Time matters

A call to prioritize brain health
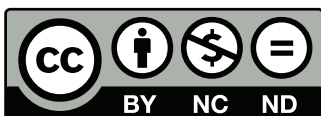
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Time matters

A call to prioritize brain health

Alzheimer's Disease International
The global voice on dementia

Alzheimer's Research UK

Make breakthroughs possible

Alzheimer's Society
United Against Dementia

The Cure Parkinson's Trust

Dementias Platform UK
Medical Research Council

The Dunhill Medical Trust

ean
european academy of neurology

European Association of Neuroscience Nurses
EANN

Welcome to the
E A D C
web site
European Alzheimer's Disease Consortium

EBC
European Brain Council

EPDA
European Parkinson's Disease Association

International Parkinson and Movement Disorder Society
European Section

jup
Jung & Parkinson
Die Selbsthilfe e.V.

THE NEUROLOGICAL ALLIANCE

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CHANGE ATTITUDES.
FIND A CURE.
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WORLD FEDERATION
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Jung & Parkinson/Die Selbsthilfe e.V.

Neurological Alliance

Parkinson's UK

World Federation of Neuroscience Nurses

Preface

Campaigns to detect disease early, provide timely intervention and communicate important public health messages have shown great success in some areas of medicine, notably cancer and cardiovascular disease. The same is not true for most conditions of the brain, including neurodegenerative diseases. Brain health is slowly becoming better understood, but much still needs to be done to manage the projected increase in the numbers of people affected by progressive neurodegenerative diseases, such as Alzheimer's disease and Parkinson's disease.

This report presents an expert, evidence-based position for policy recommendations that encourage individuals to participate actively in prioritizing their own brain health. It also challenges policymakers, researchers, funding bodies and healthcare professionals to collaborate in planning for the healthcare structures of the future.

Strategies to limit the impact of neurodegenerative diseases may be feasible once research has identified effective diagnostic tools and disease-modifying treatments. When that moment comes, we need to be prepared.

A word about language

We have referred throughout the report to 'Alzheimer's disease' (AD), which is the most common cause of dementia. However, much of the research we consulted investigates 'dementia'; in such cases, we have remained true to the original source and referred to dementia rather than AD. The course of the neurodegenerative diseases has been summarized into four phases, which are defined below.

- **At-risk phase**: the individual does not have the disease but may have been exposed to initiating events.
- **Presymptomatic phase**: neurodegeneration and pathology have begun, but there are no signs or symptoms of disease.
- **Prodromal phase**: there are signs or symptoms reflecting the underlying pathology, but these are insufficient for diagnosis.
- **Clinical phase**: the threshold for diagnosis has been met; disease may or may not be diagnosed.

We have tried to limit the use of scientific and medical terminology. However, when it is useful to introduce a scientific term, it has been highlighted in bold at first mention and also defined in the glossary on pages 44–46.

Executive summary

Brain health is about making the most of your brain and helping to reduce some of the risks to its health as you age. This report highlights the need for each of us to act now to prioritize brain health. It calls on policymakers, public health bodies and others to educate the general public about the progressive nature of the neurodegenerative diseases that are becoming increasingly widespread as people live longer.

Alzheimer's disease (AD) and Parkinson's disease (PD) are the focus of this report because they are the two most common neurodegenerative diseases. PD affects more than 6 million people worldwide; AD is the most common cause of dementia and affects approximately 50 million people.

The process of neurodegeneration begins many years before symptoms appear, and it may take years for an at-risk individual to progress through the presymptomatic and prodromal disease phases until a clinical diagnosis can be made. There is a 10–20-year 'window of opportunity' in midlife to intervene in the disease course and to potentially reduce the risk of developing neurodegenerative disease and/or delay disease progression.

The report summarizes the key risk factors for AD and PD, both modifiable and non-modifiable. It also discusses how implementing beneficial behaviours and potential lifestyle changes can improve brain health, just as these behaviours have been shown to improve cardiovascular health. **What's good for the heart is generally good for the brain** is an important public health message.

