropsychiatric symptoms	2.52	29	61.1	30.6	11.5
Diet	1.92	32.5	66.7	23.0	8.7
Total adjusted for communality					**21.7**

Table 2. Potentially modifiable risk factors for progression to dementia from MCI; their relative risk, prevalence and population attributable fraction

*Notes: *Weighted PAF is the relative contribution of each risk factor to the overall PAF when adjusted for communality*
We used population prevalence of obesity and depression as proxies for diet and neuropsychiatric symptoms respectively.

Interventions to reduce or delay conversion of MCI

People with MCI 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 no specific treatments (211). A recent NIH report recommended trials of interventions for dementia prevention encompassing multiple risk factors and targeting high risk individuals (172).

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

Cognitive interventions for MCI

A recent systematic review identified six studies of cognitive training in participants with MCI. Four studies reported significant improvements on objective memory outcomes immediately following training, however only one out of three studies including general cognitive outcomes reported benefits (212). Similarly, global cognition did not improve with cognitive training in three small trials, in one of which it was a primary outcome, and there were no consistently significant findings on other secondary outcomes (213).

Exercise interventions for MCI

There is mixed evidence that exercise can improve cognitive outcomes in MCI. In a review of 14 studies, 92% of cognitive outcomes reported were non-significant, and only 42% of effect sizes were classified as potentially clinically relevant (ES > 0.20) (214). A systematic review found memory did not improve with exercise (213). In one very high-quality study, there was no effect of a year-long moderate aerobic exercise group compared with relaxation, balance and flexibility exercise active control, although post-hoc analysis showed some effect in individual domains in woman and different effect in men (215). The results of less high quality studies were mixed but did not indicate generalised cognitive improvement compared to control (213). Overall, there is no conclusive evidence for exercise in MCI.

Medication for MCI

A recent systematic review found no evidence that any drug interventions, cholinesterase inhibitors (ChEIs) delay conversion to dementia in a general population with MCI (213). However, phase 2 studies of aducanumab in patients with prodromal or mild AD found it reduced amyloid in the brain in a dose-dependent fashion and phase 3 studies are now taking place (216).

Cholinesterase inhibitors

There was no reduction in incident AD in four higher quality trials where this was the primary outcome – two evaluated galantamine, one donepezil, and one rivastigmine (213). Donepezil improved global cognition in one high quality trial where it was a primary outcome measure, and a second where it was a secondary outcome, but global cognition did not improve in the three other large, high quality trials of ChEIs. Post-hoc analyses of RCT data indicate some benefit in specific

populations characterised by the presence of biomarkers. There was less cerebral atrophy in people taking galantamine who have the ApoE Ɛ4 allele than those with other ApoE variants (217), and cognitive response to donepezil was higher in butylcholinesterase-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.

Non-steroidal anti-inflammatory drugs

Trials have not shown non-steroidal anti-inflammatory drugs (NSAID) to be effective in MCI (213;219). One high quality study found that Rofecoxib, a cox-2 selective inhibitor increased incident cases of AD. A smaller study found triflusal (versus 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 AD. Several trials of NSAID have had to be stopped because of safety concerns. As any beneficial anti-inflammatory effect may be long-term, people with MCI may not be the appropriate treatment population (219).

Statins

We could not find any interventional trials of statins. One longitudinal observational study found statins did not affect cognitive decline in people with MCI (220).

Vitamin B and E and folic acid

Vitamin E did not reduce incident dementia or impact on a range of secondary outcomes in one high quality study (221). Two placebo-controlled trials found that B vitamins (B12 and B6 plus folate) had no significant effect on immediate memory over 6 months (215) or global cognition (222).

Ginkgo biloba

On primary outcomes, 240 mg daily Ginkgo biloba did not reduce incident dementia, AD or cognitive decline over 6 years in high-quality trials (223-225).

Key points and recommendations

Up to a fifth of people aged >65 have MCI and diagnosis rates in wealthier countries are rising. Nearly half of people with aMCI, also known as MCI due to AD, or prodromal AD, develop dementia in three years. This time is a potential intervention window to delay its onset and reduce incidence and prevalence, although there are no current effective interventions. There is evidence from longitudinal studies that addressing diabetes may help reduce conversion from MCI to dementia. Multimodal and multicomponent interventions targeting heterogeneous causes of progression to dementia in people at risk of dementia (not necessarily with MCI) may reduce risk of cognitive decline but have not been trialed in MCI specifically. Any intervention developed to reduce the progression to dementia from MCI will need to be practical and replicable so it can be scaled-up. ChEIs are not effective in MCI and should not be used.

Diagnosing

Increasing the diagnosis rate

There are now public health strategies and plans to increase the diagnosis rate for dementia in many countries, including Bulgaria, Denmark, France, Israel, Malta, Netherlands, Norway, Switzerland and the UK. The English strategy was instituted after variations in the diagnosis rate across regions of

England were highlighted (226). It consisted of three parts. Firstly, a public and practitioner information campaign, including TV and newspaper adverts to counter the argument that a diagnosis of dementia was not worthwhile, 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 (227). Thirdly, there was a monitoring and targeting of diagnosis rates at primary care level; a "quantified ambition" to reach a two-thirds diagnosis rate. Since this has started there has been diagnostic rates increases in in the UK, with a concomitant increase in the prescription of anti-dementia drugs, so that rates went up from an initial base of less than 40% in 2009 to 50% in March 2014 to 67% in November 2015 (228) (229).

Screening or case finding for dementia

Screening all older people for dementia is not recommended because of unclear benefits (230). However, case finding, i.e. searching systematically for people at high risk, may be appropriate considering that a disproportionate number of people with dementia are admitted to hospital as an emergency for physical ill-health prior to dementia being diagnosed, so that possibly 40% of older people in hospital have dementia (231). These hospital admissions typically lead to poorer outcomes and longer admissions than for people with similar physical problems but without dementia possibly because people may be treated without recognition that they lack capacity to consent to treatment or be discharged home without additional support for complex medication regimes and without participating in or understanding the discharge plan (231;232). 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 (233), only 20-50% of those with dementia have a primary care notes recorded diagnosis, and this number is less in lower-income countries (234). 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 (235-238). Yet diagnosis is often delayed for several years, resulting in increased anxiety and carer burden in the interim (236). 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 (239) 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 understand their relative's behaviour and allows them to access evidence-based therapies (discussed in more detail later) which improve coping skills, reducing their high risk of developing affective disorders (240-242). There are few adverse effects of diagnosis and most people say they would want to know if they had developed dementia (243).

Timely diagnosis is often difficult for a variety of reasons (236), such as people considering the symptoms are an inevitable part of ageing, people with memory problems being reluctant to consult their GP about their memory or denying problems when seen (237), possibly related to fear of the

diagnosis and concerns about stigma (244) as well as lack of insight. GPs may be reluctant or unsure how to make this diagnosis (245) and may 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 may be poor access to or lack of acceptance of medical care (248).

A systematic review of trials to increase dementia diagnosis rates found no clearly successful intervention (249). Although educating GPs increased their ability to diagnose dementia, this did not increase diagnostic rates in practice and local campaigns were ineffective on their own. A case-finding approach in primary care, where patients and families are asked about concerns about their memory and intent to act on them, may delineate a group who are more likely to have dementia (250). A recent intervention to increase timely diagnosis by empowering patients led to an increase in patients presenting to the GP 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 healthcare practitioners, as strategies aimed just at practitioners have been disappointing.

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 (233;252). Guidelines recommend a systematic approach: 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 may improve cognition, and the very rare reversible dementias, such as that caused by hypothyroidism or infection, e.g. syphilis or Human Immunodeficiency Virus (253).

Imaging can be either computed tomography (CT) or magnetic resonance imaging (MRI) and its purpose is to exclude rare treatable causes and to elucidate the aetiology, allowing pharmacological and psychosocial treatments to be tailored to the specific dementia subtype.

Cognitive testing

There are large numbers of short validated cognitive tests, with a recent systematic review identifying 22 (254) so 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 a 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 DLB (258;259). The Rowland Universal Dementia Assessment scale (RUDAS) (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 are part of routine clinical assessment of dementia, though in many areas there is no feasible access to neuroimaging, and some countries, e.g. 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 modality for early diagnosis due 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 in distinguishing the common neurodegenerative causes of dementia e.g. FTD from AD (263). Disproportionate hippocampal atrophy suggests AD over vascular dementia or DLB but there is overlap (264). Rates of brain atrophy on serial MRI are increased (3-4 times) in AD relative to age-matched control individuals (265)(266). A repeat scan after a year may clarify the diagnosis, distinguishing changes from natural morphological variation.

Medial temporal lobe atrophy on MRI also differentiates AD from healthy ageing; as a result these findings have been incorporated into new research diagnostic criteria for AD, prodromal AD and MCI due to AD (181). MRI also differentiates AD from vascular dementia or DLB with more than 80% sensitivity and specificity and is predictive of progression from MCI to AD with almost the same level of accuracy (267;268).

Vascular abnormalities

Evidence of significant vascular burden on imaging is a prerequisite for a diagnosis of vascular dementia. 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) as some degree of vascular change is typical in older populations without dementia and therefore is also present in other forms of dementia (270). As AD and cerebrovascular disease commonly co-exist, it is often difficult to ascribe accurately the relative contributions of each to an individual's cognitive decline. However, clinicians should ensure that substantial change, as described above, is present if the dementia is to be attributed entirely to vascular pathology.

Functional and Molecular Imaging

Positron emission tomography imaging using fludeoxyglucose (18F) as radiotracer (FDG-PET) permits in vivo assessment of brain metabolism and supports assessment of FTD, particularly when clinical evaluation is uncertain and there is little change on structural imaging. It shows focal frontal and/or temporal hypometabolism which is characterised by temporoparietal and posterior cingulate hypometabolism (181;271). Therefore in the US the use of FDG-PET for differentiating FTD from AD is 'reimbursable' by Medicare in patients who meet diagnostic criteria for both AD and FTD(272). FDG-PET has greater accuracy than imaging of cerebral perfusion with hexamethylpropyleneamine oxime SPECT (273;274).

Functional imaging is helpful clinically in distinguishing DLB from other causes of dementia as dopamine depletion can be detected by DAT (dopamine transporter) scans (275;276). In moderate dementia when DLB is suspected, a normal DAT scan reliably excludes DLB although at early stages there is a 20% false negative rate (277).

Molecular imaging of amyloid or tau is a major research advance and is a promising modality for diagnosis of AD with several amyloid PET tracers currently licensed for clinical use(278). Published “appropriate use criteria" suggest amyloid PET imaging is most appropriate where there is diagnostic uncertainty about possible AD after expert evaluation (279) and is most helpful for young-onset or unexplained progressive dementias. Cerebral amyloid plaque accumulation in AD 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 AD diagnoses. Tau imaging is currently only a research tool (279;280).

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 (CSF) or blood for biomarkers is not currently recommended clinically by any national guidelines, though the American Academy of Neurology recommends CSF testing for investigation of younger patients with dementia (281) and the European Federation of Neurological Societies recommend its use in atypical clinical presentations of AD (282). 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, as CSF changes supportive of a diagnosis of AD can be identified up to 15 years before the clinical presentation of dementia (195;283). There are wide variations in current practice globally, varying from routine use in the Netherlands and Sweden, where 40% of people with newly diagnosed dementia had a lumbar puncture (284), to infrequent use in North America, where it is reserved for research settings with strict protocols (285), reflecting uncertainty about the added value of these investigations, as heightened diagnostic accuracy does not translate to tailored drug treatments.

However, there is little doubt that analysing biomarkers improves AD diagnostic accuracy and may in future be markers of disease progression or outcome targets for clinical trials. There is a large number of potential biomarkers which represent neurodegeneration, amyloid precursor protein metabolism, tangle pathology, blood-brain-barrier function or glial activation due to inflammation (286). However, results tend to be from highly selected populations, that even a meta-analysis of many studies may produce overly optimistic performance results. There can also be reproducibility and accuracy difficulties in the measurement of amyloid (but not tau) biomarkers. A recent comprehensive meta-analysis (287), of 15 potential biomarkers across 231 studies, found that elevated levels of CSF T-tau (average ratio for AD versus control was 2·54, 95% CI [2·44-2·64]) and P-tau (1·88, 95% CI [1·79-1·97]) and low CSF Aβ42 (0·56, 95% CI [0·55-0·58]) differentiated between people with AD and healthy controls. A similar pattern distinguished between people with MCI who go on to develop AD and those who do not (average ratio 1·76 for T-tau, 1·72 for P-tau, and 0·67 for CSF Aβ42). Other biomarkers studied had limited value, except for CSF Neurofilament light protein (2·35, 95% CI [1·90-2·91]) and plasma T-tau (1.95, 95% CI [1.12-3.38]) (287).

No specific fluid biomarkers exist or are clinically recommended for DLB or the frontotemporal dementias in general, but the above approaches may differentiate these forms of dementia from AD (286;288). Specific genetic variants of frontotemporal dementia can be identified using plasma and CSF biomarker testing, such as by reduced CSF and plasma levels of the protein progranulin (288) in people with progranulin gene *(GRN)* mutations (289), but accurate prognosis or differential treatment of these FTD subtypes is not yet developed enough for clinical value. Dementia caused by rapidly-progressive prion disease is rare but may be detected with high sensitivity and specificity using CSF biomarkers (290) (286).

CSF biomarker analysis has the potential for adverse consequences. There are direct risks of pain, anxiety and post-lumbar puncture headache (285), and cost implications, although the only cost-effectiveness analysis judged it to be, at €205 (approximately £173 or USD$230), a cost-effective investigation for diagnosing likely AD in MCI (291). Diagnosis may also be delayed by additional investigations, a situation which 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 (286;288;292). Previous guidelines suggested that CSF analysis should be reserved for when rare reversible causes of cognitive decline are suspected (293) (if a history of metastatic cancer, suspicion of CNS infection, reactive serum syphilis serology, hydrocephalus, age under 55 years, rapidly progressive or unusual dementia, immunosuppression or suspicion of vasculitis) and updated diagnostic criteria for AD suggest that CSF analysis should not be routine (292).

Genetic testing

Genetic contributions to dementia are complex and genetic testing is not recommended for all due to ethical concerns about uncertain benefit and potential harm. The *ApoE Ɛ4* allele is the only genetic factor which *greatly* increases susceptibility to late-onset AD (onset age > 65 years) (294). It increases dementia risk, with heterozygotes having a three times higher risk and homozygotes risk being 15 times higher than that of *ApoE Ɛ3* homozygotes (295). As *ApoE Ɛ4* does not alone cause AD, testing for the allele is not clinically recommended (282).

