AGE UK RESEARCH

# Dementia and cognitive decline

## A review of the evidence

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2014

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# Foreword

For over a decade, Age UK has supported a unique, ground-breaking research project called The Disconnected Mind, based at Edinburgh University. It has contributed greatly to our knowledge about how our thinking skills change with age and what we can do to protect our cognitive health in later life. As well as funding, we have worked with the researchers to summarise, interpret and translate their findings. A specific report is due to be published in the next few months, however this experience has left us well-placed to speak authoritatively not only about cognitive ageing but also about dementia.

We feel that this is a good time for everyone in Age UK to catch up with the messages from the latest research on what dementia is, what it is not, and what can be done about it.

We based this evidence review on the premise that people working for Age UK will need to have clarity on the basic concepts of dementia and cognitive ageing, either in their work or personally - or both. Even in private life, we all have nearly a 50/50 chance of knowing someone with dementia, yet individually two thirds of us will never get dementia.

Dementia diseases primarily affect our brains, and the brain has been called 'the most complex object in the universe'. Although science has unearthed an astounding amount of information, many important and basic questions remain unanswered. Sometimes, however, the problem is not that there is too little information, but too much. A lot of what you may read in the newspapers and online is incomplete or simply misleading, which is rarely helpful, either professionally to Age UK or on a personal level. We have aimed here to address some issues in order to offer a clearer picture of what dementia is and is not. Our specific aims are to use our expertise and experience to:

- clarify terms and concepts
- filter out unreliable evidence
- update you on the best and most recent brain research
- save you time and effort trawling through the literature
- offer a current picture of what is generally accepted and can be trusted on cognitive decline & dementia

Su Ray and Susan Davidson

# Executive summary

This evidence review contains what Age UK Research knows and can trust on the topics of dementia and cognitive decline.

We aim to clarify these concepts and show how they differ and how they are connected. It presents in plain English complex information on how the brain changes over time, how it can age healthily and how it is affected by disease. And it outlines what is currently known about what can happen to our brains as we age, and about what may help us to cope with these changes – for ourselves as individuals, as carers and as members of society.

The main findings of our review of the evidence and our involvement in the Disconnected Mind are:

## Dementia, mild cognitive impairment and normal ageing

- Dementia and cognitive impairment are not a part of normal brain ageing; they are diagnosable conditions.
- Normal brain ageing results in an average decline in some cognitive functions (speed of thinking, working memory) across the population whereas other functions (e.g. verbal ability) are maintained.
- Mild cognitive impairment (MCI) affects between 5 and 20 per cent of the population aged 65 or over. It affects cognitive function to a greater extent than would be expected, but not to such extent that it precludes independent living
- Some cases of MCI are treatable. Some cases (one in six) progress to dementia within a year.
- Dementia encompasses different types of disease, which cause different types of damage to the brain. Dementia is as yet untreatable.
- The most common type of dementia is Alzheimer's disease, which occurs in 50 to 75 per cent of cases, the next most common is Vascular Dementia at approximately 20 to 30 per cent.

## Prevalence

- The most recent estimates of diagnosed and undiagnosed rates find that the prevalence of late onset dementia is 7.1 per cent among people of 65 or over.
- Prevalence in the population increases with age, from 1.7 per cent in 65-69s up to 41.4 per cent in people of 95 or over.
- This shows that most people do not develop dementia – even among the very oldest people, the majority (3/5) do not develop dementia.
- The total figure for the UK is 850,000 people.
- Figures need to be treated with caution because of lack of good definitions and diagnostic data.

## Causes, Risk and Protective factors

- Some forms of dementia are related to genetic inheritance. These are extremely rare in the population and have onset before the age of 60.
- Most forms of dementia have onset after the age of 65 and have mixed genetic and environmental factors.
- Some characteristics of the disease of dementia make it very difficult to conduct robust epidemiological research.
- Emergent evidence is now seen as sufficient to identify early risk factors which can be modified by public health approaches. These are:
    - Smoking
    - Obesity
    - Midlife high blood pressure (screening and management)
    - Cholesterol (screening and management)
    - Diabetes (screening and management)
    - Depression

## Interventions

- Because of issues with research involving dementia, there are no rigorously 'proven' interventions that work to prevent or reverse dementia.
- However, experts have reached a consensus of actions we can take to reduce risk of dementia:
    - Physical activity
    - Mediterranean diet
    - Not smoking
    - Not drinking excessive amounts of alcohol
    - Treat 'immediate disease precursors' like high blood pressure, obesity, and diabetes
- Protective factors include:
    - Educational level
    - Intellectual and social engagement
- Post-diagnosis treatments which have poor evidence for benefiting cognition:
    - Medication
    - Cognitive training
    - Art, music, and reminiscence therapies
- However, the evidence shows that social stimulation is beneficial for cognition and for well-being/quality of life, so these therapies could be useful for those aspects.
- Carers are often left out of the picture. Issues for carers include:
    - Suddenly going from 'spouse' to 'caregiver' with no training
    - Burden of care: lots of support is needed, including coping strategies and education about effect of dementia and changes in person over time
    - Respite is needed, and wellbeing and quality of life of carer is important
    - Carers can either enable or prevent person with dementia engaging in activities, so they need support to understand and help engagement

## Introduction

Recent qualitative research by Age UK[1] has highlighted some common attitudes and feelings about dementia among the general public. We conducted focus groups with people aged between 50 and 64, who were just 'on the cusp' of ageing. We wanted their views about the future and how prepared they felt for later life. Our sample included people from a wide range of walks of life, some being very comfortably-off, fit and healthy whereas others were in far more difficult circumstances, living on low incomes with high prevalence of health problems and disabilities. We found that even the fittest and healthiest found dementia to be a particular worry. Its occurrence was felt to be unpredictable at best and, given increased chances of surviving other illnesses such as cardiovascular disease and cancer, it was even seen by some as an inevitable stage of ageing. As one participant in our sample put it:

> *"People are staying physically healthy longer but not mentally healthy. In the past what happened was you died at the age your body wore out. Now what happens is that your body doesn't wear out, but your brain does."*

This comment suggests a fatalistic attitude towards the decline our brains as we age, and this very likely comes with fear. Our minds are the essence of our aspirations, passions, capacities and personalities, they make us who we are.

This evidence review describes how much we do know about dementia and cognitive decline and we are fast reaching consensus among experts on how it is affected by our genes, our lifestyle and our environment. The coverage and quality of evidence are not perfect, as we discuss below. This means there is controversy about the correct interpretation of the data. However, experts in the UK have recently been able to reach a pragmatic consensus for action that could be taken now, while in the interim we develop better data and better ways to research dementia.

The level of any decline and how fast it progresses are unique to the individual, and depend on many factors, including genetic factors and IQ in youth.[2] Just as we all differ in our abilities to remember things, work out problems, plan and organise the future the way these abilities change with time also differs between people. Some experience very little difference; most of us experience some changes and for some of us who are affected by one or more of the dementia diseases, the changes can be very significant.

There are, however, two pieces of good news. The first is that dementia and mild cognitive impairment are relatively rare; most older people do **not** develop dementia. Current estimates suggest that fewer than one in five people over the age of 80 have dementia, which we will discuss in the first section of the review.[3]

The second is that it is possible to reduce the risk of cognitive decline. Recent research shows that our genes are responsible for approximately a quarter of the variability in cognitive abilities as we age[4]. This means that three quarters of the influence over our cognitive ageing is via potentially modifiable factors, including some lifestyle factors we might control ourselves, such as diet or exercise. The second section of the review will discuss what we know about interventions and protective factors for good brain health.

The review concentrates on interventions for community-dwelling older people rather than those in residential or nursing care homes, because of the relevance to services Age UKs may be able to provide.

## 'Normal' brain ageing

The average adult brain is about the size of a medium cauliflower. It consists of an intricate system of nerve cells (called neurons), supporting cells (called glia) and an enormous network of blood vessels. At only two per cent of the body's weight on average, the brain receives 20 per cent of the blood supply and uses 20 per cent of the total calorie intake. Tiny blood vessels (or capillaries) carry oxygen and nutrients for the brain's cells to survive and to work efficiently. Equally important, they carry away waste products which would otherwise become toxic. To be able to function well, then, it is essential that that brain receives an excellent blood circulation.