Primary prevention strategies that encourage modification of behaviour are not the only potential interventions. Population screening or health-check programmes that aim to detect disease early have been successful in some areas of medicine (e.g. cancer and heart disease). The report explores current challenges to the introduction of such programmes in the context of neurodegenerative diseases.

To prepare for future advances, the authors recommend some specific areas for research, including continuing the search for effective diagnostic tools, biomarkers, drug targets and treatments. 'Big data' can help to identify associations between brain diseases and some of their causative factors, which could speed up the identification of drug targets. Wearable technology may also be useful in tracking an individual's disease course and enabling personalized healthcare.

Our recommendations should help those tasked with organizing health services to decide how best to prepare for the advent of national programmes that facilitate earlier detection and intervention of neurodegenerative diseases such as AD and PD. All interested stakeholders need to work together for the common goal of improved healthcare for neurodegenerative diseases. We can achieve more together than we can separately.

Policy recommendations

Health promotion recommendations

The message "what's good for your heart is generally good for your brain" needs to be widely communicated and understood. So, **policymakers** and **public health bodies** that provide health information to the general public should act on the recommendations below.

- Protect and provide the public health budgets to improve public understanding of how to promote brain health and promote a positive approach that helps to prevent neurodegenerative diseases.
- Encourage behaviours at all ages that help to improve brain health, such as healthy eating and taking adequate exercise.
- Provide a supportive environment, including national guidance and legislation when appropriate, that empowers individuals to make important lifestyle changes.
- Prepare for the likely growth in the demand for genetic testing by people who want to understand their risk of a neurodegenerative disease. This should involve establishing rigorous support systems and processes, including training healthcare professionals to counsel individuals who have undergone testing and to share their test result in an ethical and regulated way.
- Provide access to available and effective treatments in a timely manner.

Clinical recommendations

Healthcare professionals and **administrators** will continue to play a key role in the management of people with, or at risk of, a neurodegenerative disease and should act on the recommendations below.

- Refer anyone with a suspected neurodegenerative disease to specialist, multidisciplinary services, if they are available.
- Provide follow-up to individuals, in the form of multidisciplinary services, to provide ongoing, widely accessible holistic care, including prevention information, treatment options and support.

Research recommendations

Researchers and **organizations that fund scientific research** need to help healthcare professionals and society to avert a future health crisis. Further work is needed to develop treatments for neurodegenerative diseases and validate diagnostic tools to identify people at risk. Meanwhile, **healthcare decision-makers** should start to pave the way for the advent of national programmes that facilitate earlier disease detection and intervention, with appropriate consideration of the ethical implications this would entail.

To this end, the authors recommend that additional funding for research is provided in order to meet the goals listed below.

- Improve our understanding of the underlying molecular mechanisms of the at-risk and presymptomatic phases of neurodegenerative disease.
- Increase our understanding of diagnostic and progression markers, particularly during the presymptomatic and prodromal phases, to help to track the disease course and severity.
- Identify the effectiveness and cost-effectiveness of interventions to promote brain health.
- Identify which tests for disease detection and diagnosis have optimal accuracy, availability and affordability.
- Assess the relative weight of different risk factors (e.g. lifestyle, genetic and molecular factors) and the interactions between them, so that decision-makers can decide how to prioritize them and address them.
- Understand the extent to which an individual's awareness that he or she has strong risk factors for a neurodegenerative disease may motivate them to change their behaviour, and how best to support that behaviour change.
- Agree on policy and recommendations about the appropriate support required for a tested individual before and after a health check.
- Investigate the risk and protective factors involved in specific neurodegenerative diseases and neurodegeneration in general, at both the individual and societal level (e.g. by improving infrastructure and social capital).
- Develop, validate and approve tests, tools and apps for monitoring brain health at an individual level by working in collaboration with regulatory authorities and stakeholder groups, including researchers, clinicians and funding bodies.
- Ensure that data from research are made publicly available and pooled to maximize their usefulness in developing the best diagnostic tools and treatments.
- Ensure that research results are provided, in a sensitive manner, to study participants, and that appropriate support is given.