Young-onset familial AD is linked, in 50% of cases to mutations in the *APP*, *PS1* or *PS2* genes (296). Several contributory genes for the frontotemporal dementias have been identified, including *GRN*, microtubule-associated protein tau (*MAPT*) and *C9ORF72. A*gain, the clinical implications of these specific diagnoses are not sufficiently clear for routine testing (297).

Testing of patients and unaffected at-risk relatives for genetic causes of dementia is not routinely done and should only be conducted 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 AD and vascular dementia with MRI, if available. For those who cannot tolerate MRI, CT imaging should be used, and if possible comment on hippocampal volume. Vascular changes often co-exist with AD 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 AD.
CSF testing for dementia-related biomarkers is not routinely used in most countries. In most countries it is reserved for the exclusion of rare reversible causes of dementia or for possible young-onset dementia.

Treating

Principles of assessment and treatment in people with dementia

People with dementia have complex problems, as 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' (298).

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 below of considering individual needs in cognition, psychosis, agitation, depression, sleep and apathy and then discuss possible approaches to management; 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 (**D**escribe the problem, **I**nvestigate the cause, **C**reate a plan and **E**valuate the effectiveness of it) (299) which can be used as a general approach. After the sections on what treatments to use, we have discussed their delivery.

Principles of psychological, social and environmental management

There are around 100 RCTs published in the last ten years with intermediate (not high) level evidence about outcomes in dementia (300). In this section we address the evidence for management strategies for specific syndromes, like depression or agitation. We discuss in the next sections those 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 (301). There is no "magic bullet" in the treatment of dementia, that is 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 'being nice' or 'providing advice'. Rather, those that show the best results are structured and systematic. Some have published manuals and materials available to professionals working with carers and people with dementia (242;242;302-306). 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 re-assessment. Most societies place a high ethical value on autonomy (307). Therefore risk management must balance a person with dementia's rights with society's and families usually beneficent wishes to reduce risks. The general principle is of risk enablement, to allow people to have an acceptable level of risk, managed by using the least restrictive options (308). This requires an assessment of the decisional capacity of the person with dementia regarding risks (discussed further below). The risks which should be considered arise mainly because of decreased ability to maintain safety, through forgetting, apathy, decreased insight or poor judgement. These 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 (309-311).

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 these are discussed further in the family carers' section. Medication should be simplified and can be packaged in easy-to-manage forms (blister packs, dossette 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

Medication for cognition

The only approved drug treatments in many countries for cognitive symptoms of dementia are for AD, DLB or Parkinson's disease dementia (PDD). They target biochemical abnormalities consequent upon neuronal loss but do not modify the underlying neuropathology or its progression. ChEIs may partly restore the deficit in acetylcholine arising from loss of neurones in the nucleus basalis of Meynert and in the central septal area, projecting to cortical regions (312). Memantine may attenuate the toxic effects of glutamate released from degenerating neurones, although it is uncertain that this is its mechanism of action (313). No neuroprotective potential has been demonstrated in humans (314). Few studies of anti-dementia drugs provide placebo-controlled data beyond six months. They are not indicated in MCI as people with prodromal AD did not show clinically meaningful improvement or slowing of progression in trials of ChEIs, and systematic reviews of MCI trials suggest increased mortality risks (315;316).

Cholinesterase inhibitors

Three ChEIs are in routine use: donepezil, rivastigmine and galantamine. These are available respectively as a tablet or orodispersible tablet; transdermal patch or capsule or liquid; and as a

capsule. Most evidence about these three drugs for AD is summarised in the 2006 review from the Cochrane collaboration (317). All ChEIs at optimal doses, compared to placebo, show modest benefit on cognition as measured by the Alzheimer's Disease Assessment Scale -cognition (ADAS-cog) of 2.4 points (318). They also show a mean difference of 1.37 points on MMSE (*figure 6*) which is equivalent to the minimum clinically important difference (319). Studies published since 2006 confirm ChEIs' cognitive benefit of (320-322). 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 about rivastigmine in AD found a similar but slightly smaller effect (323). The very small difference in behavioural symptoms on the neuropsychiatric inventory (NPI) (324) (mean difference -2.44, 95% CI [-4.12 to -0.76]) is not a clinically-significant difference. Though these studies do not exclude people, they have not purposively recruited participants with neuropsychiatric symptoms, so this finding may be limited to people with relatively minor symptoms. We report ChEI's effect in specific syndromes later in this report.

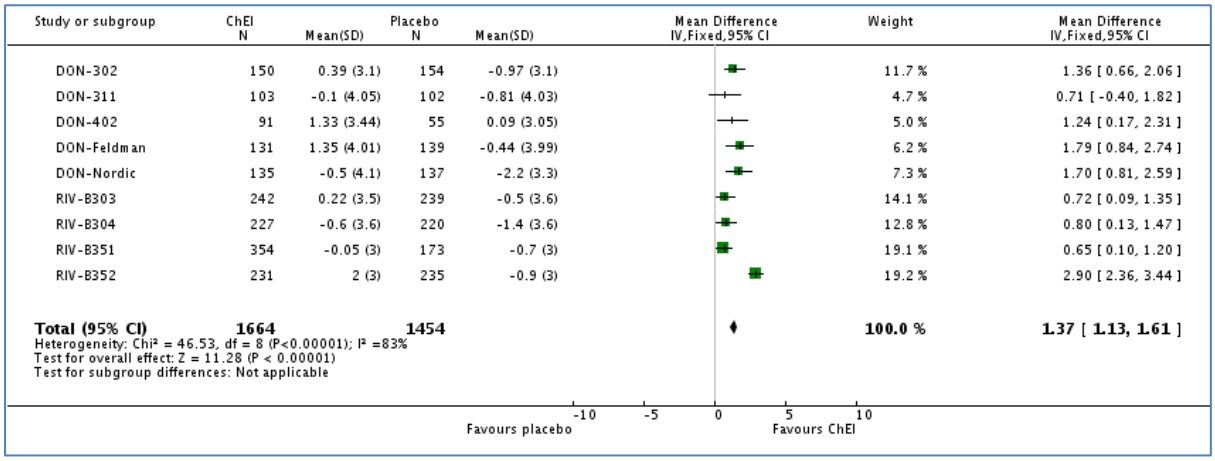

Figure 6. Effect of cholinesterase inhibitors at optimum dose on cognition, measured by MMSE, in Alzheimer's disease; mean change in score from baseline at 6 months or later

Figure reproduced from Birks *et al* (317)by permission of the *Cochrane Database of Systematic Reviews*

Key: DON- = donepezil trial; RIV- = rivastigmine trial

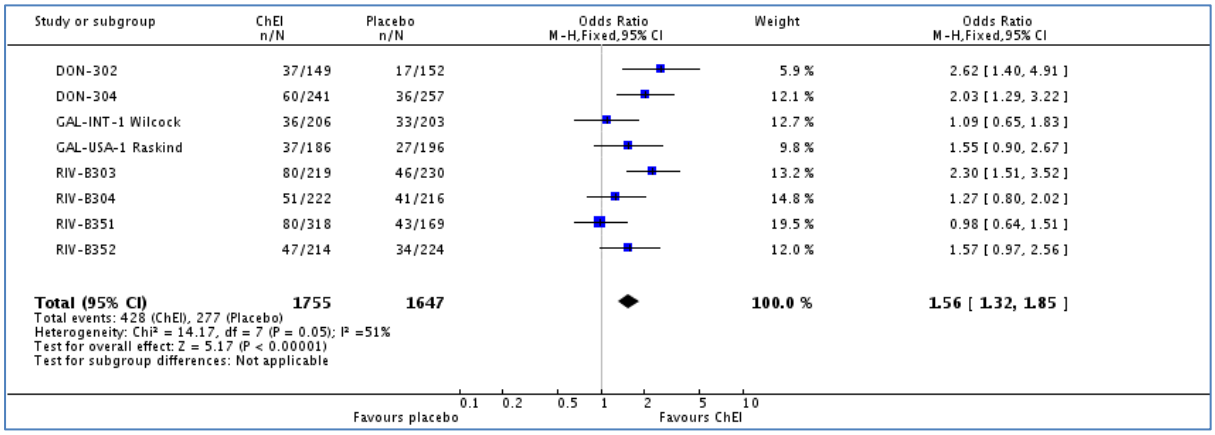

Figure 7. Effect of cholinesterase inhibitors at optimum dose on global assessment, measured by CIBIC-Plus, in Alzheimer's disease; mean change in score from baseline at 6 months or later

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Key: DON- = donepezil trial; GAL- = galantamine trial; RIV- = rivastigmine trial

ChEIs are sufficiently clinically- and cost-effective for NICE to recommend any of them for managing mild-to-moderate AD (325). It is not currently possible to assess who are responders based on their initial response to medication, so treatment should continue if the patient agrees to and tolerates the medication. The ChEIs 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 report higher withdrawals due to adverse events in those taking ChEIs than placebos.

As trials of ChEIs have not usually continued over years, it was previously unclear if ChEI treatment benefits continued as AD progressed. However the DOMINO trial, a well-conducted double-blind discontinuation study, found that donepezil cessation (replaced by a placebo) in those with moderate-to-severe AD (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 (326) (327). These results suggest ChEIs should be continued for people whose dementia has become severe.

The potential for greater benefit from higher ChEI doses is theorised from imaging showing that 10mg of donepezil resulted in inhibition of only 19-27% of cerebral cortical acetylcholinesterase activity (328;329). A double-blind RCT on 1371 people with moderate-severe AD found that, after 24 weeks, those taking a 23mg donepezil tablet per day scored 2.2 points higher on the 100 point Severe Impairment Battery than those continuing to take 10mg daily. There was no difference in clinician assessment of overall severity and functioning and more people in the high-dose group (18.6% versus 7.9%) withdrew from the study due to adverse events, most commonly gastrointestinal (330). Post-hoc analyses suggested greater benefit of high-dose donepezil for severe dementia but this was not replicated in a study, which found no significant difference between 10mg and 23mg donepezil tablets in severe dementia (331). While the US FDA has licenced a 23mg donepezil tablet, and it is used in the US in later stages of AD (332), the clinical-effectiveness remains uncertain. Rivastigmine 24 hour patches come in doses of 4.6mg, 9.5mg and 13.3mg. The OPTIMA trial (333;334) found that the 13.3 mg patch was better than the 9.5mg patch for ADL (at week 48) and cognition (at week 24) in people with mild-to -moderate AD.

ChEIs are also used for DLB and both rivastigmine 6-12mg and donepezil 5 and 10mg have been found in double-blind, placebo-controlled trials to be safe and well tolerated, with a cognitive effect, and a reduction in visual hallucinations (335;336). Meta-analyses find that ChEIs improve cognition and global function in DLB and PDD (337;338). Only the largest of four trials assessing behaviour showed a nominally significant, and very small, effect on behaviour. ChEIs or memantine are not recommended for vascular (339) or frontotemporal dementias (340).

Memantine

Memantine is a non-competitive modulator of the NMDA receptor and normalises glutamatergic neurotransmission. It prevents excitatory amino acid neurotoxicity (341). It is usually given up to a dose of 20mg/day. A meta-analysis summarised three trials on 1291 patients with moderate-to-severe AD (MMSE 3-14) and three unpublished studies in 997 patients with mild-to-moderate AD, all lasting six-months (342). 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 CIBIC-plus 0.28, 95% CI [0.15-0.41]). In the mild-to-moderate groups, there was a marginal beneficial effect on cognition which was not accompanied by effects on behaviour or everyday functioning.

Two trials of memantine in mild-to-moderate DLB found improvement in global impression (343;344), and one of these found improvement in mean behavioural symptoms (343), but no benefit in other clinical domains. A marginal benefit for cognition in mild-to-moderate vascular dementia did not equate to any global or functional improvement.

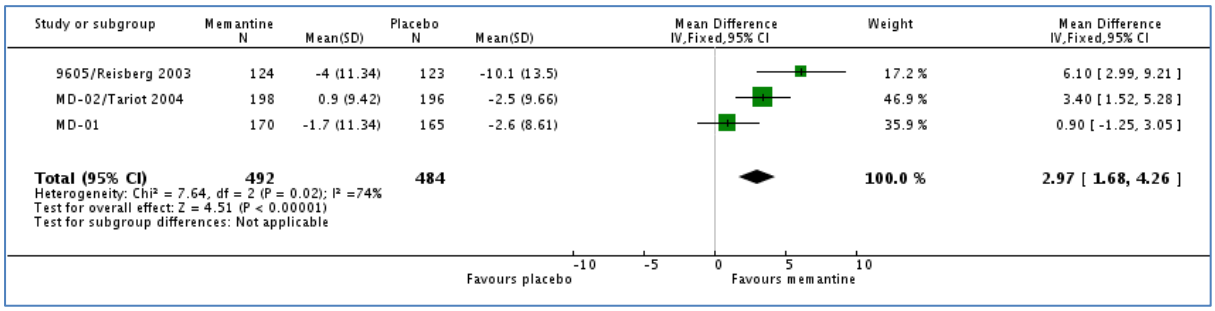


Figure 8. Effect of memantine at optimum dose on cognition, measured by the severe impairment battery, in moderate to severe Alzheimer's disease; mean change in score from baseline at 6 months or later

Figure reproduced from McShane *et al* (342) by permission of the *Cochrane Database of Systematic Reviews*

A consensus panel made a tentative positive recommendation for the benefit of a combination of memantine and ChEIs in moderate-to-severe AD on the basis of a recent meta-analysis showing small but significant benefit for global assessment, cognitive ability and neuropsychiatric symptoms without major differences in adverse events rate (345). The single study considering the combination of high-dose rivastigmine patch (13.3mg/24 hours) and memantine for severe AD found no additional therapeutic benefit but that this combination was safe (346).

There are no controlled data on the memantine's efficacy beyond six months and no studies to determine whether it can delay progression from MCI to dementia. Memantine is an option for managing moderate AD for people who cannot take ChEIs, and for managing severe AD (325). An extended release formulation of memantine at a higher dose of 28mg daily is licenced in the US for moderate-to-severe AD and has a more convenient dosing schedule. A placebo-controlled trial found it was effective in people with moderate-to-severe AD (347) 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 AD and comprises docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), uridine-mono-phosphate (UMP), choline, phospholipids, folic acid, vitamins B6, B12, C, E, and selenium. These are hypothesised to be useful as precursors and co-factors for the formation of neuronal membranes and consumption of souvenaid increases their levels (348;349). However, a double-blind trial of 527 participants with mild-to-moderate AD showed no difference in the ADAS-Cog outcomes (350). A systematic review and meta- analysis found good quality studies with a total of 1011 participants and no difference in global cognition, functional levels or behaviour (351).