Neurons generate and carry electrical signals which provide information to and from our muscles, glands and sensory organs (skin, eyes, ears, tongue and nose), via the spinal cord. Inside the brain itself there are approximately 100 billion neurons. Each neuron makes on average 1,000 connections to other cells in the brain, producing around 100 trillion connections in the brain.

In basic shape, neurons are similar to trees. The mid part is usually a simple trunk-like structure (called an axon) and either end forms a complex, similar to twigs at one end of a tree and roots at the other. Signals are generated at one end of the neuron, carried along its axon in one direction only, and communicated at the other end (e.g. by generating signals in other neurons). The parts of the brain where signals are communicated between neurons is sometimes referred to as 'grey matter; the parts where the electrical signals are carried along the neurons are often referred to as 'white matter'.

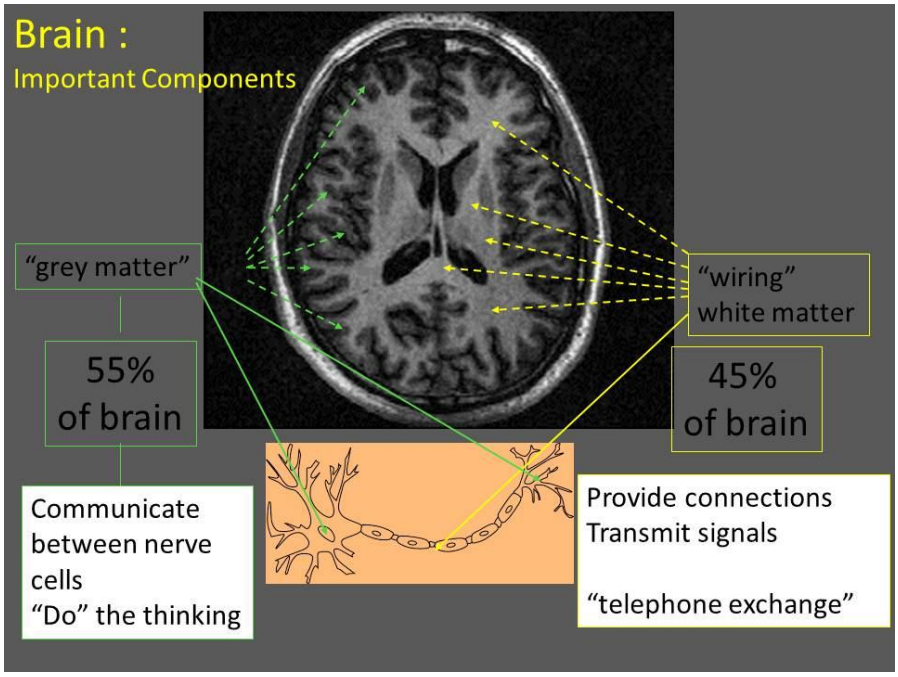


**Figure 1 Brain magnetic resonance scan from the Brain Research Imaging Centre, Edinburgh; image prepared by JM Wardlaw**

Different parts of the brain very basically correspond to different activities of the body (see Fig. 2) and the brain controls all our functions, behaviour and thinking.

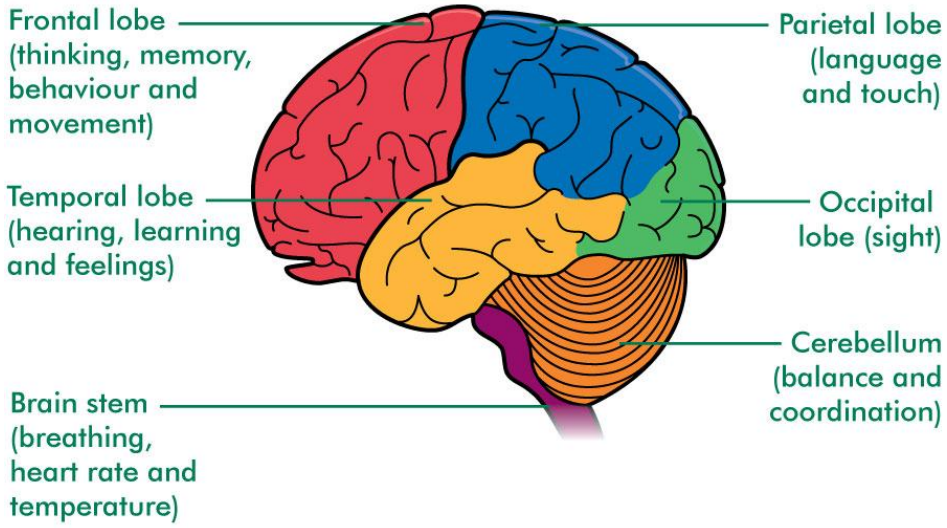


**Figure 2 Brain area and function**

There are 3 types of function:

1. automatic functions including breathing, heart rate, digestion, body temperature control, regulation of hormones, etc;
2. movement, balance posture and speech via our muscles (often referred to as 'motor function' by clinicians);
3. thoughts and emotions, including recognition of faces, sounds, smells, etc., learning, memory, comprehending speech, making decisions, planning and organising.

The third function is known to scientists and clinicians as 'cognitive function' and is commonly believed to decline in older age. However, age-related declines in mental abilities are highly variable between different people and whereas average declines may be seen across the population, this reflects considerable decline in some, a little in most and none at all in others[5] . Some aspects do not tend to decline with age, whereas other areas of function do show some decline, on average, across the population. Cognitive skills that are more likely to endure with age include vocabulary, information and comprehension, Capacities that show more decline on average include the type of memory that lets us hold a telephone number in mind long enough to dial it (called 'working memory'), processing ('thinking') speed, and 'executive' functions (planning, organising, managing time, etc.)[6]. These declines can begin in middle age, or even earlier.

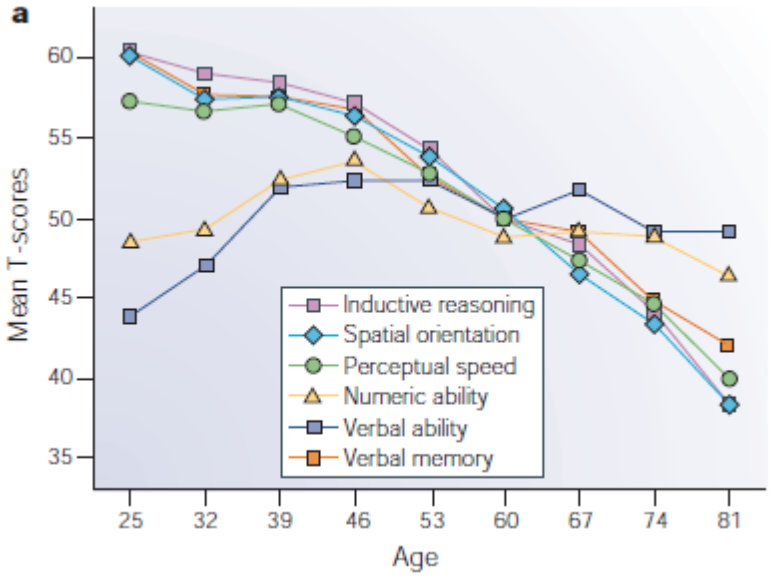


**Figure 3 Aspects of cognitive decline across the population**

The figure above shows cognitive decline in the participants of the Seattle Longitudinal Study[7]. Perceptual processing speed declines from before the age of 55, whereas verbal ability is relatively constant until much later in life.

## Mild cognitive impairment

Commonly reported functional memory problems include the following

- ✓ Names of people, places,
- ✓ Misplacing things
- ✓ Keeping track of schedule of commitments
- ✓ Forgetting to carry out an intended activity
- ✓ Numbers & passwords
- ✓ Remembering what was said or decided upon

Most of us notice such memory problems from time to time, they are commonly-known features of normal cognitive ageing, and also of mild cognitive impairment (MCI)[8]. However, MCI is a condition that can be screened for (see, for example, the Six Item Cognitive Impairment Test or 6CIT).[9] There are a number of forms, but the most common, 'amnestic' MCI, is characterised by a set of problems with short term memory, planning, language, and/or attention which decline more rapidly than they would in normal, age-related cognitive decline, but not to the extent that they interfere with a person's day-to-day life.