1 The impact of neurodegenerative diseases

Key points

- Neurodegenerative diseases are becoming more common as people live longer, but they are not an inevitable consequence of normal ageing.[2]
- Worldwide, Alzheimer's disease affects approximately 50 million people[4] and Parkinson's disease affects more than 6 million people;[32] these numbers are rising.
- The costs of neurodegenerative diseases are borne by society (e.g. medical costs, social care, loss of workforce hours) as well as by individuals and their families, as progressive disease affects their health-related quality of life and capacity for independent living.[27,34,40]

Brain health is about making the most of your brain and helping to reduce some of the risks to it as you age. **Neurodegenerative diseases** are long-term progressive conditions that cause a decline in brain health and result in premature death. Age is the strongest risk factor for neurodegenerative diseases,[1] and these diseases are becoming more common as people are living longer. It is becoming increasingly important to put strategies in place to intervene early in the development of neurodegenerative diseases, in order to reduce the burden on individuals, society and healthcare systems.

There are many neurodegenerative diseases and they cause lasting damage to the **central nervous system**. **Neurodegeneration** is not an inevitable consequence of normal ageing but a consequence of disease-related (**pathological**) processes in the brain that result in a loss of function of the nervous system.[2] The two most common neurodegenerative diseases are **Alzheimer's disease** (**AD**) and **Parkinson's disease** (**PD**), and these are the main focus of this report. Some, but not all, neurodegenerative diseases are causes of dementia.

Alzheimer's disease is the most common neurodegenerative disease

AD is the most common neurodegenerative disease and the most common cause of dementia.[3] It involves the progressive loss of **neurons** (specialized cells in the brain) that affect behaviour, memory and several conscious processes (**cognitive domains**). The resulting reduction of mental abilities or processes (**cognitive impairment**) interferes significantly and progressively with a person's ability to maintain the activities of daily living.[4]

The loss of neurons in AD results in a greater decrease in brain volume (**brain atrophy**) than occurs in normal ageing.[3] The presence of **amyloid-β** plaques and **tau protein** 'tangles' in brain tissue is characteristic of AD.[3,5] The abnormal processes that underlie the development of AD are various and not fully understood.[6–8] Risk factors for AD will be described in **Chapter 3**.

Early symptoms of AD may include memory loss, poor concentration, confusion, mood changes and difficulty with carrying out daily tasks or following general conversation (**Figure 1**).[9,10] Damage to specific areas of the brain or nervous system results in symptoms such as: impairment of language and of the ability to comprehend or produce speech; impairment of the ability to read or write (**aphasia**); failure to recognize people or objects (**agnosia**); inability to perform complex motor acts (**apraxia**) and the impaired ability to organize, plan and conduct a set of actions in an efficient manner (**executive function**) (**Figure 1**).[11,12]

Alzheimer's disease
- Problems with memory
- Inability to process sensory information, such as touch
- Problems with executive function
- Depression
- Mood changes
- Language impairment
- Inability to perform complex movements