Key points and recommendations

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

Other cognitive interventions

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

Cognitive stimulation therapy (CST) 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 (*Box 2*). Cognitive rehabilitation aims to improve everyday function by helping the patient set individual goals, and devising strategies to achieve these (352) and may be useful for patients with mild-to-moderate AD, for whom individualised goals to improve specific functions could improve function and quality of life. A large multicentre study of goal orientated cognitive rehabilitation in mild AD is currently underway (353). Cognitive training involves theoretically-driven strategies or exercises targeting specific cognitive domains, usually with an adaptive level of difficulty. Cognitive training may have benefits in healthy older adults but not for those with MCI, as detailed above.

What is Cognitive Stimulation Therapy?

The aim of Cognitive Stimulation Therapy (CST) is to actively mentally stimulate participants through cognitive activities and reminiscence, multi-sensory stimulation and group social contact. Each session is led by a facilitator. The standard CST model is a group intervention of 14 themed sessions, each lasting approximately 45 minutes 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:

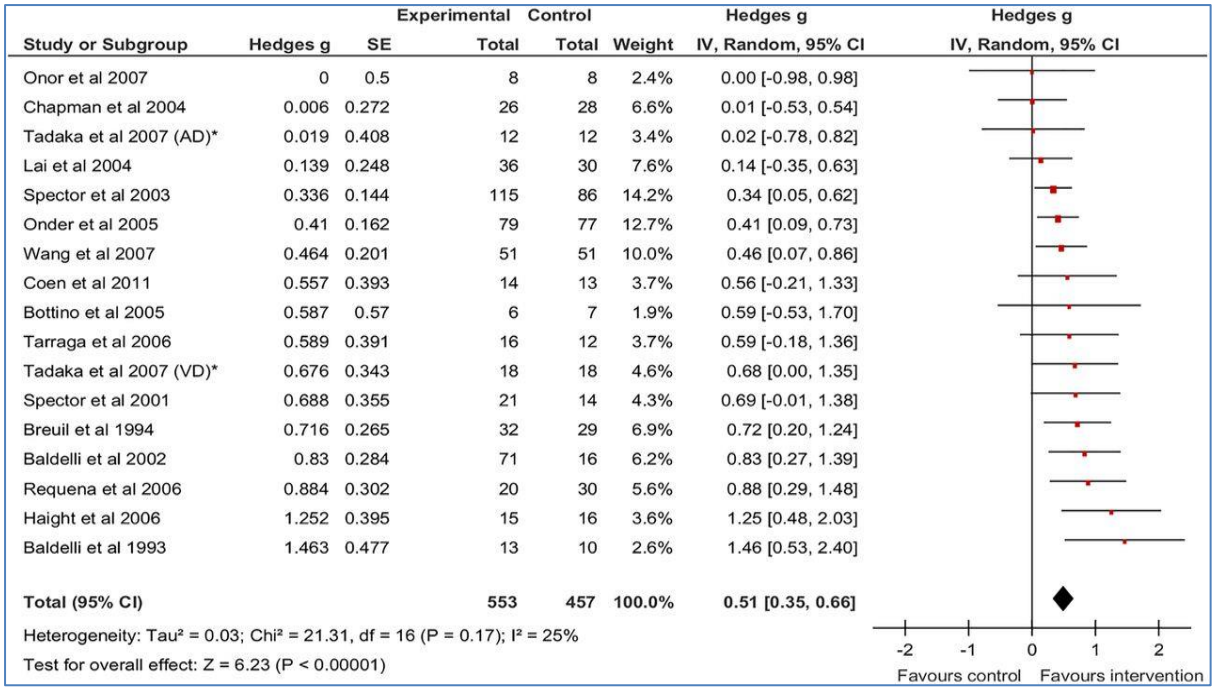
- A non-cognitive warm-up activity (e.g. soft ball game and song).
- Elements of 'reality orientation' including a board displaying personal and orientation information.

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

Box 2. Cognitive stimulation therapy

Cognitive Stimulation Therapy

CST (354) is the psychological approach with the strongest evidence for improving cognition. Recent meta-analyses find that CST benefits general cognition (Hedges g effect size = 0.51, equivalent to a mean difference of CST vs control of 1.78 points (95% CI, [1.23-2.33]) on the MMSE (*figure 9*) (355)), comparable with ChEIs although, unlike in ChEI trials, the control group in CST trials has no placebo therapy (356). A Cochrane Review has found that CST may improve self-reported quality of life (SMD = 0.38, 95% CI [0.11 - 0.66]), but had no significant effect on ADLs (SMD = 0.21, 95% CI [-0.05 - 0.47]) (356). CST 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 a lack of active control interventions, few attempts to blind raters and limited follow-up studies to clarify how long effects last (355). The group-based and multi-component nature of CST also means it is unclear which aspects of the intervention are the most useful, and whether the social element is crucial , a distinct possibility, as individualised CST has not been found to be effective (357). Overall, while clearly efficacious the evidence that this reaches the threshold for a minimum clinically important difference is debatable, and it may not be effective in all settings.



Study or Subgroup	Hedges g	SE	Experimental Total	Control Total	Weight	Hedges g IV, Random, 95% CI
Onor et al 2007	0	0.5	8	8	2.4%	0.00 [-0.98, 0.98]
Chapman et al 2004	0.006	0.272	26	28	6.6%	0.01 [-0.53, 0.54]
Tadaka et al 2007 (AD)*	0.019	0.408	12	12	3.4%	0.02 [-0.78, 0.82]
Lai et al 2004	0.139	0.248	36	30	7.6%	0.14 [-0.35, 0.63]
Spector et al 2003	0.336	0.144	115	86	14.2%	0.34 [0.05, 0.62]
Onder et al 2005	0.41	0.162	79	77	12.7%	0.41 [0.09, 0.73]
Wang et al 2007	0.464	0.201	51	51	10.0%	0.46 [0.07, 0.86]
Coen et al 2011	0.557	0.393	14	13	3.7%	0.56 [-0.21, 1.33]
Bottino et al 2005	0.587	0.57	6	7	1.9%	0.59 [-0.53, 1.70]
Tarraga et al 2006	0.589	0.391	16	12	3.7%	0.59 [-0.18, 1.36]
Tadaka et al 2007 (VD)*	0.676	0.343	18	18	4.6%	0.68 [0.00, 1.35]
Spector et al 2001	0.688	0.355	21	14	4.3%	0.69 [-0.01, 1.38]
Breuil et al 1994	0.716	0.265	32	29	6.9%	0.72 [0.20, 1.24]
Baldelli et al 2002	0.83	0.284	71	16	6.2%	0.83 [0.27, 1.39]
Requena et al 2006	0.884	0.302	20	30	5.6%	0.88 [0.29, 1.48]
Haight et al 2006	1.252	0.395	15	16	3.6%	1.25 [0.48, 2.03]
Baldelli et al 1993	1.463	0.477	13	10	2.6%	1.46 [0.53, 2.40]
Total (95% CI)			**553**	**457**	**100.0%**	**0.51 [0.35, 0.66]**

Heterogeneity: Tau² = 0.03; Chi² = 21.31, df = 16 (P = 0.17); I² = 25%
Test for overall effect: Z = 6.23 (P < 0.00001)

Figure 9. Effect of Cognitive Stimulation Therapy vs usual care on cognition, measured by the MMSE

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Cognitive training

There are relatively few RCTs on cognitive training in dementia , and their small sample sizes, outcome measures variability, and multiple techniques used, making it difficult to evaluate single strategies. A recent meta-analysis to evaluate cognitive training for common clinical outcomes of general cognition (MMSE and ADAS-Cog) found only four RCTs reporting them. The pooled effect sizes were small and non–significant (e.g. for the MMSE effect size of 0.22, 95% CI [-0.75 to 1.18]) (355). Similarly a recent Cochrane Review including six studies with a total of 173 participants found no significant effects of cognitive training on global outcome measures or activities of daily living in patients with AD and vascular dementia (358). However, an RCT of 18 x 30 minutes sessions of either adaptive chunking training or a control intervention over 8 weeks for 30 patients with mild AD led to improvements in verbal and general memory and further testing of adaptive training is required (359).

Cognitive rehabilitation

There are few trials of cognitive rehabilitation in people with dementia. In a recent RCT, 653 patients with mild AD (mean MMSE 21.6) were randomised to group cognitive training, group reminiscence therapy or individualised cognitive rehabilitation weekly for 12 weeks, then 6-weekly for 21 months. There was no reduction in rate of cognitive decline compared to usual care but the individual cognitive rehabilitation group demonstrated significantly lower functional decline at 24 months. Neither intervention (versus controls) was superior on secondary cognitive, functional or behavioural outcomes (360).

Key points and recommendations

Group CST improves cognition in patients with mild-to-moderate dementia. It is unclear whether the active component is cognitive or social as individual CST 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 of four RCTs of exercise interventions in AD reported a significant overall standardised mean difference (SMD) on cognitive outcomes compared to controls of 0.75 (95% CI [0.32-1.17]) (361). In contrast, a recent Cochrane review of nine studies with 409 participants did not find a significant difference and rated the quality of evidence as very low (362). The Finnish Alzheimer Disease Exercise Trial reported a year-long programme improved executive function, measured on clock drawing test, (effect size in the home-based exercise group d = 0.25 (95% CI [0.06-0.48]) vs d = -0.10, (95% CI [-0.27-0.16] in control group), but not in verbal fluency and there were no effects in other domains (363).

However, in the Cochrane review there was an overall significant benefit of exercise on ADLs (SMD = 0.68 (95% CI [0.08-1.27]), in six trials with 289 participants (362). The functional benefits are illustrated by the FINALEX trial, in which 210 home dwelling patients with AD were randomised 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 (mean change -14.4 (95% CI [-10.9 to -18.0])) (364).

Overall, RCTs examining exercise interventions in dementia are few and limited by small sample sizes, lack of blinding, 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 relationship between exercise and cognition exists, and that high intensity exercise gives more beneficial cognitive effects (365). It has been hypothesised that there is an intensity threshold beyond which cognitive benefits become more pronounced (366). Supporting this hypothesis, a sub-analysis of the ADEX trial (367) found that high-intensity training is required for cognitive improvement in mild AD patients. Participants performing higher intensity exercise with >70% maximum heart rate (n= 66) improved in the primary cognitive outcome vs control, whereas those doing moderate intensity exercise had no significant improvement (368).

Key points and recommendations

Engaging in exercise is helpful for a variety of reasons including cardio- and cerebro-vascular 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 it is not clear whether they help cognition. The most persuasive evidence to date on exercise is for high intensity interventions to help cognition in mild AD. It is unknown whether exercise programmes that reach the aerobic fitness thresholds which affects hippocampal volume or BDNF levels in non-AD participants conveys cognitive benefits.

Neuropsychiatric symptoms

Neuropsychiatric symptoms (NPS) in dementia are common, generally increasing with stage of dementia and affecting nearly everyone with dementia at some point during their illness (369;370). Although there are many different symptoms they often co-occur and there are several different models of how they cluster, for example, into affective, psychotic and other symptoms (371). They also vary with the underlying cause of dementia, with visual hallucinations being common in Lewy body dementia (372). They are frequently persistent, with one study reporting that 81% of people with NPS have symptoms 18 months later (373), although this varies according to the specific symptom – apathy and hyperactivity, (agitation, disinhibition, irritability, aberrant motor behaviour and euphoria) are particularly persistent (374). Factor analysis of cross-sectional data from the European Alzheimer's Disease Consortium has suggested four NPS sub-syndromes with overlapping symptoms: psychosis (delusion, hallucination and sleep disorder), affective (depression and anxiety), apathy (apathy and appetite disorder) and hyperactivity (375). The overlap between these symptoms highlights the need for careful assessment of symptoms and potential causes, advocated by the DICE approach (376) discussed above, and in this section, we present the best evidence supporting the management of these syndromes. We discuss providing pleasant events and maximising communication as strategies to prevent and manage agitation, as that is where there is evidence, but 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 (373;377).

Types of psychotic symptoms in dementia

Delusions are the most common psychotic symptoms in people with AD. Delusions 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 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 to 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; these symptoms can be associated with family carer distress, risk of care home admission, worse general health and increased mortality (378). In AD, psychotic symptoms are associated with more rapid cognitive decline and this trajectory precedes psychotic symptoms onset (378-381).

Psychotic symptoms are prominent in DLB where well-formed visual hallucinations are a core diagnostic criterion, but seem to be less common in frontotemporal dementia (382), excepting some rare genetic forms (383). 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 AD and psychosis (384). Misinterpretations of reality by a person with

dementia are often contributed to by sensory deprivation, vision loss, hearing loss and inappropriate sensory stimulation, and may increase the risk of psychosis (385).

Principles of assessing and managing psychotic symptoms in dementia (Figure 10)

This 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.

People with dementia are vulnerable to delirium in which psychotic symptoms can be prominent, so this should also be considered. Treating the underlying causes of delirium will often relieve symptoms. In patients who are not distressed by their psychosis, management may 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 (detailed in the next section) and benefits of antipsychotic treatment will often lead to the conclusion that they are not indicated (386). In DLB, where antipsychotics are more likely to cause side-effects, rivastigmine (or donepezil) (335;336) are helpful for visual hallucinations but antidepressants galantamine, do not seem to be effective (335;387).

Antipsychotic use in dementia

Antipsychotics may cause particular harm in dementia; side effects include sedation, extrapyramidal symptoms and increased risk of cerebrovascular events and mortality (388;389).

Harmful effects of antipsychotics in dementia

People taking antipsychotics have higher mortality rates (22.6%-29.1%) than those taking other psychotropic medications (14.6%), except for anticonvulsants (390). Concerns began in 2002 (391). The US Food and Drug administration issued a “black-box warning” about atypical antipsychotics in 2005, expanded to include first generation or conventional antipsychotics in 2008. Mortality on typical antipsychotics including haloperidol appears to be up to twice that of risperidone with greater risk at higher doses (388;392-394). Those who have been recently started on antipsychotics seem to be particularly at risk, especially in the first 30 days (394;395).