Although assessments exist, there is no clear, agreed definition of MCI in comparison to the cognitive changes of normal brain ageing, and different studies, based on differing definitions, estimate a prevalence of between 5 and 20 per cent in the older population.[10] This equates to between 0.5 million and 2 million people in the UK.[11]

Importantly, research shows that people diagnosed with amnestic MCI have an increased risk of developing dementia, but only about 1 in 6 eventually do.[12] Furthermore, for some people MCI is the result of a curable condition such as stress, anxiety, depression, physical illness or the side effects of medication.

## Dementia

Dementia is a set of behaviours or 'symptoms' which suggest difficulties with cognitive function. The most common symptoms include: memory loss, confusion, mood and personality changes, problems with planning and doing tasks in the right order. Dementia is diagnosed when the symptoms cause such problems with the everyday tasks of daily life that the person affected cannot carry on living independently, without care, any longer.

Dementia is an 'organic' disorder, meaning there is an associated physical deterioration of the brain tissue, which can be seen via a brain scan or, after death, at autopsy. Dementia is progressive – the damage and symptoms get worse over time. It is therefore not a normal result of aging, but rather is the result of a disease.[13]

It is likely that damage to the brain starts decades before the real-world symptoms begin to show. This very long latent period has made a cure for dementia very difficult to develop, since deterioration has progressed so far by the time the symptoms are apparent. It also makes the identification of risk factors and protective

factors via observation studies more difficult. We don't know the effects of the 'pre-symptomatic' brain damage, and what might look like a robust association between, for example, cognitively-stimulating activities and a lowered risk of dementia might in reality be an effect of early brain damage causing pre-symptomatic people to be less willing or able to take up cognitively-challenging activities. The same could be true for physical activity, diet, or any other factors that show an association within epidemiological research.

In addition, definitive clinical trials are difficult and expensive to conduct, as they would need to be undertaken over decades. Treatment or prevention may need to be started in midlife to delay or prevent dementia at age 80 or over.

## Cognitive reserve

Although the body of knowledge about changes to brain tissues associated with different diseases of dementia is very well established, other research has found that the full picture is not as simple as it may sound. Science has deduced a great deal of knowledge about the biological structures and processes of the brain but we still cannot state how such phenomena produce our incredibly complex personalities, thoughts, behaviours and capacities.

Key research illustrating how much more there is to find out shows that people with advanced pathological brain changes do not always display symptoms of dementia.[14] For example one UK study found that one third of people with no diagnosable dementia symptoms at death had similar levels of damage to the brain as did people who had probable or definite Alzheimer's.[15]

This phenomenon has led scientists to coin the phrase 'cognitive reserve', theorising that disruption to the structure and physiology of the brain can be accommodated by some people, to some extent, via their own ways of processing information.[16] It is possible that such people had larger brains and more neurons ('brain reserve'), or are able to process information in different ways within what remains of their healthy brain tissue, to maintain cognitive skills ('cognitive reserve').

The theory of brain reserve is controversial. Brain size is related to early developmental factors such as birth weight and early nutrition. A recent review of these sorts of factors and dementia found that the 'little' evidence available did point to an association between head circumference and incident dementia across diverse regions of the world.[17]

Cognitive reserve, on the other hand, refers to how flexibly and efficiently a person can make use of available brain reserve. The research literature uses proxy measures such as levels of education, IQ, literacy, occupational attainment and engagement in leisure activities when exploring cognitive reserve in the context of dementia risk. This will be discussed later in the Evidence Review, under 'Protective factors'. However, neuropsychological research has used techniques such as brain imaging to explore the different ways that older people process information when they are performing cognitive tasks. One study found that older people had lower scores on a declarative memory task than did young people (as expected) and there was high variability between the scores of the older folk (also as expected). Of those

who had poor memory, their pattern of processing was similar to the young people (who did considerably better), mainly using only the left hand side of the brain. However, for those older people who did much better at the task, their pattern was different – they used the right side as well as the left. The authors suggest that this pattern might have 'provided compensatory encoding resources', resulting in better cognition.[18]

## Types of dementia

There are over 100 types and many causes of dementia. Alzheimer's is the most common form of the disease, accounting for approximately two thirds of dementia cases in the UK. Vascular dementia is the next most common.[19] Mixed pathologies are, however, thought to be more common than any 'pure' form of the disease, in particular Alzheimer's with vascular dementia, and Alzheimer's with Lewy Body dementia[20].

### Alzheimer's Disease

This is the most common cause of dementia, occurring in two forms. One relatively rare but important form is termed 'familial' or 'early onset' Alzheimer's which is thought to account for fewer than one in 1000 cases.[21] Typically, people with this form are diagnosed with it before the age of 60-65, some may develop it as early as their 30s. The genetic causes of familial Alzheimer's have been identified and if a parent has the disease it usually means the individual has a 50 per cent chance of having inherited it.

Far more common is late-onset Alzheimer's, which is diagnosed at the age of 65 or over, becoming increasingly common with older age. The genetic basis for this form of dementia is far less clear (see below).

For both forms of the disease, symptoms are similar although decline of cognitive abilities in the familial form might occur at a faster rate. During the course of the disease, the structure of the brain changes, leading to the malfunction and eventual death of neurons. This initially affects particular areas of the brain which are important for learning new information and goes on to affect all areas of cognitive function. After death, changes to the structure of the brain and tissue loss for a person who had Alzheimer's can be clearly seen at autopsy (Fig. 4).

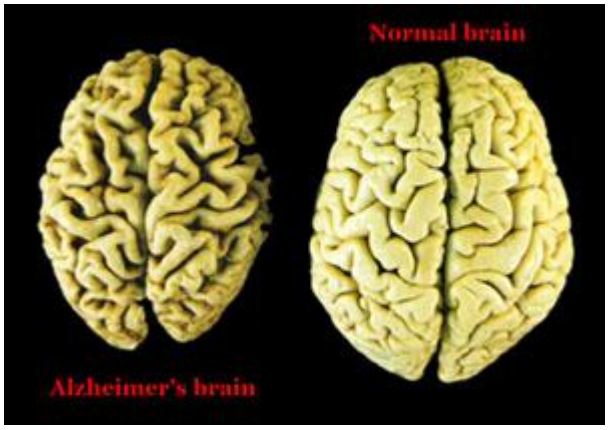


**Figure 4 Tissue loss in Alzheimer's vs healthy brain**

## Vascular dementia

In vascular dementia, restrictions in the blood vessels of the brain disrupt the oxygen supply to the tissue. As previously discussed, without an excellent blood supply neurons cannot function. Neurons, when they die, cannot be replaced by the body. The symptoms of vascular dementia can occur either suddenly, following a stroke, or over time, through a series of small strokes. Symptoms tend to be impaired judgement and inability to plan a series of steps to complete a task, rather than memory loss.

Table 1: Common dementia subtypes; source Prince et al, 2014

| Dementia subtype | Early symptoms | Tissue damage | % of dementia cases |
|---|---|---|---|
| Alzheimer's Disease | Impaired memory, apathy and depression, gradual onset | Cortical amyloid plaques and neurofibrillary tangles | 50-75% |
| Vascular Dementia | Similar to AD but memory less affected, mood fluctuations more prominent; physical frailty, stepwise onset | Blood supply to critical regions of brain, or more diffusely. | 20-30% |
| Lewy Body Dementia | Marked fluctuation in cognitive ability; visual hallucinations; Parkinsonism | Cortical Lewy bodies | <5% |
| Fronto-temporal Dementia | Personality changes; mood changes; disihibition; language difficulties | No single pathology – damage limited to frontal and temporal lobes | 5-10% |

Find out more, including fact sheets, on the Alzheimer's Society webpage http://www.alzheimers.org.uk/Facts_about_dementia/What_is_dementia/ or NHS Choices website http://www.nhs.uk/Conditions/dementia-guide/Pages/causes-of-dementia.aspx .