Parkinson's disease
- Problems with thinking and memory
- Hallucinations
- Sleep disorders
- Depression and anxiety
- Loss of sense of smell
- Walking with a stooped posture
- Slow movement and rigidity
- Tremor
- Small handwriting
- Lack of function of the body's unconscious systems, including constipation and urinary symptoms
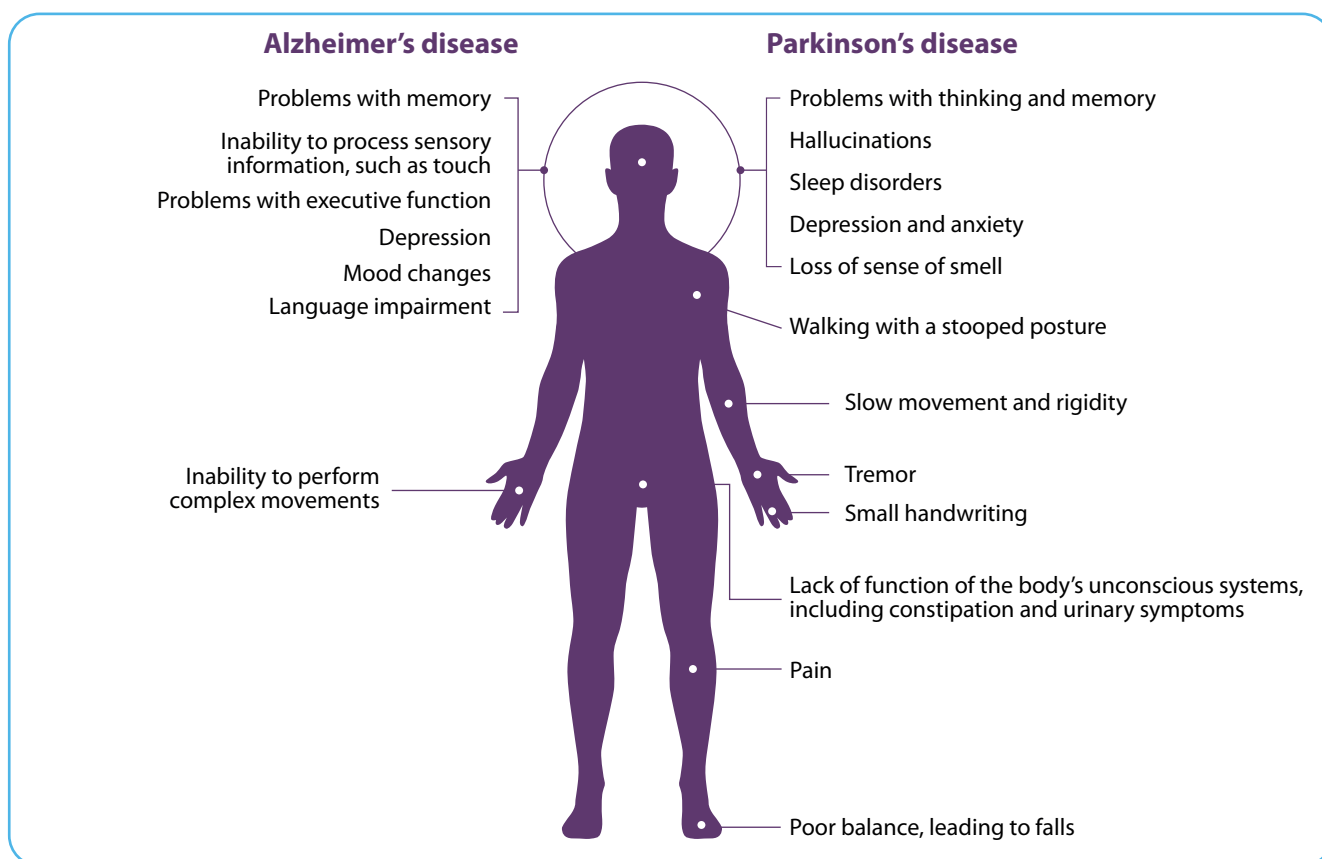- Pain
- Poor balance, leading to falls

Figure 1. The symptoms associated with Alzheimer's disease and Parkinson's disease affect many aspects of normal functioning and appear at different stages of the disease.[9–12]

Parkinson's disease affects the whole nervous system

PD is diagnosed by observing abnormal control of movement (**motor control**), including progressively slow and small movements (**bradykinesia** and **hypokinesia**, respectively), stiffness (rigidity) and tremor,[13] in contrast to the cognitive changes that are among the presenting signs and symptoms of dementia and AD.[12] PD in the later stages is also characterized by balance problems due to a loss of **postural reflexes**, which often results in falls.[13,14] Many people with PD have motionless faces (**hypomimia**), small handwriting (**micrographia**) and an altered way of walking, including a stooped posture[13] (**Figure 1**). In addition to these movement symptoms, PD affects many aspects of an individual's daily life, and can cause insomnia and several sensory problems, including reduction of sense of smell. PD also causes some dysfunction of the body's automatic (autonomic) systems, including constipation, urinary symptoms, sexual dysfunction, and pain.[13] Cognitive symptoms also occur commonly in people with PD. These all contribute to the lower health-related quality of life (**HRQoL**) of people with PD than of the general population.[15]