In the US, antipsychotic prescription began to reduce before the official warning and then decreased more sharply from 2005 to 2007 (391). In 2009, in the UK, it was calculated that two-thirds of the 180,000 people with dementia who were prescribed these drugs may not need them and their administration was related to an estimated 1800 excess deaths (or 1%) and 1600 excess strokes annually (396). 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 3-monthly review. An audit of practice in 2012 showed a large reduction in prescribing along with an increase in the dementia diagnosis rate (397).

More recently a meta-analysis of RCT of risperidone in dementia patients (1,009 risperidone, 712 placebo) found lower relative risk of cerebrovascular events in those treated with risperidone who had depression or delusions associated with dementia, compared to those without; and a reduction in relative risk of death in those with depression (398). Antipsychotics cause more cognitive impairment than placebo (399;400). In most people with AD, the adverse effects of conventional antipsychotics and the newer atypical anti-psychotic medication offset their benefits (401).

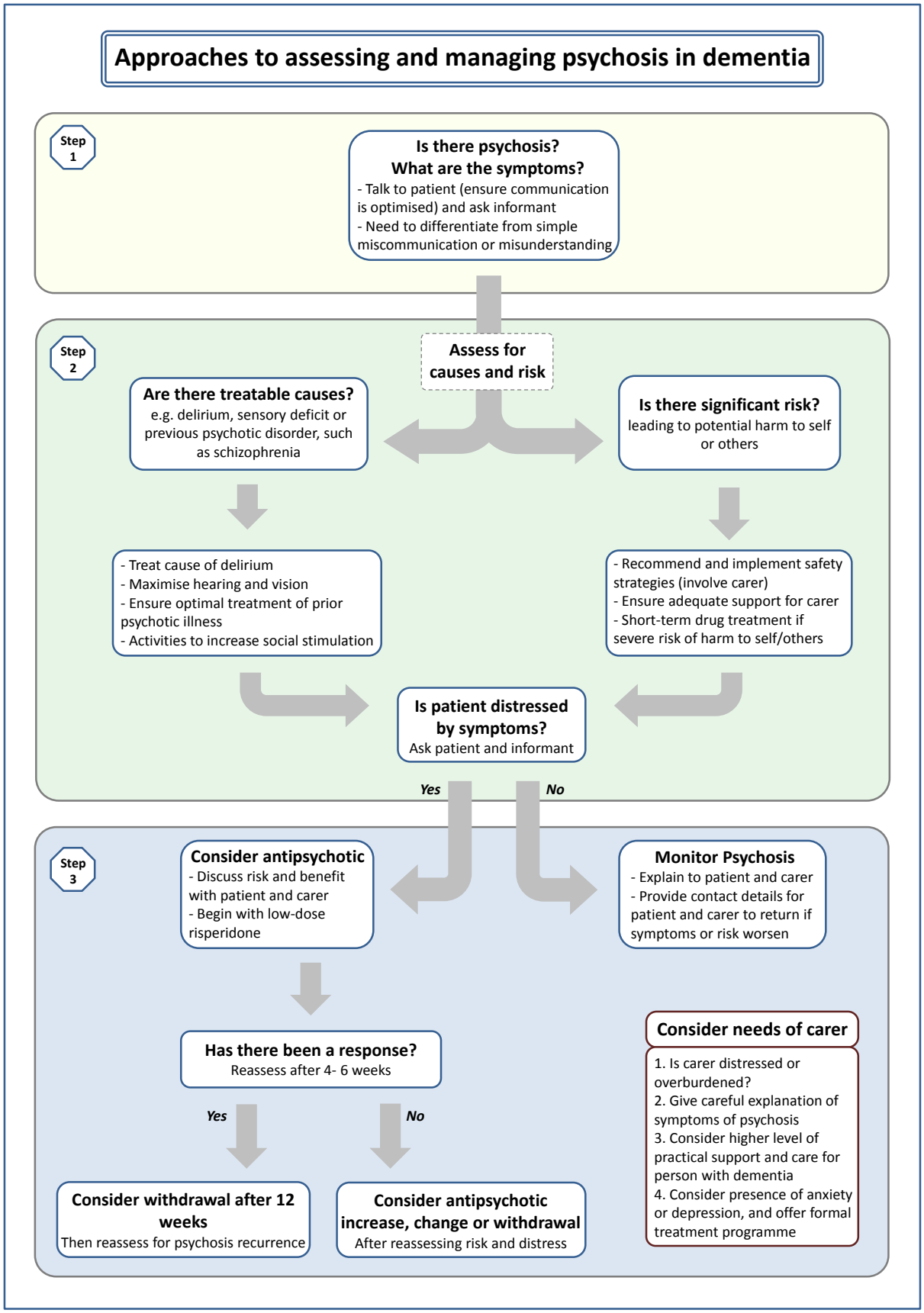


Figure 10. Approaches to assessing and managing psychosis in dementia (see text for further details)

Indications for using antipsychotics in people with dementia

Antipsychotic medication should only be used when symptoms cause distress or increased risk; for example 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 titrated upwards, changed or stopped altogether. There is limited evidence for the efficacy of antipsychotics in treating psychosis in dementia; this is mainly for risperidone 0.5-1mg, the only antipsychotic specifically licensed for use in dementia in US, Europe and UK; with some evidence for aripiprazole (376;389). For other antipsychotics, lack of evidence of efficacy is not necessarily evidence of lack of efficacy but pooled study data suggests that quetiapine and olanzapine are not effective (389;402-404).

Withdrawal of antipsychotics

Even when antipsychotics are effective, treatment discontinuation should be considered after up to 12 weeks. One double- blind RCT of antipsychotic discontinuation found that for most people with AD who have been on antipsychotics for prolonged periods, withdrawal had no detrimental effect on cognition or functional status, but those with the most severe neuropsychiatric symptoms may have benefited from continuing on antipsychotics (405). In patients with dementia and psychosis with agitation, who had taken antipsychotics for 32 weeks, discontinuation caused more relapses (60% on placebo vs 33% remaining on risperidone) (406), and this is supported by other studies (407). Withdrawal of antipsychotics should be considered for all but with caution for those who had associated agitation and distress.

Key points and recommendations

New onset psychosis may be due to treatable causes such as delirium or related to hearing loss and other sensory deprivation. These 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 minority of patients who are very distressed or are at risk to themselves or others may benefit from medication in addition to psychological, environmental and social approaches.

There is some evidence to support the use of antipsychotic drugs, particularly risperidone 0.5 -1mg, 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 should be reviewed and withdrawal considered after 12 weeks.

Medications should "treat to target".

Rivastigmine and donepezil may be helpful in hallucinations in DLB.

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 (408;409). The behaviours are often accompanied by a feeling of inner tension, although this is more difficult to detect in people with more severe dementia. The cause of these symptoms varies. They

may 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 that reduces abilities to communicate, satisfy or even know their needs, and makes it more likely they will repeat a behaviour (409-411). 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, although not in the neuropsychiatric inventory (NPI) (409). In many studies and in the NPI agitation subscale, a person with agitation (or aggression) is described as being uncooperative or difficult to handle (324).

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 (377). The rates vary depending on the setting, but are more common in care homes, possibly partly because the symptoms are associated with the breakdown of care in domestic settings and care home admission. The symptoms are persistent (374), so that nearly 40% of those with significant agitation still had symptoms six months later (377) and 60% of those with aberrant motor behaviour on the NPI, such as pacing or doing things repetitively, remained symptomatic 18 months later (373). Caring for an agitated person with dementia is more difficult and time consuming that caring for those without agitation; the additional costs of managing agitation account for around 12% of the costs of dementia (412).

Assessing and managing agitation in dementia

Figure 11 outlines approaches to managing agitation in dementia. This 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 may be physically unwell, in pain or delirious. Carers should be consulted about the likely causes of the behaviour, including triggers, and unmet needs. Carers' reactions to agitation may relieve or increase it. Overstimulating or complex environments may also exacerbate agitation.

Personal care

Communication skills and person-centred care are about considering what the person with dementia understands, is trying to say and what they want, rather than being focused on completing a task, like 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 may not understand or remember this. When that happens, well-intentioned, necessary care may be experienced as assault and the person may become agitated. The principles of communication are to:

- Identify yourself and others if patient does not remember.
- Explain what is happening, when it is happening, one step at a time (as the person with dementia may 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 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.

Box 3. Example of communication skills and person-centred care for agitation during personal care

Treating agitation in dementia

Interventions to improve communication as treatments for agitation

A recent systematic review of RCTs calculated standardised effect sizes (SES) of psychological and social interventions for agitation immediately and in the longer term *(figure 13)* (413). Interventions focused on staff in care homes improving communication with residents with dementia and identifying their wishes (called person-centred care, communication skills training or adapted dementia care mapping), decreased symptomatic and severe agitation immediately (SES 0.3 to 1.8; SES= 1.4) and up to six months afterwards (SES = 0.2 to 2.2; SES = 1.5). Box 3 exemplifies use of communication skills to decrease agitation.

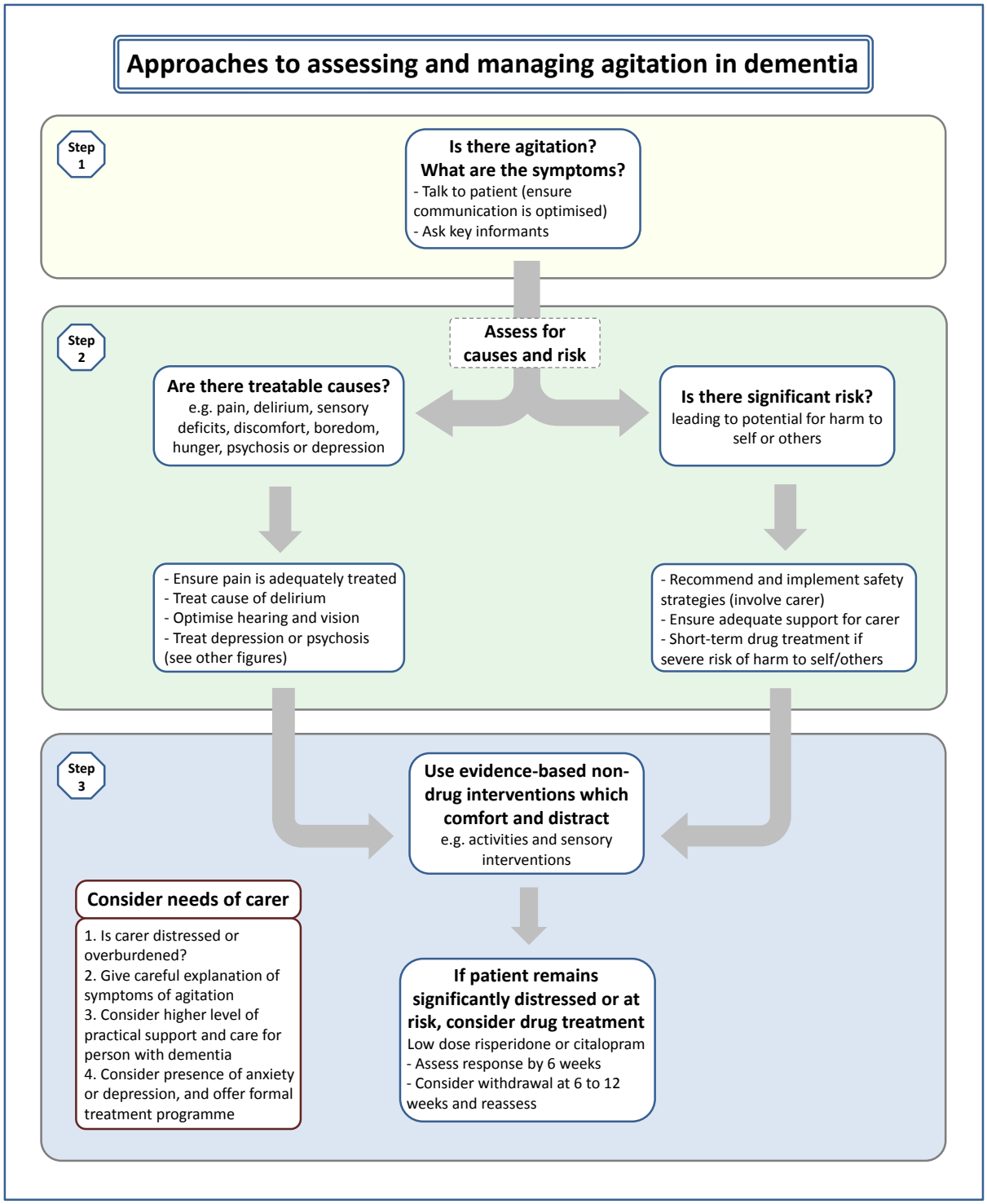


Figure 11. Approaches to assessing and managing agitation in dementia (see text for further details)

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; support self-esteem; build neural

connections through complex interactions; and promote a sense of role continuity, purpose or personhood, self-identity and meaning (169).

Activity can be a therapeutic agent to target agitation in individuals with dementia at home (414), in hospitals (415) or in residential settings (413;416), while they are engaged in it. One systematic review found that activities in care homes reduced participants' levels of agitation significantly during the activity (SES =0.2 to 1.05) as did music therapy using a protocol (SES =0.5 to 0.6) (*figure 13*) (413;414). It was unclear whether individualising activities further reduced agitation, perhaps because the activity was effectively individualised as those able and interested engaged in it. There was no evidence effects lasted beyond the intervention period, or for benefit in severe agitation (417). As activity reduces supervision time, it may be cost-effective (415).

As cognition deteriorates, the types of activities people like and can do, and the frequency and level of participation they can manage change (168), as ability to initiate, plan, and organise activities deteriorates. Figure 12 summarises strategies for individualising activities and pleasant events for individuals with varying cognitive levels for therapeutic use (418;419) (169;420).