## Tests and diagnosis of dementia

It can be difficult to objectively assess cognitive function, especially in older people for whom other issues can interfere with assessment such as hearing or sight loss, or certain medications. The most widely-used assessment is the Mini Mental State Examination (MMSE). It is a series of questions that test mental abilities such as memory, attention, and language; examples of tasks asked of the person being tested include:

- to give the current date and time
- to name the place they are in (the country, town, district, hospital and ward)
- repeat a list of three words, and learn them for recall after another task has been completed

- name common objects such as a pencil and a watch
- copy a diagram of a pair of intersecting pentagons[22]

An indication of dementia on a test such as this will prompt further specialist assessment, including physical examinations, blood and urine tests, more detailed memory assessment and perhaps brain scans.[23]

Unfortunately, once symptoms have appeared, the degeneration of the brain tissue will have been going on for some time and therefore be fairly advanced. Scientists are currently looking for simple diagnostic tests which give an earlier indication of the disease. Very recent research indicates that a worsened sense of smell could indicate the development of MCI or Alzheimer's.[24] Another test has been reported which detects the presence of a particular protein in the eye which is a 'biomarker' for Alzheimer's. This test involves applying an ointment to the inner eyelid and scanning the eye with a laser the day after.[25]

The progress of dementia, in terms of the changes to the brain tissues and / or the changes in symptoms and behaviour for the individual, is so variable between people that it is difficult to monitor the efficacy of therapeutic interventions. Age UK is right at the forefront of developments in cognitive testing with the Disconnected Mind project at Edinburgh University, which may eventually help to address this issue. In 2014, a paper was published in which visual speed was linked to cognitive decline.[26] These promising findings hold the potential for a simple way of testing how our thinking skills are changing, by measuring how well we are doing visually. More research is needed but these findings, from a study funded by Age UK, are an important new domain for research.

## Prevalence

Prevalence means the proportion of the population who have the disease at any particular point in time. Cognitive decline occurs along a continuum, and as yet there are no clearly set boundaries between normal, mild cognitive impairment and dementia that are agreed by all. Consequently there is no standardisation in the methods of research, leaving comparison of findings difficult to interpret. This makes reliable evidence on prevalence, risk and protective factors difficult to compile

It is commonly accepted that dementia is under-diagnosed, for example the 2007 Dementia Strategy by the Department of Health (DH) estimated that only one third of people with dementia received a formal diagnosis.[27] Other estimates have found only around 43 per cent of people with dementia have been diagnosed.[28] For many people, diagnosis does not happen until they come into contact with health services for other reasons than cognitive decline, for example hospital admission.[29]

One of the key objectives of the DH 2009 Dementia Strategy was to obtain accurate, early diagnosis and intervention for all. NHS England has a commitment to increase the dementia diagnosis rate to 67 per cent by March 2015. If this target is reached, two thirds of people with dementia would be diagnosed.

However, research studies conducted in specific community or care settings can provide estimates based on both 'diagnosed' and 'undiagnosed' rates, albeit with differing definitions and coverage between different studies. An important project which employed a technique of expert appraisal and consensus on previously conducted prevalence studies provides the best estimates we currently have. Age-specific rates are shown in Table 2.[30]

**Table 2 Age specific rates of undiagnosed and diagnosed dementia**

| Age specific, estimated percentages of diagnosed and undiagnosed dementia in the UK - 2014 | | | |
|---|---|---|---|
| | Male | Female | Total |
| **60-64** | 0.9 | 0.9 | 0.9 |
| **65-69** | 1.5 | 1.8 | 1.7 |
| **70-74** | 3.1 | 3.0 | 3.0 |
| **75-79** | 5.3 | 6.6 | 6.0 |
| **80-84** | 10.3 | 11.7 | 11.1 |
| **85-89** | 15.1 | 20.2 | 18.3 |
| **90-94** | 22.6 | 33.0 | 29.9 |
| **95+** | 28.8 | 44.2 | 41.1 |

These estimates suggest that most older people do **not** develop dementia. There is clearly an increase by age group, however even among the oldest group of people in their late 90s the majority are free from dementia. Other estimates concur, finding that less than 20 per cent of people over the age of 80 have dementia.[31] Based on these rates, the overall prevalence of late onset dementia is 7.1 per cent for people over 65, resulting in an overall figure of 850,000 people in the UK in 2015.

## Diagnosed Dementia

The Quality Outcomes Framework records dementia diagnoses in participating General Practices in England.[32] A provisional figure for 2013/14 shows a prevalence of 0.61 per cent (for the whole population) or 326,350 diagnosed cases. Comparing geographically, prevalence is higher in the North and the South of England (0.68 and 0.67 per cent respectively); somewhat lower in the Midlands and East of England (0.62%) and much lower in London (0.39 per cent).[33]

Around one third of those diagnosed with dementia live on their own in the community.[34] About two-thirds of people living in care homes, or 275,000 people, have diagnosable dementia (ie. dementia that has progressed enough to be readily diagnosed by a professional).[35]

## Causes, risk and protective factors

Research continues to uncover aspects of dementia that help to understand the disease, however the causes are still unknown. The change from healthy ageing to dementia is described by researchers as a series of events that occur in the brain over a decade or longer.[36] This gradual process, which results from some, as yet unknown, combination of biological, genetic, environmental, and lifestyle factors, eventually sets some people on a course to MCI and possibly dementia. Other people, whose genetic makeup may be the same or different and who experience a different combination of factors over a lifetime, continue on a course of healthy cognitive ageing.[37]

### Genetic causes and associations for Alzheimer's

Early onset, or familial, Alzheimer's affects people at a relatively young age (ie. they are diagnosed before the age of 60). It has been well established that this form of the disease is inherited in approximately 80 per cent of cases.[38] Early onset Alzheimer's is very rare in comparison to the late onset disease, however it still affects at least 17,000 people in the UK.[39]

The more common late onset Alzheimer's affects around 850,000 people in the UK and has a far more complicated genetic basis that is still unclear (see Fig. 2). One variant of a particular gene (ApoE) has been established as a risk factor (ApoE 4), increasing risk up to 10 times, whereas another variant of the same gene (ApoE 2) has been found to be mildly protective. A growing number of genes have been identified as having some, low, impact on risk of developing the disease. In general, the higher risk genes are the least frequent in the population, and those that have the lowest associated risk (or are slightly protective) are more common.

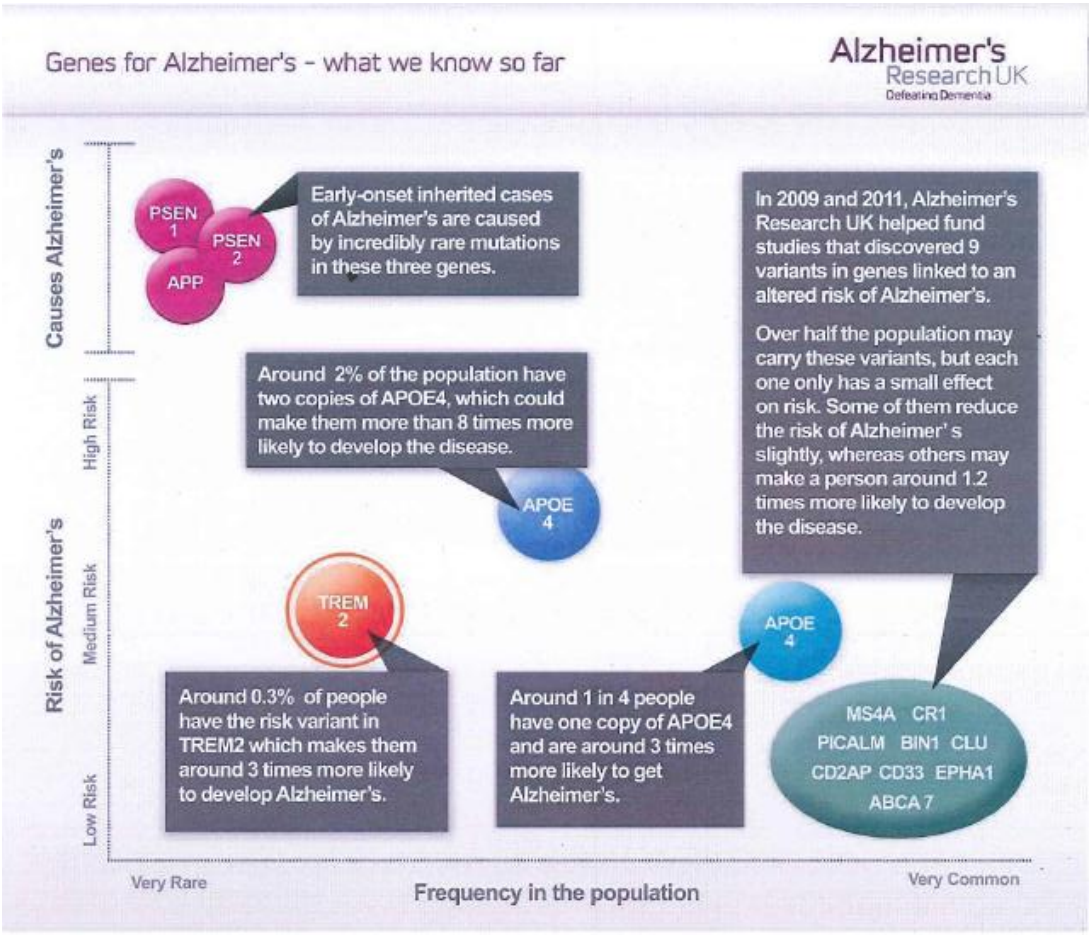


**Figure 5 Genes for Alzheimer's – reproduced from Alzheimer's Research UK**

Figure 2 illustrates the current knowledge of the genetic bases for Alzheimer's. Within the population, the rarest genes carry the highest risks and so give rise to the rarest occurrence of disease – for example for early onset Alzheimer's, three genes have been identified which are viewed to be causal of the disease. The more common occurrences of variants of genes are associated with much lower risk of developing the disease, indicating that the development of the disease is greatly affected by other factors.

## Genes for other types of dementia

There are no established genetic causes for the more common forms of vascular dementia. Some studies have shown that a gene increasing the risk of late onset Alzheimer's (ApoE4) is also linked to vascular dementia, although the association is much weaker than that for Alzheimer's. Importantly there are known genes that contribute to underlying diseases associated with Vascular Dementia, which are high cholesterol, high blood pressure and diabetes. Fronto-temporal dementia often runs in families and in some cases is inherited as a change to a single gene. Dementia with Lewy Bodies is not well understood genetically. In common with the other dementia diseases this too has some rare, familial cases and more common cases which are not linked to family history.

For more information, see *Genetics of Dementia* by Alzheimer's Society - http://www.alzheimers.org.uk/site/scripts/documents_info.php?documentID=168

## Other risk factors

The following evidence on lifestyle and environmental factors is based on epidemiological, or 'observational' studies. These determine common factors in the population that might point to how or why dementia occurs in certain groups of people and not in others. As discussed previously (see Prevalence), the data on dementia and cognitive decline are likely to be greatly underestimated due to incomplete screening and inconsistent diagnosis within the population. In addition, different epidemiological studies may also apply different criteria to identifying cases. It should therefore be borne in mind that evidence on risk and protective factors is indicative at best, showing associations with certain factors, but not causes. In fact, in 2010 the US National Institutes of Health (NIH) issued a 'State-of-the-Science Conference Statement'[40] on the prevention of Alzheimer's and cognitive decline, stating;

> '*Currently, firm conclusions cannot be drawn about the association of any modifiable risk factor with cognitive decline or Alzheimer disease.'*

However, other commentators suggest that while technically correct, this view largely misses the point; the standards of proof are at fault as they can never be ethically met.

Meanwhile, in the UK a pragmatic approach has been adopted, accepting that the evidence in general provides 'emergent associations' rather than conclusive proof. In early 2014, 26 national organisations and 32 dementia and public health specialists signed a consensus document (*The Blackfriars Consensus on promoting brain health*).[41] The authors highlight that there has been comparatively little research activity on preventing or delaying dementia (through modifiable risk factors) compared to biomedical research focused on finding a pharmaceutical cure. Nevertheless they conclude that there are enough data to warrant public health and other approaches based on the 'possibility' of dementia risk reduction in the population. They state:

> '*The scientific evidence is evolving rapidly and sufficient to justify considered action and further research on dementia risk reduction, both by reducing the modifiable factors and improving the recognised protective factors.'*

The authors of this paper also highlight the time lag in benefit of targeted action on the emergent risk factors, now, in particular those that are modifiable throughout the life course, to prevent or delay dementia in old age. If this can be achieved it needs to start now.

## Age

For all dementias which are not linked to family history, older age is associated with higher prevalence. There is enough evidence on this to warrant the consensus message, 'Dementia is a common syndrome closely associated with ageing, with

some known underlying causes and others which are less well understood.'[42] Age is not, of course, a 'modifiable' risk factor in the sense that individual lifestyle changes or policy or service interventions can make any differences. However, age ranges can be used to target initiatives, particularly if specific trigger points or 'sensitive' periods over people's lifetimes can be identified.

## Modifiable risk factors

The World Alzheimer Report 2014[43] provides the most thorough and up to date analysis of modifiable and protective factors at the time of writing. The authors group these factors into 4 domains:

1. Developmental – factors arising during the neonatal, infancy and childhood periods of the lifecourse
2. Psychological / psychosocial -
3. Lifestyle – behaviours or habits that are modifiable by individuals
4. Cardiovascular – specifically, cardiovascular diseases that are seen as risk factors (or 'precursors', in some cases), to dementia.

Summary tables of all the risk and protective factors are extracted from the report and included in the Appendix to this Evidence Review. In the following section we review those factors that are likely to be of significance to Age UK.

### *Cardiovascular risk factors*

High blood pressure, high cholesterol, diabetes and obesity are well established modifiable risk factors for cardiovascular diseases such as heart disease and stroke. These tend to increase with age across the adult life course and are common by midlife. People who experience a stroke are at approximately twice the risk of developing dementia, with the three years following the stroke being the highest risk period.

All of the cardiovascular risk factors may increase the risk of dementia by increasing the risk of hardening of the arteries (and inflammatory and thrombitic effects of vascular disease). This has an effect not only on vascular dementia, but also on Alzheimer's and mixed dementias.

The cardiovascular risk factors may work jointly, however research has looked at them independently and shows:

- Particularly strong evidence for midlife high blood pressure and any dementia; there is disagreement over whether this holds for Alzheimer's (or whether the effect is skewed by vascular dementia). It may be that midlife is a particularly 'sensitive period' for high blood pressure leading to dementia of any kind, including Alzheimer's, in later life. The occurrence of high blood pressure in late life is not associated with dementia.
- Obesity is likewise associated with increased risk when its onset is in midlife. One study showed that people admitted to hospital with obesity when they were aged between 30 and 39 years were at significantly higher risk than those aged 40 to 49 when obesity was first recorded. The relative risk

reduced with age of onset of obesity, until at 70 to 79 there was no increased risk and at 80 or over there was actually a reduced risk of subsequent dementia.[44]

- High cholesterol (or, more accurately, dyslipidaemia, which encompasses either high levels of 'bad' cholesterol or low levels of 'good' cholesterol) shows inconsistent findings in terms of dementia risk. There is currently no evidence that preventing or treating high cholesterol will affect cognitive decline, Alzheimer's or other dementias.
- In general, most studies have found that diabetes in late life, and probably midlife, is associated with an increased risk for dementia, particularly vascular dementia.

A decline in blood pressure level, body mass index and total cholesterol, however, precedes and predicts the onset of dementia, particularly Alzheimer's, by five to 15 years.

Notwithstanding this rather mixed picture, some research does suggest that public health measures targeting prevention of heart disease and stroke in England might have led to a concurrent reduction in age-specific dementia rates.[45] Whereas cardiovascular health is improving in high income countries (through good screening and treatment of risk factors), it is deteriorating in middle- and low-income countries where people are taking up Western lifestyles without the necessary screening and treatment. This is of great concern in terms of the global burden of dementia in future.

### *Depression*

Meta-analysis which pulls together the findings across a range of studies and analyses them together shows that depression and risk of dementia are related.[46] However, there are a number of explanations for the relationship, including:

i. A person becomes depressed as a result of noticing symptoms of cognitive impairment or dementia (for example, feeling worried or hopeless about losing mental capacities), or from being diagnosed with dementia, which is likely to be very distressing.
ii. Depression is an early symptom of dementia. Given that changes to the brain might be occurring 20 to 30 years before anyone is diagnosed, depression might occur as a result of these changes, and appear to be unrelated if it's onset is so far in advance of a dementia diagnosis.
iii. Depression is a causal risk factor, or it is independently associated with dementia.