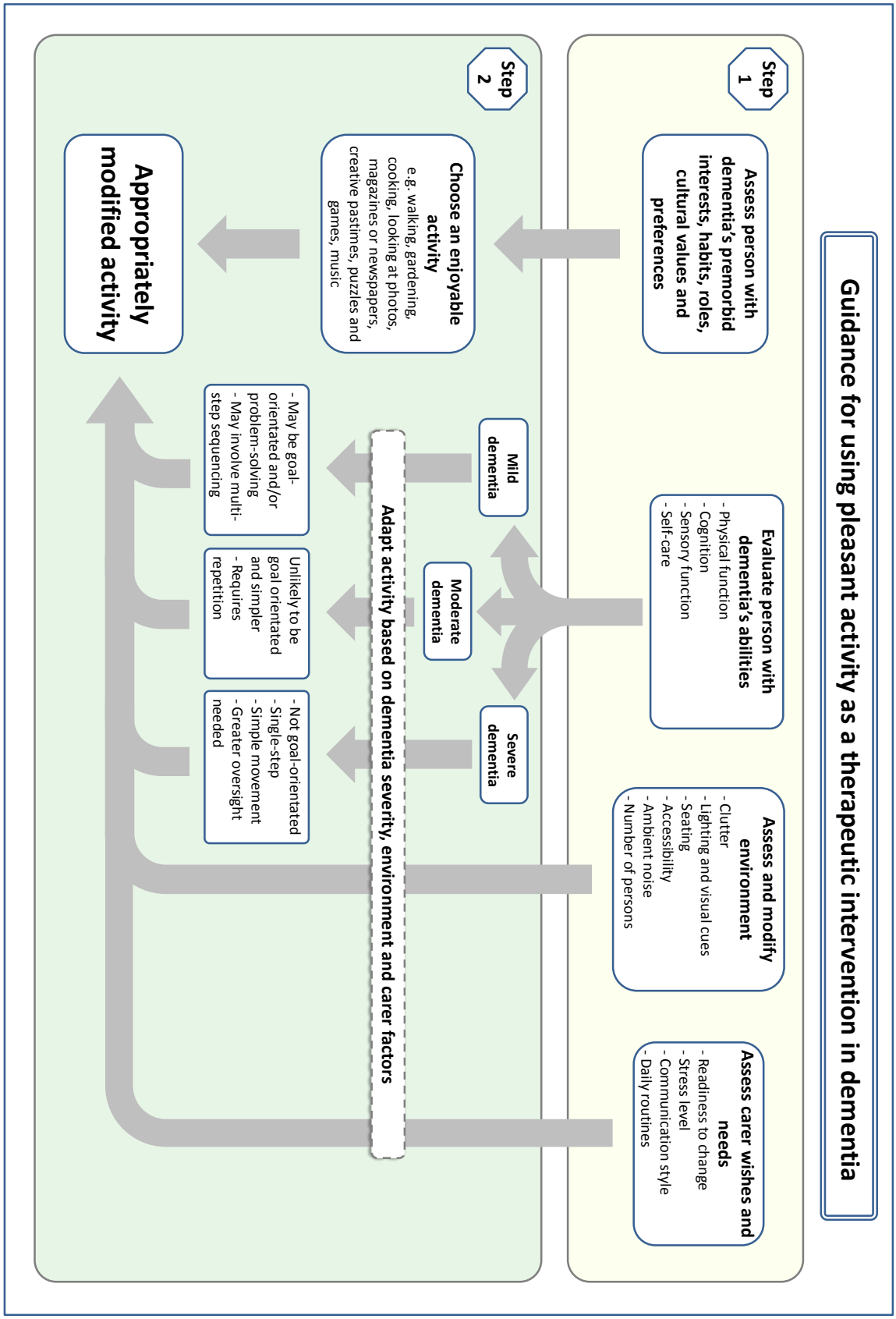


Figure 12. Guidance for using pleasant activity as a therapeutic intervention in dementia

Figure inspired by Regier *et al* (421)

Social engagement and sensory interventions for agitation

Social engagement is a necessary condition for wellbeing throughout life, and the lack of it may cause agitation in people with dementia. It encompasses physical proximity to others, eye contact, conversation and sensory stimulation including touch. It is suggested that social activity may improve quality of life among people with dementia although this has not been shown in high quality RCTs (422).

A systematic review found that clinically-significant agitation reduced during sensory interventions, including massage (413). For many successful group interventions, positive social engagement may 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 (423). Training staff how to communicate with people with dementia during personal care may be useful. In the U.K., 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 every day communication and interaction with people with dementia (424).

A before-after intervention study in 111 nursing home residents with severe dementia found live social stimuli (e.g., with people) decreased agitation more than activities (e.g. folding envelopes; reading; music) (425). Similarly, one-on-one social interaction, music, and watching a videotape reduced agitation (426). 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 which may be an activity rather than a simulated presence (427). Another open study offering social interaction, environmental modification or personalised music, found that social interaction was most often effective (428). An open study 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 (419).

Reviews of studies of simulated presence therapy using audiotapes of families found inconclusive evidence of efficacy in any domain (239;429). Unpleasant stimuli, that are experienced as an invasion of personal space or threat may cause agitation (430).

Other non-pharmacological interventions for agitation

Aromatherapy and light therapy have not been found to be effective for agitation (*figure 13*) (413). There is no evidence from RCTs that exercise reduces agitation in care home residents (413).

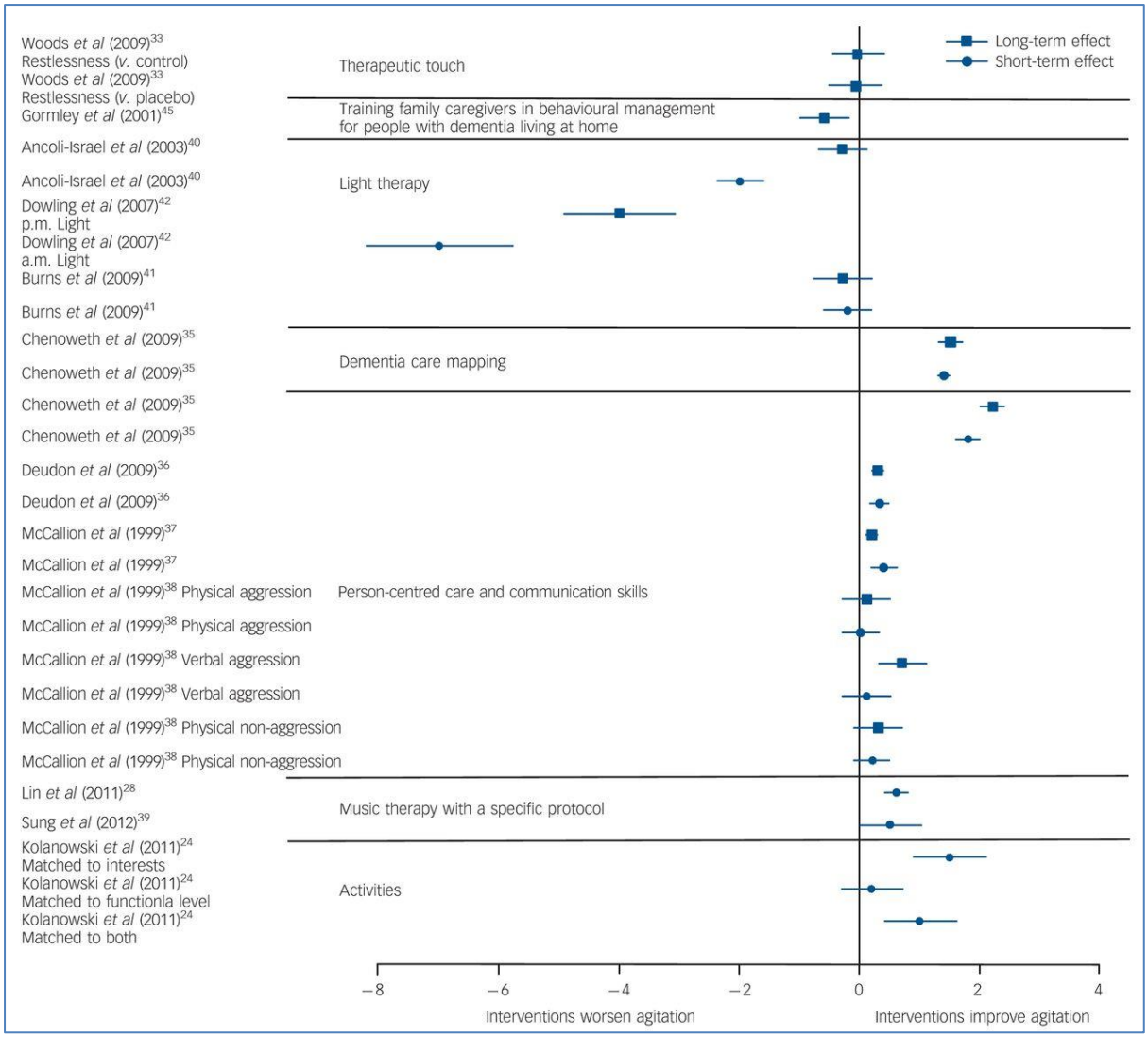


Figure 13. RCTs of effect of psychosocial interventions vs controls for agitation in dementia; standardised effect size and 95% confidence intervals, where calculable, for agitation immediately and in the longer term

Figure reproduced from Livingston *et al* (413) by permission of *The Royal College of Psychiatrists*

Drug treatment of agitation

Antipsychotics for agitation

Antipsychotics were the first choice drugs for agitation in dementia, until evidence of their harmfulness demonstrated the need for cautious prescribing and monitoring. Antipsychotics have limited efficacy for aggression; risperidone at a modal daily dose of <1 mg improved agitation and psychotic symptoms, particularly where aggression was the target symptom; possibly more in severe aggression, with a difference of around 1-1.5 points on the Cohen Mansfield Agitation Inventory (CMAI) subscale when compared to placebo (431). Haloperidol also has effects on aggression though not on other symptoms of agitation. Olanzapine, and quetiapine did not improve psychosis, aggression, or agitation but aripiprazole may improve agitation (431). Overall risperidone has the best evidence for benefit of any atypical antipsychotic, but only over 12 weeks (431). Withdrawal

trials of antipsychotics do not find an effect on agitation or neuropsychiatric symptoms except for those who have most severe symptoms (405;432).

Other drugs for agitation

Drugs for cognition, including donepezil and memantine have not been shown to be useful for agitation in RCTs and agitation can be an adverse effect of ChEIs (433;434). A double-blind RCT of memantine withdrawal suggested no advantage in the treatment of neuropsychiatric symptoms including agitation (435).

Citalopram showed efficacy for agitation with a 0.93 point difference on the Neurobehavioral Rating Scale agitation subscale (NBRS-A) and clinical global rating (the co-primary outcome) and a 2.4 point difference in the total CMAI compared to placebo, although it causes QT prolongation (436) and worsening of cognition (437). Notably about half of patients responded later in the course of the 9 week clinical trials (438). Pharmacokinetic studies suggested that (R)-citalopram enantiomer, more than the (S) enantiomer accounted for a significant proportion of the adverse effects and deteriorating cognition, as well as less likely treatment response (439) and this may be a future avenue. Like other SSRIs, citalopram can cause akathisia and other extra-pyramidal symptoms (440), although they do so less commonly than antipsychotics. An analysis to assess heterogeneity of response showed that it was not effective for those with more severe agitation, with more impaired cognition and in patients who resided in long-term care (441). It showed no efficacy on the agitation scale of the neuropsychiatric inventory (442). The dose used was 30mg and the maximum dose usually used for people over 60 or 65 in both the UK and FDA labelling is 20 mg(443)

Citalopram was compared to antipsychotics in two earlier trials for behavioural symptoms, including agitation and psychosis in hospitalised non-depressed patients with dementia, where it was no less efficacious than the antipsychotic but both showed low tolerability with more than half of participants dropping out due to illnesses, side-effects and lack of efficacy. In one trial, citalopram (mean dose of 31.1mg) was prescribed at a higher dose than now recommended and risperidone was given at a mean dose of 1.36mg; drop outs were very high for both drugs at 44% for each over the 12-week trial, but there were fewer adverse events with citalopram (444). In the second trial, citalopram 20mg was more effective than placebo for agitation for up to 17 days; discontinuation rates for citalopram, perphenazine 6.5mg and placebo were all over 50% for all three groups (445).

A recent pilot RCT of dextromethorphan/quinidine suggested benefit in the treatment of agitation with good tolerability (446) and further RCTs are underway.

A non-placebo-controlled trial of stepwise increase in analgesia over 8 weeks for residents with moderate-to-severe dementia and behavioural disturbances in a nursing home found a 7 point difference in the CMAI and a decrease in general neuropsychiatric symptoms four weeks after the end of the study (447) although the reduction of 13 points in the CMAI in the placebo arm of another trial in care homes (433) suggests cautious interpretation. Preliminary evidence has suggested effects of carbamazepine and mirtazapine, which are currently being trialled in the UK.

Key points and recommendations

Agitation may be due to discomfort, physical illness, delirium or pain which require treatment. Carer response and overstimulating environment may also worsen agitation.

There is a human need for social contact and this 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. They 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 significantly distressed. Antipsychotics are of limited efficacy in agitation in dementia but risperidone 0.5 to 1mg daily may be used for severe aggression, to prevent harm to the patient or others. Citalopram also might benefit agitation – especially in those with milder AD 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, hyponatremia, akathisia and other extra-pyramidal symptoms (448).

Depression

Depression is common in 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 (449). It is distressing, reduces quality of life, exacerbates cognitive and functional impairment, and is associated with increased mortality and carer stress and depression (450;451). Many people with mild depression improve without specific treatment although the services they see are likely to address, at least in part, situational factors predisposing to depression, such as loneliness, under-stimulation from lack of activity or a depressed carer, (452). Those with depression in dementia are likely to have a different neurochemistry compared with those who have had depression without dementia and this might partly explain the poorer response to antidepressant treatment (453;454)

Evidence for treatment of depression in dementia is heterogenous. While somewhat speculative, it is likely that depression in dementia differs from depression in those without dementia in biological, psychological and social terms (452;455). One suggested classification of depressive features in dementia includes: (1) a group where depression is situationally determined as a reaction to the impacts of dementia; (2) a homophenotypic group where the syndrome looks like depression but may differ biologically and be related to neurodegeneration and (3) 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. While we do not know from trial evidence, it is likely that a previous good antidepressant response will predict future response.

Principles of assessing and managing 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 significant risk, particularly of harming themselves intentionally or by self-neglect, and address these using strategies, possibly including hospital admission if at serious risk. Hypoactive-type delirium or pain may present with depressive features so these should be considered and if present treated. Careful assessment is required to differentiate the features which can be part of dementia, such as apathy, poor concentration or memory; from a depressive disorder and delineate the severity of depression.

Treatment should be tailored to the patient's needs and wishes and depend on the depression's severity, as detailed below.

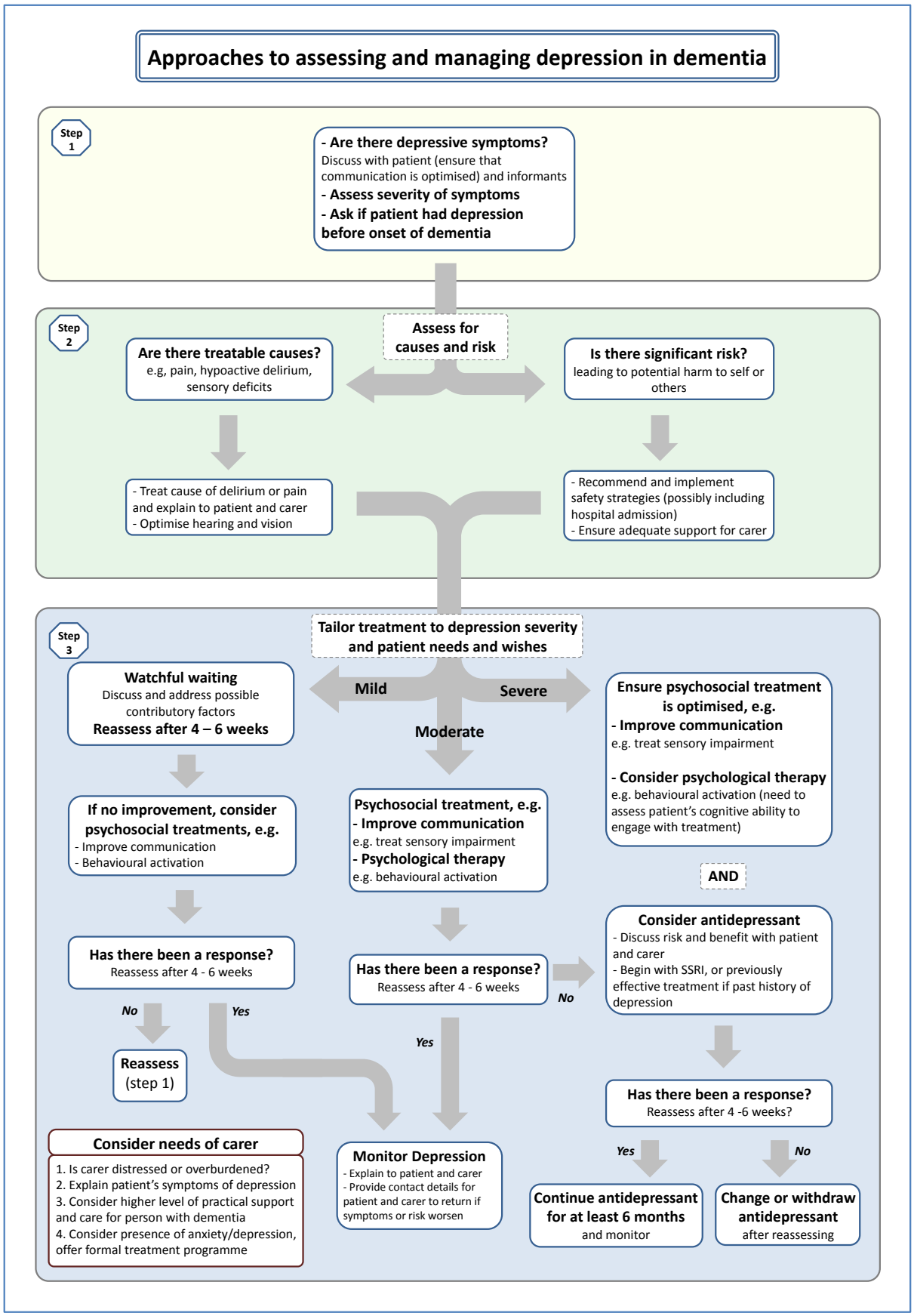


Figure 14. Approaches to assessing and managing depression in dementia (see text for further details)

Treating depression in dementia

Psychological therapy including cognitive therapy and behavioural activation for depression

There is inconclusive evidence that psychological therapies may have an effect in treating symptoms of depression in people with dementia. A recent systematic review and meta-analysis identified six RCTs of psychological therapies involving 439 participants with dementia and depression or depressive symptoms. Overall, psychological therapies including CBT, 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 there the quality of the evidence was limited(456). Only one of the individual studies was effective (*figure 15*) (457). 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 (457), although this evidence was also of low quality. There is also preliminary pilot study evidence that behavioural activation including pleasant events and engaging in activities may reduce depression (171).

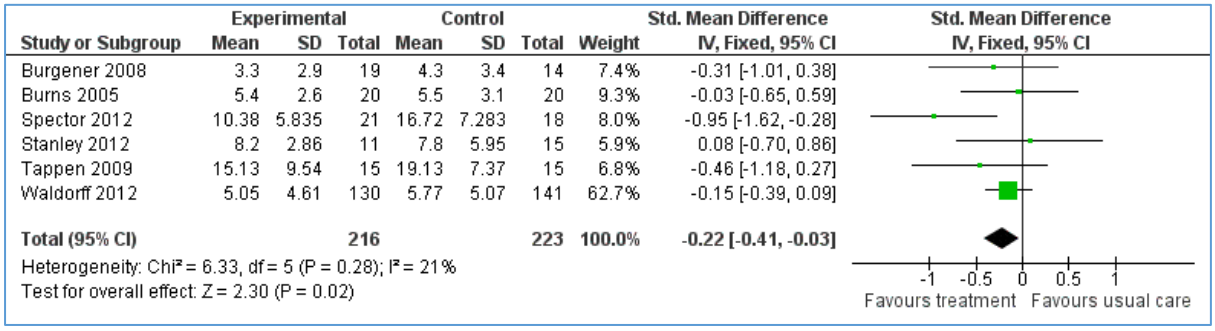


Figure 15. Effect of psychological treatment vs treatment as usual; outcome is depression

Figure reproduced from Orgeta *et al* (456) by permission of the *Cochrane Database of Systematic Reviews*

Exercise for depressive symptoms

A recent Cochrane review found no significant benefit from exercise on depression (SMD 0.14, 95% CI [-0.07 to 0.36]) (336). However the RDAD (Reducing Disabilities in Alzheimer's Disease), based on the Seattle protocols (414), 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 AD and there was a small (possibly not clinically-significant) difference in depressive symptoms but exercise may not have been the active component (304).

Drug treatments for depression

Antidepressants are often the first-line therapeutic option for depression in dementia; but lack definitive evidence for their effectiveness (458). Despite this, people with AD are three times as likely to be prescribed antidepressants as those of the same age without dementia (459).

The Cochrane review of antidepressants for treating depression in dementia concluded that the evidence for clinical-effectiveness was equivocal and weak (460) and that the small possibility of positive effect was driven by the preliminary DIADS study of sertraline which was highly positive (461). Since that review, the much larger DIADS-II (n=131) (462;463) and HTA-SADD (n=326) (452) 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 indication of a difference according to the severity of depression. Few trials have investigated the effects of newer, non-SSRI antidepressants on depression in dementia but the HTA-SADD trial found that mirtazapine, a noradrenergic and specific serotonergic antidepressant, was also no better than placebo treatment over 13 and 39 weeks. There are a few older and generally smaller trials which have investigated tricyclic antidepressants and monoamine oxidase inhibitors (460). Although an earlier study recruited 694 patients to compare moclobemide 400mg to placebo; only 511 participants had dementia (all types), it did not use outcome measures validated in dementia, and it is not possible to separate the data of those with dementia from the rest of the participants who had cognitive decline (464). 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 (454). The lack 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.

There are very few data on the response to antidepressants in people who have a pre-existing history of depression, predating the first symptoms of dementia may be similar to that in depression without dementia. As discussed above, depression may be a prodromal symptom of dementia but can also occur in those who have a long past history of depressive disorder. However it is plausible that there might be attenuation in the treatment response due to the neurodegeneration and neurochemical changes that are part of dementia. 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 those who have a past history of treatment response to antidepressants prior to their developing 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 dementia is weak. There is also no good evidence that antidepressants are effective in improving other outcomes, such as ADL, cognition, clinical severity, or carer burden. There are however harms that are attributable to antidepressants, which are common and sometimes serious (discussed in agitation section, above) (436;437;452;462). In view of these adverse effects and the lack of evidence for positive effects, they should not be used in those without a history of depression in younger age, unless psychosocial treatments are unsuccessful. Some individuals may benefit from antidepressants but we do not have trial data with which to identify this group. Clinical decision making will as always rely on an individualised assessment of risks, harms and potential benefits. The

dilemma of using antidepressants in dementia is highlighted by the apparent paradox that once started, they may be difficult to stop and it is unclear how long they should be continued. The one RCT of antidepressant discontinuation was in nursing home residents with dementia and found that discontinuation led to increased depressive symptoms (465). While this suggests efficacy in this group, it may also be that the increase in depressive symptoms is a transient withdrawal syndrome. There are no similar studies in community settings or those 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. There is inconclusive evidence that increasing activity, decreasing isolation and talking therapies may help depressive symptoms and we await definitive trials. In the meantime these 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 prior to the dementia or the patient has not responded to social or psychological treatment and is moderately or severely depressed.

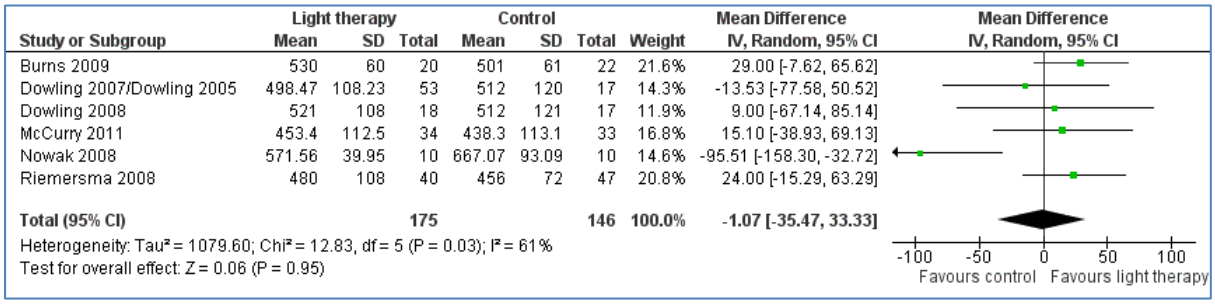
Stopping antidepressants in people with severe dementia can lead to increased depressive symptoms.

Sleep

Sleep disturbances in older people with dementia are aetiologically heterogeneous and complex, occurring in 25-55% of those with neurodegenerative dementias (466-468). They may be caused by one or more of pain and physical health conditions; anxiety; lack of activity and neurodegenerative changes. Impaired melatonin production occurs in AD and other dementias because of Suprachiasmatic Nucleus neuronal loss (469;470), 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, significantly elevating care costs (471). A Cochrane review found no definitive evidence from trials of pharmacological treatments for sleep in older people with dementia (ChEIs, donepezil and galantamine; antidepressants, trazodone and mirtazapine; or melatonin and ramelteon) and there were no RCTs of benzodiazepines or non-benzodiazepine hypnotics (472).There was some suggestion that trazodone 50mg may be useful but no large trials.

Bright light therapy used in this group, without measuring patients' individual disturbed circadian rhythm has also been ineffective (*figure 16*) (473). Most evidence about sleep hygiene and light comes from small, often pilot, studies with low methodological rigour, leading to insufficient and conflicting evidence (474). Nevertheless preliminary evidence from a pilot RCT of 36 participants suggests that light therapy, and activity may help sleep, as may education and behavioural techniques (475). Light therapy may 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.

As there are currently no treatments with definitive evidence of effectiveness, health teams use a mixture of sleep hygiene measures and psychotropic medication, extrapolated from other conditions. Patients in nursing homes taking benzodiazepines or Z-drugs (the non-benzodiazepine sedatives, e.g., zopiclone, eszopiclone, zaleplon, zolpidem, or zelmid) had worse sleep at baseline than those who did not, but over a year both groups deteriorated with those taking hypnotics doing no better than those who did not (476). Benzodiazepines also immediately increase the risk of falls (477). Thus without definite benefits, and with strong evidence of harm including increased mortality in general populations of older people (478), z-drugs and benzodiazepines should be avoided, if possible (472).



Study or Subgroup	Light therapy Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Burns 2009	530	60	20	501	61	22	21.6%	29.00 [-7.62, 65.62]
Dowling 2007/Dowling 2005	498.47	108.23	53	512	120	17	14.3%	-13.53 [-77.58, 50.52]
Dowling 2008	521	108	18	512	121	17	11.9%	9.00 [-67.14, 85.14]
McCurry 2011	453.4	112.5	34	438.3	113.1	33	16.8%	15.10 [-38.93, 69.13]
Nowak 2008	571.56	39.95	10	667.07	93.09	10	14.6%	-95.51 [-158.30, -32.72]
Riemersma 2008	480	108	40	456	72	47	20.8%	24.00 [-15.29, 63.29]
Total (95% CI)			**175**			**146**	**100.0%**	**-1.07 [-35.47, 33.33]**

Heterogeneity: Tau² = 1079.60; Chi² = 12.83, df = 5 (P = 0.03); I² = 61%
Test for overall effect: Z = 0.06 (P = 0.95)

Figure 16. Effect of 10 days to 10 weeks of bright light treatment on total sleep duration

Figure reproduced from Forbes *et al* (473) by permission of the *Cochrane Database of Systematic Reviews*

Rapid eye movement (REM) sleep behaviour disorder

Rapid eye movement (REM) sleep behaviour disorder occurs commonly, in around 20% of DLB patients and in Parkinson's disease dementia (468). 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 bed-partner (479;480). Practical measures to prevent injury from falling out of bed, for example, a bed rail, can be used and low-dose oral clonazepam (0.25 to 2mg) can suppress REM sleep. Cohort studies have found that it works well in most people; studies of melatonin in non-responders are very small (372;480).

Key points and recommendations

Sleep disorders are aetiologically heterogenous and the cause of sleep problems may be pain or discomfort as well as dementia. There are preliminary indications that sleep may respond to a combination of tailored light therapy and sleep hygiene.
There is no definitive evidence that any drug management works in sleep disorders in most dementias and they can harm.
REM sleep behaviour disorder in the Lewy body dementias may respond to low dose clonazepam.

Apathy

Apathy is one the commonest and most persistent neuropsychiatric symptoms (374). In a review of the largest non–pharmacological intervention studies. Fifteen of seventeen studies of tailored activity and eight of the nine studies using non-tailored activity reported a positive or partly positive

outcome (481). In the Improving Well-being and Health for People with Dementia (WHELD) study, antipsychotic review combined with social activity or exercise led to a reduction in apathy as a secondary outcome (482). The ADMET (Alzheimer's Disease Methylphenidate Trial) with 60 people given 20 mg methylphenidate or placebo found no difference in the apathy evaluation scale but more people in the intervention group rated as mildly to markedly improved (483) Therefore, although there are no definitive trials on management of apathy, there is an indication that interventions that increase activity or methylphenidate may be helpful. Figure 12 summarises strategies for using activity with people with dementia.