### *Personality and life events*

There is a lot of interest in the issue of stress over an individual's lifetime and the effects this can have on their health, including cognitive function. However, it is difficult to measure 'stress' in an objective way as individuals can respond differently to similar situations, and researchers believe that the person's response is more important than is the stressful event. One way of looking at this is to explore personality. Psychological research has established that personality traits, measured

by psychometric tests, remain fairly stable throughout adulthood and can be used as an indicator of how an individual responds to potentially stressful situations. The most widely used model of personality today measures traits across five factors.[47] These are neuroticism, extraversion, openness, agreeableness and conscientiousness. The risk of both dementia[48] and cognitive decline are higher for people with high levels of neuroticism. The trait of conscientiousness was associated with lower levels of cognitive decline.[49]

### *Smoking tobacco*

Current smoker status is associated with increased risk for cognitive decline, but the picture for past smoking is less consistent.

A recent systematic review[50] and meta-analysis found that:

- There were significantly more new cases (ie. higher incidence) of Alzheimer's per year among current smokers compared to people who had never smoked. There was also a trend towards higher incidence for vascular dementia and any form of dementia, but this was not statistically significant.
- Ex-smokers were at a similar risk to those who had never smoked, for all types of incident dementia.
- Ex-smokers and current smokers combined had higher risk for Alzheimer's and a non-significant trend for vascular and other dementias.
- Inconsistent evidence concerning how much people smoked.
- Insufficient evidence to look at how APOE genotype affected the relationship.

### *Drinking alcohol*

Alcohol has both damaging and protective effects for the brain, depending on how much people drink. Very heavy drinking, to the point of alcoholism, is a known cause of dementia.[51] [52] It results in the loss of brain tissue, particularly in areas of the brain related to memory and visuospatial functions.

There are also, however, mechanisms by which alcohol can be protective of brain tissue, for example by increasing 'good' cholesterol which, in high concentrations, lowers 'bad' cholesterol and thereby protects cardiovascular health. This might explain findings for research which shows that people who drink alcohol are at lower risk for Alzheimer's and other dementias than are people who abstain. Moderate drinkers (1-14 units per week for women and 1-21 for men) have lower risk than do abstainers, and heavy drinkers (more than 14 units for women or 21 for men per week) have similar risk to abstainers.[53]

### *Physical inactivity*

There is considerable controversy over the link or otherwise between physical activity or exercise and risk of cognitive decline or dementia. This is mainly due to difficulties in conducting research which is good enough to provide conclusive proof. Some issues that affect how we interpret findings include:

- Funding randomised, controlled trials with sufficiently long follow-ups to ascertain whether the outcome is due to the effect of physical exercise on dementia, or the effect of dementia on the person's physical activity.
- Differences in the measurement of physical activity, dementia and cognitive decline between observational studies.

However, the link between physical activity and cardiovascular health (e.g. protection against high blood pressure, diabetes, high cholesterol and obesity) is well established, and these diseases in turn have been shown to be high risk factors for cognitive decline and dementia. Whether physical activity is independently related to dementia is not fully agreed between scientists, however for the purposes of Age UK this might be a moot point. The Blackfriars Consensus suggests that the urgency of taking preventive action is high because of the long latency period of the disease, which starts in midlife and necessitates a lifecourse approach. Waiting for standards of proof which might be impossible to obtain may be an impractical approach in this case. The best available evidence[54] suggests that high physical activity levels are associated with a 43 per cent reduction of risk compared to low levels.

### *Diet*

There is currently insufficient evidence on the relationship between the Mediterranean diet, B, C or E vitamins, flavonoids or omega-3 oils and cognitive function. There is some evidence that people with Vitamin B deficiency might benefit from supplementation but as yet there is no conclusive evidence.

Some studies support the role of anti-oxidants, B vitamins, and Omega-3 fatty acids in cognitive health.[55] [56] [57] [58] However, these seem to only work as factors in food; supplements have not shown to be effective.[59] The most validated scientific dietary advice for good cognitive health and reducing dementia risk is to take a 'Mediterranean diet' – rich in vegetables, legumes, fruit, nuts, cereals, fish, and moderate amounts of alcohol and low in meat, poultry and dairy products.[60] On the other hand, a diet high in sugar, cholesterol, and trans-fats seems to lead to poorer cognitive condition for older people.[61]

### *Cognitive stimulation*

Consistent results from a large number of observational studies that measured cognitive activity in late life suggest that this might be 'beneficial for both brain structure and function'. However, since the brain damage of dementia is likely to have started over a decade prior to noticeable symptoms, this might be reverse causation whereby a pre-symptomatic person with dementia feels less willing or able to take up cognitively stimulating activities. Authors of the report suggest that, in particular, video games (including smartphone applications) are worth studying because their usage has increased dramatically and is highly prevalent across society. Even small effects of these may have significant public health outcomes.

*Protective factors – education and occupation*

It has been found that people with higher IQ, level of education, occupational complexity, or participation in leisure activities with social networks tend to show less severe symptoms in the presence of the disease of dementia.

## Interventions for cognitive decline and dementia

There is no cure for dementia nor for most cases of MCI except those that are caused by stress, anxiety/depression, medication, or certain medical conditions.[62]

However there is still much that can be done to:

- prevent dementia or delay its onset by reducing associated risk factors through public health approaches and lifestyle modification,
- slow down the progression of dementia or MCI, through drug treatments and / or lifestyle change, and
- focus on quality of life, enabling those with a diagnosis to live as well as possible with the condition.

### Preventative interventions

As discussed under 'Other risk factors' above, UK experts, policy makers and researchers have reached consensus regarding some actions towards possible reduction of risk of dementia in the population. Whether such actions prevent occurrence or delay onset is unclear, however either scenario would be desirable and of benefit to individuals and their families, and to society as a whole. Emergent evidence suggests that lifestyle factors contributing to cardiovascular health are also likely to benefit cognitive function in later life. These factors include:

- Physical activity
- Mediterranean diet
- Not smoking
- Not drinking to excess

In addition, interventions to address the 'intermediate disease precursors' such as raised blood pressure, raised blood cholesterol, obesity and diabetes through screening, early detection, treatment and good management of the condition are thought to help reduce risk, progression and severity of dementia.

Protective factors which are associated with cognitive reserve include educational level and intellectual and social engagement.

A study in Wales that followed over 2,000 middle-aged men for 35 years found that while exercise is the most significant factor, other lifestyle behaviours – such as healthy diet, not smoking, and low amounts of alcohol – have large effects on the risk of developing dementia.[63] Following participants for such a long time may help

control for 'reverse causation' (that is, that people take low levels of exercise because they are already developing dementia).

The evidence strongly suggests that the most effective interventions for warding off and even improving cognitive decline, in healthy older people as well as those with mild cognitive impairment and dementia, would at the least involve regular physical exercise. Studies have shown a strong link between cognitive function and physical function,[64 65] as well as activities of everyday living.[66 67] Adding in eating a healthy diet, quitting smoking, and including engaging activities and social interaction should strengthen the protective effects and even some reversal of decline.[68] If only half of the men in the Wales study had taken up one additional health behaviour, 'then during the following 30 years there would have been a 13% reduction in dementia, a 12% drop in diabetes, 6% less vascular disease and a 5% reduction in total mortality.'[69]

Physical exercise could be aerobic, resistance, and balance, or a combination of these. Stretching exercises only saw no benefit in cognition.[70] Exercise frequency reported to show benefits were between 3-5 times per week, and 30 minutes to 1 hour in length.[71] Group interventions have not been demonstrated as being more or less effective than individual ones, but they would have added benefits of being more cost-effective, and be able to include social engagement.[72]

Whereas experts[73] suggest that older people should be included in targeted programs for smoking cessation, detection and treatment of hypertension, reduction in obesity and increasing physical activity, it is unfortunately true that self-directed uptake of an overall healthy lifestyle in the UK is quite poor.[74 75 76] Offering services directly to older people which engage them to participate in healthy lifestyle choices, based on well-researched attitudes and experiences, could be beneficial.[77]

In one example, a recent Finnish study has found promising results at two year follow up with 1,260 participants aged 60-77. The intervention included nutritional guidance, physical exercise, cognitive training, and social activities, and management of vascular risk factors. The control group received regular health advice. After two years, cognitive performance was measured by a comprehensive neuropsychological test battery. They found a significant beneficial effect on overall cognitive performance in the intervention group. The beneficial effect was seen in each cognitive domain: memory, executive function, and psychomotor speed. Drop-out rate was only 11 per cent, and participants' experiences were very positive. These results highlight the value of a multi-domain approach that is effective for several cognitive functions. An extended follow-up (7 years) with a sustenance intervention is planned to evaluate longer-term effects on Alzheimer's or other forms of dementia.[78]

## Post-diagnostic interventions

For those who have been diagnosed with MCI or dementia, the progression of the disease and the impact it can have on their capacities and their lives is dependent to some extent on their overall health.