Caring and supporting

Family carers as decision makers

Family carers are the most important resource available for people with dementia (233). 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 (236;237;484;485). A substitute decision maker's best interest decision includes consideration of what the person would have wanted rather than the decision maker's judgement of beneficence. *Figure 17* sets out, as an example, the process of assessing mental capacity within the UK legal framework. There is substantial variability regarding legal issues between countries, and between states in the United States.

Families report that the most difficult decisions to support people with dementia to make or to 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; together with 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 (486-488). Driving is frequently contentious and some places, for example, 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.

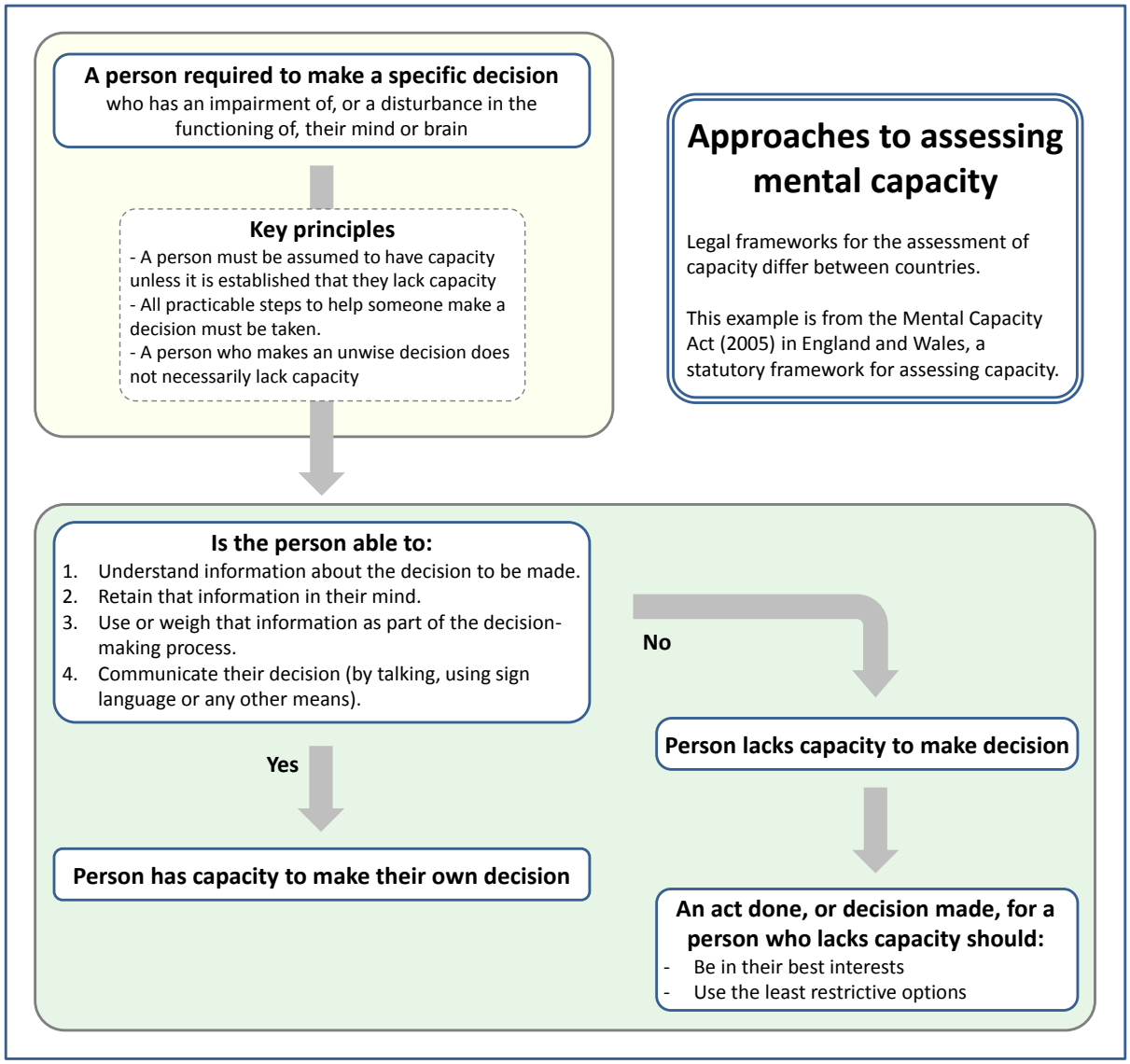


Figure 17. Approaches to assessing mental capacity

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 is most commonly enacted for financial decisions but may 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 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 (236;237;486;489). Proxy decision-making is facilitated by discussions while a person with dementia retains some ability to consider what may happen in future (486;490). Families may require support, immediately after diagnosis and subsequently, and this may usefully be delivered as a professionally supported decision aid. These provide structured information relevant to the decision, which can then be discussed with a knowledgeable facilitator (488;490). 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, reduced carer decisional conflict in one small non-blinded RCT (491). 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 as people with dementia frequently lose mental capacity to make complex decisions. People may be able to contribute to decisions but not make them independently. Capacity is situation specific. Early and ongoing capacity assessment is helpful. Healthcare 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.

Using structured decision aids may 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 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 (241;492). Family carers have worse physical health, more absences from work and report lower life quality than non-carers (493). Spouses of people with dementia are at increased dementia risk (494). Female, co-resident carers and those 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 (301;495). Carer depressive and anxiety symptoms impact not only the individual but also their relative with dementia and wider society, as carer psychological morbidity, particularly depression, predicts care breakdown and therefore care home admission (496), and elder abuse (497). 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 (498). It is therefore important to know how to effectively prevent or manage such symptoms.

Specialist, individually tailored, multicomponent psychological support to family carers, in which carers make active choices eg the REACH (Resources for Enhancing Alzheimer's Caregiver Health) intervention significantly reduce the rate of, although not necessarily the time to, care home admission (499-501). 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. 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 which were needed (301;502). Cognitive behavioural therapy (CBT) and other therapies developed primarily to target depression do not effectively treat carer anxiety (495). 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 these problems, rather than expecting the person with dementia to change (300). The mechanism of these effects may relate to carers changing their coping strategies and using more acceptance-based or emotion-focussed strategies (503;504).

Education increasing knowledge about dementia is always part of a successful multicomponent intervention but by itself does not seem to improve carers' mental health (505) (506). Similarly, group behavioural therapy, support by trained experienced family carers, support for patient and carer together and two years of education, group reminiscence therapy, counselling and social support were not effective carer interventions (507-509) (510).

One continuing mixed individual intervention for carers was effective by eight months (but not at 4 months) in reducing depression, continued working three years after the intervention started and delayed nursing home placement (511). 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 support as needed. It was also successful in reducing care home admission (303). 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 (512).

The START intervention (Strategies for Relatives) 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 left the carer with their own manual with a plan to continue strategies they had found effective (513). It was successful in reducing anxiety and depressive symptoms and both preventing and treating depression in carers and is cost-effective (242;514;515). 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 (516). It is being implemented in the UK and, as it is delivered by supervised psychology graduates rather than highly trained clinical psychologists, it is practical. There is evidence that the REACH intervention programme may generate savings in carer time and therefore in cost but it is expensive as it is delivered by clinical psychologists (517).

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 may work for an extended period and may prolong the time 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 there is evidence.

Protecting

Definitions of abuse

Abuse is defined as "a violation of an individual's human and civil rights by another person(s)" (518) 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, for example, 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 (519). 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 may avoid the implication of intent which 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 (*box 4* for case example).

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 may 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. Over a third of family carers report the person for whom they care behaves abusively towards them (520). Abuse may be reciprocal as people with dementia who are verbally or physically abusive towards carers are especially likely to be abused (497;520).

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 (497;521). That is, unsurprisingly, distressed carers who have more to cope with are more likely to act abusively. 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 in countries where people with severe dementia are more commonly cared for in their own homes (522), and high rates of abuse in care homes in countries where most people with severe dementia live in this setting (522).

Prevalence of abuse for people with dementia

Elder abuse is inherently difficult to study. It is hidden, often perpetrated against vulnerable people, by those on whom they depend. Prevalence estimates are influenced, and possibly underestimated, by the inability, fear or embarrassment of older people to report it. Some studies have asked paid or family carers to self-report these behaviours and they appear willing to but may not see as abusive behaviour (519) 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 (523;524), making intervention difficult.

Surveys recording abusive behaviours, without implication of intent, which is generally a legally determined construct, or blame, which is socially determined find that it is more likely to happen to people with dementia. Six percent of older people in the general population reported that they have been subject to significant abuse during the past month; among frail older people, nearly a quarter reported significant levels of 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) (519). Sixteen per cent of staff in care homes, where most people have moderate or severe dementia, had witnessed significant psychological abuse (525).

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 as 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 agreed they would give that consistent message. They reassured the son that regular contact would help and he started this using skype. 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.

Box 4. Case vignette of abuse in dementia and management strategy

Approaches for preventing and reducing abuse in people with dementia

Abuse may go unacknowledged if they feel there are no better management options and is under-detected and under-reported (526). Staff who detect abuse may 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 (527). Encouraging naming and reporting of abusive behaviour is an important first step to reducing it. There is good evidence that interventions can effectively increase professionals' knowledge about abuse and their ability to detect and manage it (528;529).

Managing the most serious cases of abuse, including financial abuse, physical violence and 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 seeking to reduce abusive behaviour, target physical restraints, in care home or hospital settings and often show this is possible using person centred approaches (530). Restraints are defined as anything restricting movement, such as bilateral bed rails, belts, and fixed tables in a chair. They can cause distress, violate human rights, impair future mobility and skin integrity and usually do not prevent falls. Restraints may sometimes be because of society's unwillingness to provide adequate dementia care resources. Care workers delivering care with inadequate training and resources may use restraints to try to prevent harm. The judgement of what is restraint may be granular. Bed rails may be used only to prevent someone with excessive movement during sleep falling out of bed. It might be neglectful abuse not to use them. One carer briefly and gently holding a person's hand during personal care so they do not hit another carer is proportionate and may 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 sedating medication or physical restraint to manage symptoms that may cause harm. Psychotropic medication to manage agitation and aggression would generally be considered more acceptable. By contrast, the Netherlands has traditionally prefered seclusion and physical restraint in preference to medication, although this is changing (531). In the UK and US , there have been well publicised cases of relatives placing cameras in care homes and witnessing abuse. Using monitoring technology to detect harm to people with more severe dementia is one way of detecting abuse to stop it. However, it may 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.

There are few examples of intervention studies including elder abuse as an outcome aside from restraint. This may 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 (525). In the only intervention study to measure abusive behaviour by family carers as an outcome, found no evidence that the START (STrAtegies for RelaTives) intervention reduced abusive behaviour (514;532). For ethical reasons researchers intervened to manage abuse in both groups, which may have masked any intervention effect. Interventions that aim to reduce burden of care, carer distress and neuropsychiatric symptoms in people with dementia may prevent abuse in community settings but currently there is no evidence demonstrating 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 just be allowed to continue.

Key points and recommendations

One in four vulnerable older people may experience abuse and only a small proportion is reported. Many older people who experience abuse have dementia. Most abusive behaviour happens where

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.
There is good evidence that person-centred care reduces restraint use in care homes and hospitals and should be implemented.
Identifying abusive behaviour accurately is a prerequisite of testing interventions to reduce it; for paid carers this probably needs anonymous reporting. We can measure abuse in a reliable and valid way. Interventions to increase professionals' knowledge about, ability to detect and manage abuse are needed.

Dying

Dementia shortens survival, even after controlling for age and multi-morbidity. This varies between populations and progression may be faster in woman participants and those with younger onset dementia (533). A UK population study found a median survival time from diagnosis of dementia to death of 4.1 years (534). In a primary care study, where diagnosis sometimes occurs at a late stage, median survival times from diagnosis were 6.7 years in those diagnosed at age 60-69, falling to 1.9 years for those diagnosed at age ≥ 90 years (246). Dementia was the sixth leading cause of death in the US in 2011 and 600,000 Americans with AD died in 2014 (535). Given its increasing prevalence it is predicted that one in three people over 60 years old will die with dementia (18).

Defining optimal end-of-life care

Despite this, dementia is often not perceived to be life-limiting or terminal and there is sometimes a failure to adopt a palliative approach to care (536-538). This may result in poor management of symptoms towards the end-of-life, causing considerable distress to the person with dementia and their family.

Specific difficulties in caring for someone with dementia at the end-of-life include:

A person with dementia may lose cognitive abilities, function, and capacity, in contrast to cancer and other advanced chronic diseases. They may be unable to make decisions about their care and treatment or express their needs and wishes as death approaches.
There is considerable prognostic uncertainty; the course of dementia is unpredictable and varies greatly between individuals. Prognostic tools have been developed but there is little evidence 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 (539).
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 (540) or developing strict criteria for when the person with dementia should be able to access hospice care (541). This is in keeping with the goals of palliative care(542):

> *"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."*

The European Association of Palliative Care has defined optimal palliative care for people with dementia (543). 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 healthcare team and societal and ethical issues. Their model of care stresses the importance of changing care goals throughout the course of dementia (*figure 18*).