Factors particularly amenable to change include:

- Social isolation
- Cognitive stimulation
- Prompt treatment of infection
- Prompt treatment of depression

Notwithstanding the problems involved in researching dementia and finding a cure, many of the challenges of living with the disease can be ameliorated, and there are many ways of supporting people and carers through their experience of dementia.[79]

While the symptoms caused by physical damage to the brain are not yet preventable, having dementia can bring with it difficulties that can be reduced or prevented.

A key example would be social isolation. Many people find mental illness and disability anxiety-provoking topics and if a colleague, friend or family member is diagnosed with dementia they may find it easier to avoid their company. Social withdrawal is not a symptom of dementia, but the person with the diagnosis finds themselves in a more socially isolated position, and this might be happening at a time when they need even more social support than did prior to their illness. Good information, advice, advocacy and emotional support services, soon after a person has received a diagnosis, can be instrumental in reducing these sorts of problems.

Systematic reviews have found evidence that participating in stimulating and social activities can reduce the risk of developing dementia.[80 81] These activities can also help reduce depression and feelings of loneliness in people with dementia, increasing quality of life and self-confidence.[82]

In addition, pain and ill-health can also cause many changes in the way a person with dementia behaves,[83] leading to commonly-used terms such as ‘challenging behaviour’ and ensuing management of these behaviours using sedative drugs.

### Drug treatments

Although the majority of research funding has been directed at finding a drug treatment, such a cure for dementia or MCI remains elusive. The prolonged pre-symptomatic stage of dementia may mean that the disease is so far progressed by the time symptoms are apparent that it has become too late to reverse the damage to the brain. Equally, drugs developed to slow the progression of dementia have mixed success and do not work for everyone.[84 85] Some short-term gains in memory have been demonstrated in some individuals, but the effects are usually small and do not last.

Other suggested medications include non-steroidal inflammatory inhibitors (NSAIDs), oestrogen replacement therapy, and ginko biloba. There is no robust evidence that any of these therapies work to reduce risk or progression of cognitive decline, and even some evidence that oestrogen could increase risk.[86] Various vitamin and other supplements have also not shown to improve cognitive risk or decline.[87]

Drugs are, however, commonly used to manage other conditions or behaviours associated with dementia. Commonly, people with dementia exhibit what is termed

'challenging behaviour' (such as aggression), which can make caring for them very difficult, both for family or other non-professional carers, and care practitioners alike. 'Anti-psychotic' medication (e.g. drugs developed to treat symptoms such as delusion or paranoia) might be prescribed in these cases, however the National Institute for Clinical Excellence recommends that such drugs are used sparingly and only for a short time.[88]

It could well be that being diagnosed with MCI or dementia, or even pre-diagnostically noticing the signs, can be distressing and result in depression in some people. Responding appropriately to symptoms of depression is very important and anti-depressants might be helpful in some cases alongside appropriate emotional support, talking therapies, information, advice and advocacy.

Blood pressure medication has been shown, in one study, to ameliorate cognitive decline in dementia.[89]

### Cognitive interventions

Cognitive interventions are usually separated into three categories (although some people use them interchangeably, especially in non-academic literature): Cognitive Stimulation, Cognitive Training, and Cognitive Rehabilitation. Simon and colleagues[90] define these as:

> *Cognitive stimulation comprises involvement in group activities that are designed to increase cognitive and social functioning in a nonspecific manner.*
>
> *Cognitive training is a more specific approach, which teaches theoretically supported strategies and skills to optimize specific cognitive functions.*
>
> *Cognitive rehabilitation involves an individualised approach using tailored programs centred on specific activities of daily life. Personally relevant goals are identified, and the therapist, patient and family work together to achieve these goals (e.g., joining a social group).*

Cognitive training is the most widely-studied intervention of these three, possibly because it is the most specific and hence the most amenable to experimental study. Generalised cognitive or memory improvement through 'mental exercise' have not been proven to be effective, especially in randomised, controlled trials.[91] Where improvements have been seen, they are usually limited to the specific cognitive task engaged in the intervention, rather than any wider effects that could improve the person's capacity for independent living.

It is interesting to note that in some studies, even if objective measures of cognitive function did not show improvement, subjective measures did.[92] In other words, people *felt* as if their memory had improved as a result of the intervention, even if their test scores showed no improvement. This is an important finding in terms of the well-being or 'morale' of the person with dementia.

## Physical exercise

It is important to note that in all of the studies mentioned here, the benefits of physical exercise only last for at most a few months after exercise interventions have ceased. Therefore, physical exercise in the case of cognitive function is the same as it is in the case of cardiovascular function, ie. it needs to become a lifestyle change rather than a one-off, time-limited intervention.

For people with MCI (who have an increased risk of eventually developing dementia), several studies show improvements in cognitive function through physical activity. One study reported modest improvements in cognitive function after six months.[93] Other studies have shown that physical activity benefits memory,[94 95 96] attention,[97] executive functions[98 99] and cognition in general.[100 101]

For people with dementia, several research studies have shown physical activity to be beneficial in terms of their cognitive function. For example, people with Alzheimer's showed significant cognitive improvements when doing cycling training and somatic and isotonic-relaxation exercises.[102 103] The reasons why physical exercise might improve brain function (whereas 'brain training' does not), has been explored by researchers. Studies have shown that in people diagnosed with Alzheimer's patients, cardiorespiratory fitness has been associated with brain volume, in terms of the overall amount of brain tissue and the volume of white matter.[104] Perhaps importantly, the parts of the brain most associated with memory are notably affected.[105]

As well as cognitive function, exercise can also improve strength, cardiovascular fitness and, some argue, 'challenging behaviour'.[106 107 108 109 110]

However, despite positive effects of exercise on depression in healthy older adults, the research findings on depression in people with dementia are mixed.[111]

## Other cognitively-stimulating activities

While targeted memory or 'brain training' has shown poor results, other types of everyday mental stimulation does seem to improve cognition or delay decline. Examples are speaking a second language[112] or reading.[113]

Reminiscence Therapy has been used as a way of promoting well-being in older people since the 1950s. There is no 'standard' model for providing this therapy, but in general the idea is to enable or encourage people to think or talk about personally significant events that occurred in the past. The lack of a definitive service model makes this type of intervention difficult to study via experimental research, and indeed literature review finds that many studies that have tried to evaluate these therapies have been assessed to be of poor quality. However, meta-analysis has found evidence that reminiscence therapy can improve well-being and reduce depression, even if improvements in cognitive function are not well-evidenced.[114]

For a couple of decades, art therapies (art, music and dance) have also been used as an appropriate intervention for people with dementia, to provide cognitively stimulating activities and to improve well-being.[115] As in the case for reminiscence

therapy, there is no definitive model for any of the arts therapies and therefore the same difficulties apply in terms of providing empirical evidence of their effectiveness. Recent literature reviews of art therapy for people with dementia have found that it has not been studied robustly or systematically enough to say whether or not it is effective in improving cognition, well-being, or anything else.[116] [117]

Music therapy has been used to improve symptoms of dementia such as apathy, depression, irritability, agitation and anxiety, euphoria, hallucinations, and disinhibition. However, as with the other therapies discussed above, high-quality evidence for the efficacy is lacking. Two recent meta-analyses found the effects of music therapy on anxiety symptoms were moderate, the effects on depression and behaviour were small, and there was not enough evidence to support any beneficial effect of music therapy on cognitive function or activities of daily living.[118] [119] Important factors for success seem to be a long intervention period (greater than 3 months)[120] and the effectiveness of the therapist in engaging with the clients.[121]

The research-based evidence for providing large-scale services focusing on cognitive interventions, reminiscent therapy, or art therapy for decline is not yet robust enough,[122] however this does not mean they have no value. Case studies and anecdotal evidence suggest that recipients of these therapies and their carers can get enjoyment out of these activities, no studies have found any negative effects, and these interventions may be falling victim to unrealistic standards of proof.

### Improving living environments

Other types of interventions that have been found to be important to help people with cognitive decline and dementia live at home as long as possible are safety adaptions in the home, such as grab rails and dealing with tripping and falling hazards.[123]

## Living with dementia or cognitive decline

For most of us, the right to make choices about our own lives is key to our quality of life and wellbeing. For someone diagnosed with dementia, this right comes into question when their capacity to understand a situation, reason and make decisions is uncertain. Having reduced cognitive capacity can make a person more vulnerable to exploitation or abuse, however it also brings vulnerability to overprotectiveness from others, for example loved ones or professional carers, which can also result in restricting someone's access to choice. Although assessment tools have been developed to measure quality of life in people with dementia,[124] we could find no research on the views of people with dementia about quality of life and access to choice.

The Mental Capacity Act 2005[125] aims to protect the interests of people who have reduced capacity to make decisions. It defines five statutory principles which aim to both protect people who lack capacity and help them take part, as much as possible, in decisions that affect them:

1) Every adult has the right to make his or her own decisions and must be assumed to have capacity to make them unless it is proved otherwise.

2) A person must be given all practicable help before anyone treats them as not being able to make their own decisions.
3) Just because an individual makes what might be seen as an unwise decision, they should not be treated as lacking capacity to make that decision.
4) Anything done or any decision made on behalf of a person who lacks capacity must be done in their best interests.
5) Anything done for or on behalf of a person who lacks capacity should be the least restrictive of their basic rights and freedoms.

The balance between empowering people to participate in decisions that affect them while providing proportionate, appropriate protection from risk of harm needs to be considered. Arguably it is often neglected when developing organisational policy and services, and people with dementia are not consulted because assumptions are made about their capacity to participate, or risk of distress or harm from being consulted.

An important area that has not been addressed in research so far is the extent to which people with dementia and carers wish to access dementia-specific services or whether they would prefer to access dementia-friendly, generic services and in which instances.

## Conclusion

Although a drug cure for dementia or cognitive impairment remains elusive, there is still much that can be done to prevent or delay the onset of either condition, slow down progression of either condition, and most importantly for Age UK, to improve people's well-being while living with these conditions.

Age UK, as the largest charity for older people, could be in a unique position to provide dementia-friendly support and services which do not define people by their dementia, rather are inclusive of their needs in a generic setting. We could also supplement our evidence-based guides on healthy ageing with messages on healthy cognitive ageing.

Appendix A – Risk factors for dementia (reproduced from World Alzheimer Report 2014)

| | Direction of Association | Sufficient number of cohort studies to draw meaningful conclusions | Consistency across studies | Evidence type (robust, moderate, insufficient) | Notes |
|---|---|---|---|---|---|
| **Psychological factors – midlife** | | | | | |
| Depression | ↑ | No | n/a | Insufficient | Metaregression indicates smaller effect sizes (closer to the null) for studies with longer follow-up periods. However, limited evidence on midlife exposure |
| Anxiety | ↑ | No | n/a | Insufficient | One cohort study suggesting possible increased risk |
| Sleep disorders | ↑ | No | n/a | Insufficient | Very few long-term cohort studies |
| Psychological distress | ↑ | No | High | Insufficient | Indirect evidence using personality type as a lifelong stable proxy for the likely intensity and duration of stress response. Neuroticism positively associated and conscientiousness negatively associated with dementia/ AD risk |
| **Psychological factors – late life** | | | | | |
| Depression | ↑ | Yes | High | Moderate | A strong and consistent association observed across many studies. However, this may reflect reverse causality (see midlife above) |
| Anxiety | → | No | n/a | Insufficient | One case-control and one cohort study – no association observed |
| Sleep disorders | ↑ | No | n/a | Insufficient | Suggestive evidence from a small number of cohort studies. Various self-reported exposures. Short follow-up. Reverse causality not excluded. |
| Psychological distress | ↑ | No | n/a | Insufficient | See midlife (above) |

| | Direction of Association | Sufficient number of cohort studies to draw meaningful conclusions | Consistency across studies | Evidence type (robust, moderate, insufficient) | Notes |
|---|---|---|---|---|---|
| Lifestyle factors – midlife | | | | | |
| Smoking | ↑ | No | Low | Moderate | Late-life studies include retrospective assessment of lifetime smoking history, and support hypothesis. Midlife exposure in long-term cohort studies may underestimate effect due to mortality/ competing risk |
| Alcohol | → | No | n/a | Insufficient | Very few studies |
| Micro- and macronutrient deficiency | → | No | n/a | Insufficient | Very few studies |
| Physical activity | ↓→ | No | High | Insufficient | Only three long-term cohort studies with mixed results |
| Cognitive stimulation | ↓ | No | n/a | Insufficient | Supportive evidence from case-control studies, prone to bias. Only one long-term cohort study, with high attrition and imprecise exposure measures |
| Lifestyle factors – late life | | | | | |
| Smoking | ↑ | Yes | Moderate | Moderate | Dose response effect for incidence of AD. Possible effect on VaD and any dementia. |
| Alcohol | → | No | Moderate | Insufficient | Moderate drinkers have a lower risk of dementia and AD than abstainers. Unclear if this is causal or reflects confounding by reason for abstaining. Upper safe limit of 'moderate' drinking and impact of heavy drinking is unclear |
| Micro- and macronutrient deficiency | → | Yes | Moderate | Insufficient | With the exception of Mediterranean diet (one positive trial), suggestive evidence from observational cohort studies has not been confirmed in supplementation trials. However, RCTs are few in number and often of poor quality. They do not always focus on those with micronutrient deficiencies |
| Physical activity | ↓→ | Yes | High | Insufficient | Duration of follow-up is a major determinant of heterogeneity of effect, with inverse association seen mainly in short follow-up studies. High probability of reverse causality. RCTs needed to clarify this |
| Cognitive stimulation | ↓ | Yes | High | Insufficient | Consistent risk reduction associated with performance of cognitively stimulating activities. Reverse causality remains to be excluded. RCTs needed to clarify this. |

| | Direction of Association | Sufficient number of cohort studies to draw meaningful conclusions | Consistency across studies | Evidence type (robust, moderate, insufficient) | Notes |
|---|---|---|---|---|---|
| Cardiovascular risk factors - midlife | | | | | |
| Hypertension | ↑ | Yes | High | Robust | Consistent evidence from 5 studies across four cohorts. Evidence stronger for any dementia, and VaD, than for AD. |
| Obesity | ↑→ | No | Low | Insufficient | Inconsistent findings for association with midlife BMI. Problems with bias and residual confounding. Possibly more consistent association with central obesity. |
| Cholesterol | ↑ | No | Low | Insufficient | Inconsistent findings. Hypothesis supported mainly by two Finnish long-term cohort studies |
| Diabetes | ↑ | No | Moderate | Moderate | Evidence is somewhat indirect, from health care record linkage studies, and subject to bias. However, longer duration of diabetes is associated with higher dementia risk. Only one long-term cohort study, with no association. |
| Cardiovascular risk factors – late life | | | | | |
| Hypertension | ↓→ | Yes | High | Robust | Cross-sectional studies show lower BP level in people with dementia and AD relative to controls. Decline in BP predicts the onset of dementia and AD, but this is unlikely to be causal. RCTs suggest no cognitive benefit or harm associated with the treatment of hypertension in older people in general, or those with dementia. |
| Obesity | → | Yes | High | Robust | Several studies. No association. However, decline in BMI from mid- to late-life predicts dementia onset but this is unlikely to be causal. |
| Cholesterol | → | Yes | Moderate | Moderate | No effect of cholesterol lowering with statins on cognitive outcomes. No association of total cholesterol (TC) with incident dementia, but effects of cholesterol subfractions need to be explored further. However, decline in TC from mid- to late-life predicts dementia onset. |
| Diabetes | ↑ | Yes | High | Robust | Highly consistent evidence for a strong association between diabetes and the incidence of any dementia, AD and VaD. Particularly strong effect on VaD. Possibly mediated through poor glycemic control. Mixed evidence for cognitive benefits of optimising glycemic control |

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