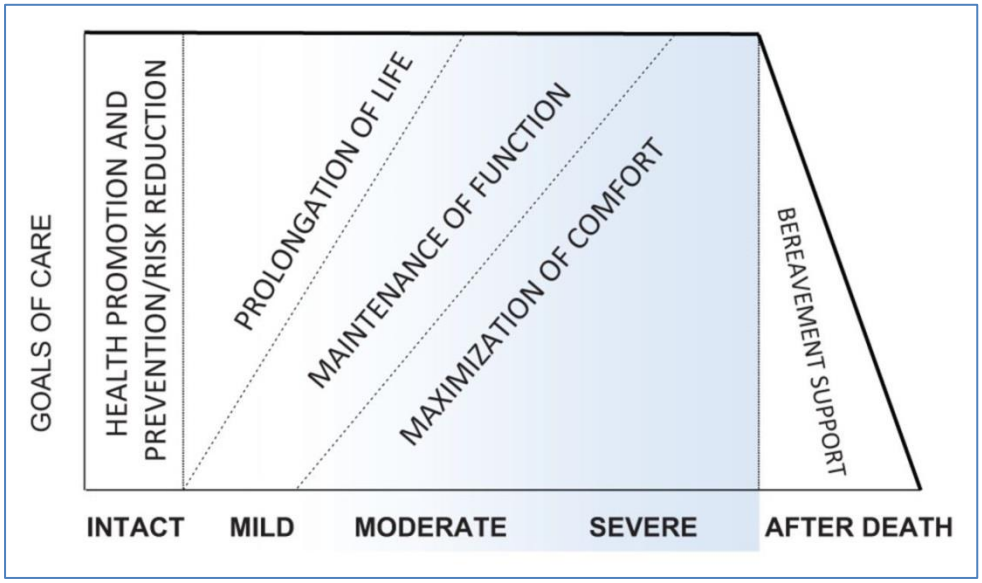


Figure 18. Model of palliative care in dementia; from European Association of Palliative Care White Paper

Figure reproduced from van der Steen *et al* (543) by creative commons license https://creativecommons.org/licenses/by-nc/3.0/

They acknowledge the vital role played by carers and family members who may experience distress, and "anticipatory" grief (544). Family carers are frequently “decision makers” and may make difficult and emotionally demanding choices at the end-of-life, for example, regarding feeding and resuscitation, as discussed in the caring and supporting sections above.

Key challenges in end-of- life care for people with dementia and their families

End-of-life care research has focussed 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 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 (545;546).

People with advanced dementia experience a range of symptoms, which may be poorly detected and under-treated (547). Pressure sores, agitation and swallowing difficulties are common and the

total symptom burden is similar to those dying with cancer (538;548). People with advanced dementia are often immobile, bed bound, at risk of aspiration and have impaired immunological function increasing their risk of pneumonia, urinary and other infections (549). Assessment and management of pain is essential as, untreated, it leads to declining quality of life, depression and may worsen agitation and other neuropsychiatric symptoms (550). There are many tools to assess pain in dementia (551), however, they also measure distress and "discomfort" which may be caused by factors such as cold, poor positioning, boredom or lack of social contact (552) (553).

Using artificial nutrition and hydration (ANH) (including intravenous fluids and parenteral feeding) in advanced dementia is particularly difficult and emotive. There is little evidence that ANH reduces the risk of aspiration pneumonia, prolongs life or improves nutritional status or quality of life (554). Difficulty swallowing and decreased appetite, sometimes secondary to lower calorie requirements, are common features of advanced dementia (555). Families are concerned that their relative will feel hungry or thirsty; the provision of food and assisting with eating is often a way to enact their care for their relative. Practices about using percutaneous endoscopic gastrostomy (PEG) and nasogastric tubes varies between countries (556;557), and across different US states (558), possibly because of legal differences

Directly transferring interventions and models from the cancer field may not work. In contrast to 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(552). 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 are effective in improving knowledge and increasing bereaved family members' satisfaction with end-of-life care (559;560). Research has focussed on specific interventions, such as pain management, or when not to treat e.g., with antibiotics, rather than active palliative interventions (561). Complex interventions taking into account variation between care homes and the need for coordinated multidisciplinary care have been developed but need further testing (5;559). Most people with dementia prefer to die in their usual place of residence and improving continuity of care could decrease costs by reducing emergency department visits and hospitalisations which usually do not prolong life but 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 dementia's earliest stages, may struggle to imagine their future self and make definitive plan, (562). There is little evidence whether advance care plans, made soon after the diagnosis of dementia change outcomes or improve the "quality of death". People with dementia, and their family and friends find advance care planning discussions helpful but value these as an ongoing process rather than committing an advance care plan to paper (563) (564). 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 person with dementia's distress (565). This provides a strong rationale for providing maximal comfort and quality of life as death approaches.

Key points and recommendations

People with dementia may be unable to communicate their needs, so assessment and management of pain and discomfort is key to providing good end-of-life care. There is prognostic uncertainty, so

the priority is adopting a needs-based care approach focusing on the person with dementia and their carers. Optimal palliative care for people with dementia recognises the role of family members and that they may experience distress and "anticipatory" grief. Training and educating nursing home staff on end-of-life care is effective in improving knowledge and increasing satisfaction with such care in bereaved family members and should be routinely implemented.

Delivering

Case management models for people with dementia

Case management is delivered by a specific individual or a team to integrate the complex network of health and social care professionals needed in dementia and respond to patient needs, through an individualised, collaborative, evidence-based plan of care with and for patients and family needs (211). It 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 and provide access to resources, plans of care, assessing environmental needs and educating and supporting carers, implementing plans, monitor and reassess (566;567) (568). There is variability on its content and implementation among and within countries (568). Case management is based on chronic disease management models, that improvement in care incorporates patient, provider, and system level interventions (569). It uses an inter-professional teams, including physicians, nurses, psychologists, physical and occupational therapists, and social worker to address patients' and families' complex medical, psychological and social needs (570)(571)(572). Additional support includes assisting with decisions about finances and healthcare and referral to key services such as transportation, home assistance, meal delivery and adult day programmes (572). Care management on the other hand refers to general co-ordination of care but the terms are often used synonymously (573).

Family carers often do not know about available services (574) so do not request or use them. The organisation of care provision differs between countries and services may be free at the point of delivery, or require individual purchase, sometimes with reimbursement. However, people with dementia use less healthcare even when freely available, than others with similar health needs; instead they use social care, and typically family carers provide more care rather than increase care access (575;576). Increasing rates of service utilisation by family carers would require professionals making the dementia care system 'visible' throughout dementia's course, so that the right support can be identified and accessed (577).

Studies of case management models for people with dementia

Table 3 shows case management approaches. Recent systematic reviews (568;578-580) and meta-analyses (499;581) of case management in dementia included 23 trials from nine countries. Over two thirds of the studies (70%) were of poor or fair quality, and evaluated interventions that varied in content, duration (most 12-18 months), setting (e.g. primary care, social services), integration with health systems, care team composition, intensity and mode of contact, whether they interfaced with patients, carers, or both, and which outcomes targeted. Case management approaches also differ in the extent to which they are adapted to meet individual needs targeting specific outcomes (582) or use specific guidelines whereby the same intervention is offered to all individuals (583).

These reviews show that case management has a low to moderate effect on improving patient quality of life, and on adherence to practice recommendations and did not lead to decreased costs.

They found case management reduced carer burden and depression (moderate effect size), but there was little evidence that these approaches benefit patients on outcomes such as neuropsychiatric symptoms, cognition, function or mortality (578-580).

Long-term care placement was the primary outcome in about half of the RCTs. Case management was associated with a low reduction on risk of nursing home admission up to 18 months (when intervention duration was < 2 years) (579;580), but did not affect resource utilisation or healthcare costs over 1 year. However, continuity of care (patients seeing fewer different clinicians, despite their comorbidities) is associated with less hospital admissions and lower costs of care (584). Few studies have specifically examined cost-effectiveness (578;580)..

Case management provided by social workers as part of collaborative care in the US reduced care inequalities (585). The US Care of Persons with dementia in their home Environment study (COPE), a multidisciplinary study with patients receiving healthcare and carers receiving advice found that at 4 months there was less functional dependence although this difference had disappeared at 9 months (586). Alternative models of case management for dementia, like the Maximizing Independence at Home model (MIND at Home), are emerging using well-trained, non-clinical staff as the front line coordinators, supported by nurses, physicians, and social worker, with preliminary evidence suggesting these models, which may be scalable with a larger potential workforce able to care for persons with dementia, have the potential to improve care for persons (298;582).

Key points and recommendations

Case management connects and facilitates access to different types of needed services for people with dementia. There is a lack of high-quality effectiveness and cost-effectiveness data. There is also heterogeneity between case management approaches, lack of manualised practice and standardisation, and limited information on how and what to implement. It should incorporate evidence-based interventions as best practice in dementia care. It may improve patient 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.

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.

Table 3. Approaches to case management in dementia

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 may not offer specialist dementia services (587), despite around 80% of residents having dementia (588-591) (592;593) (594).

Care homes are highly complex and differ in terms of organisational characteristics (e.g. 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) (595). 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 (596;597).

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 (498) (598). Some residents' have more social support, reduced isolation and improved care when they move to a care home and their quality of life improves (599) (600). A systematic review of interventions found that it is likely that interventions that incorporate person-centred care, activity and sensory stimulation decrease agitation (595). However, a meta-analysis of care home interventions found that the evidence was not enough to recommend any particular programme or compare effectiveness (601).

Person-centred care can be taught to staff and increases job-satisfaction (602). The STAR (Staff Training in Assisted-living Residences) study was a pilot intervention with only limited evidence but initial positive results (302). It 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 hadg fewer affective symptoms and staff a less adverse reaction to residents' behavioural difficulties. It has now been translated into practice (603;604). Increasing international concern about high levels of psychotropic medication use, particularly antipsychotics (605), has led to decreased use for people with dementia as discussed above. Interventions such as educating and supporting care home staff or multicomponent interventions have reduced short-term inappropriate prescribing of antipsychotic medications in care homes but evidence of long-term effectiveness and sustainability is still needed (606). However, a recent study in care homes which already had low levels of antipsychotic use, found that reducing antipsychotics, without adding other intervention, is not helpful for neuropsychiatric symptoms (607). Implementing effective interventions have required significant training and longer term supervision or working alongside care-home staff for a prolonged period(608).

Care transitions from acute care to care home settings require addressing communication barriers between hospitals and nursing homes and between families and care home staff to improve outcomes for patients by lowering incidence of both transfer and transfer-related harm, such as mistakes in medication (559;609;610) (611).

Leadership in care homes

Leadership can play an important role in implementing evidence-based practice and is a key tool in facilitating care home changes (612). It can ensure consistent implementation and sustainability, instil values consistent with high quality care, such as cooperation between care home staff and healthcare professionals (613); ensure quality standards and procedures are in place (614); and foster a climate that recognises skills and advances employees' careers (615;616). This will require available resources and work is currently ongoing about how this can be achieved (424).

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 'age in place', that is in their own home (617). Estimates indicate that 45% to 67% of residents of such facilities have dementia, of whom more than half have moderate-to-severe dementia and at least one neuropsychiatric symptom (618;619). People with dementia living in these settings often do not access treatment (618;620). Integration of dementia services in these settings, staff education and training, and monitoring of psychotropic medication may improve treatment and care for people with dementia (621).

There is increasing interest in 'home-like' residential care models and developing 'fit for the future' residential settings (622). Examples include the Eden Alternative and other small-scale facilities which are sometimes specifically designed for people with dementia (623). There is currently a lack of defined key characteristics of these models and information about outcomes (624). Some studies indicate that people with dementia might benefit from them in their physical functioning (625-627) however comparative-effectiveness and cost-effectiveness research is incomplete (624).

Key points and recommendations

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

Technological innovations in dementia care

Table 4 gives an overview of current and possible future uses of dementia-related devices.

The huge advances in the development of healthcare devices including electronic health records, portal technologies and wireless communications (628) which are likely to play a key role in dementia care in future. Given the progressive nature of dementia, certain devices may have a 'window' of usefulness to people with dementia and their carers (629). While somewhat overlapping, dementia healthcare 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 (630);
2) Monitoring; including sensors (motion; infrared; video; pressure, moisture; vital sign measurement and video) to detect changes in the person with dementia's environment or health status (628;630;631);

3) Assistive- include cognitive aids (e.g. reminder systems for medication management); ADL assistance; and safety devices (e.g. electrical outlet shutoff devices) (628;630;631).

4) Therapeutic -include those that address communication, companionship and activity (628) (630). Despite recent interest in the animal assisted interventions in long-term care settings, often using social assistive robots (SARs) there are very few well-controlled studies (632;633)

5) Carer supportive (630;634) - technology either to assist carers with the care of the person with dementia or support their own well-being (630;635;636).

Purpose	Type of health-care device	Example of use
Diagnosis and assessment	Computerised diagnostic assessment	Neuropsychological assessments
		Video-conferenced examinations
	Detecting progression	Wearable sensors to detect changes in gait or ADLs
	Virtual reality	Assessment of ADLs, e.g. meal preparation
Monitoring	Environmental Sensors	Detection of changes in movement, e.g. falls
		Sensors to detect and intervene in environment, e.g. heat, gas
		GPS locating devices
		Remote viewing camera
	Physiological Sensors	Devices measuring pulse, BP, O_2 saturation, blood glucose, sleep
		"Smart garments" with sensors which send biometric data
Assistive technology	Cognitive Aids	Reminder systems, e.g. medication management
		ADL prompting, e.g. tool that prompts user through handwashing
		Cognitive training
	ADL Assistance	Robots to assist eating, washing and mobility
	Safety	Electrical outlet shutoff 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	Supporting reminiscence-based communication between people with dementia and their carers
		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
		Web-based tools to support carer decision-making
	Peer support	Carer online phone support groups

Table 4. Possible use for technological innovations in dementia care

Challenges and priority areas for the future

Technological innovations for people with dementia and their carers is an area of significant growth, but there are few rigorous RCT studies for most devices for people with dementia, with most research exploring feasibility, and acceptability (637), rather than clinical-effectiveness. The existing literature concentrates on technical aspects of delivery or physical disability (634). Many of these devices are not implemented and evaluated. Despite the potential applicability of technological innovations, there are important challenges to be addressed.

Ethical challenges: 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 (638). The development and use of devices used to restrict or restrain people with dementia raise additional concerns.

Key points and recommendations

Advances in the use and application of technological innovations may aid 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, currently evidence on the effectiveness is lacking for most devices. 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.

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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. Here 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 current evidence and the conclusions we have reached transparently. From this evidence and 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. We therefore 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 what to do 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 will be unused. Delivery of interventions will vary according to the health system, with some countries having healthcare free at point of delivery for all and others having to implement this as part of a programme. Interventions, which 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.

While dementia is due to brain pathology, 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, as well as societies in which people with dementia are accepted and 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 takes place within, rather than separate from, society so we become truly dementia friendly.

Authors' contribution

Gill Livingston (GL), Andrew Sommerlad (AS), Naaheed Mukadam (NM), Vasiliki Orgeta (VO) and Jonathan Huntley (JH) drafted and redrafted the whole report.

NM, AS and GL conceived the new PAF calculation and NM led the statistical analysis.

Sergi Costafreda led the new meta-analysis for hearing impairment and dementia risk.

All authors contributed to sections of the reports and all revised the paper critically for important intellectual content.

GL is guarantor.

Partners

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