Disruption to voluntary control of movement is caused by the loss of neurons, and results in the characteristic signs and symptoms of PD.[16] The key pathological changes of PD are:

- the loss of neurons, primarily in a region of the brain called the **substantia nigra**, that release a chemical called dopamine, which is involved in movement (the lack of this chemical results in symptoms of PD)[17]
- the presence of abnormal clusters of proteins, called **Lewy bodies**, also in the substantia nigra and other areas of the brain.[16,18]

A diagnosis of PD cannot be clinically confirmed until significant symptoms appear that characterize a lack of motor control.[19] Although these symptoms allow diagnosis of PD, many patients also experience the non-motor symptoms described previously.[20] Major depressive disorder has been reported in 17% of people diagnosed with PD;[13,21] however, a systematic review found milder forms of depression present in 35% of patients.[21]

People with PD often recall an earlier phase, before diagnosis, during which they experienced non-motor and subtle motor symptoms, including pain, sleep disturbance, depression and **autonomic dysfunction**.[22,23] This phase of early symptoms is known as the **prodromal phase**, and is discussed later.

> **As a caregiver, one of the biggest sources of distress for me was that my Nan became argumentative and difficult, something that I found hard not to interpret as being ungrateful – despite knowing it wasn't as simple as that. When you are trying your best to provide the most stimulating and appropriate care but receive no positive feedback, it is hard, emotionally, to continue with a positive attitude.**
>
> **Everyday life can be challenging. Lack of sleep can be a big problem, particularly if the carer must continue working. The carer might think a day out together would be nice, but in my experience that became more challenging and distressing as time went on. My Nan needed reassurance about how long it would take to get there, what we would eat, where we would get petrol, what route we would take – she didn't even drive! But her distress was real.**
>
> **The visual disturbances secondary to dementia can cause distress. My Nan went through a phase of seeing black spots on clothes and work surfaces. She was constantly trying to clean these spots off and, when she couldn't, became very frustrated. She refused to put on those 'dirty' clothes, so just the simple act of getting dressed became a battleground.**
>
> *Ruth's story*

The disease burden is growing

In 2016, 3.5% of total global deaths were registered as attributable to dementias (including AD), making dementia the fifth highest cause of death. This is predicted to rise to 7.1% by 2060.[24,25] AD affects approximately 50 million people worldwide and accounts for 60–70% of dementia cases;[4] approximately one new diagnosis of AD is made every 3 seconds.[26] The 2015 Alzheimer's Report anticipated that the overall number of people with dementia will double every 20 years, reaching 74.7 million by 2030, probably owing to the expanding population size.[27] Age is the biggest risk factor for AD and other dementias;[28] hence, the number of people affected is increasing worldwide as life expectancy rises.[28–30] The increases in the number of people living with AD and dementia have been in line with the increasing average age of the population.[3,31]

The proportion of global deaths attributable to PD in 2016 was 0.4%; this is predicted to rise to 0.6% by 2060.[24,25] PD affects more than 6 million people globally.[32] The overall number of people with PD is expected to double over the next 20 years, meaning it will affect 2% of people over 60 years of age and up to 6% of people over 80 years of age.[33] However, the increase in PD may be linked to other risk factors in addition to increasing age, because the proportion of people living with PD appears to be increasing faster than expected if age were the only contributing factor.[32]

These data must be treated with caution because there have been changes over time in diagnostic criteria and in the thresholds needed to reach diagnosis of neurodegenerative diseases. In addition, changes in national or local quality targets or in funding for health services might have increased the incentives to record more diagnoses. So, the number of diagnoses has indeed probably risen, but the rise will be partly attributed to these changes in diagnostic practice.

The socioeconomic burden will continue to grow

The financial cost of neurodegenerative disease to society is considerable, both in terms of **direct** (e.g. medical) and **indirect** (e.g. sick leave) **healthcare costs** and in terms of the significant loss of workforce hours (**Figure 2**). The ageing population is leading to an increase in the demand for healthcare, placing a burden on healthcare systems and on informal carers in the community.[27,34] The number of unpaid carer hours and the impact of the unpaid hours on depleting the workforce are substantial and are increasing in line with a growing vulnerable population.[28]
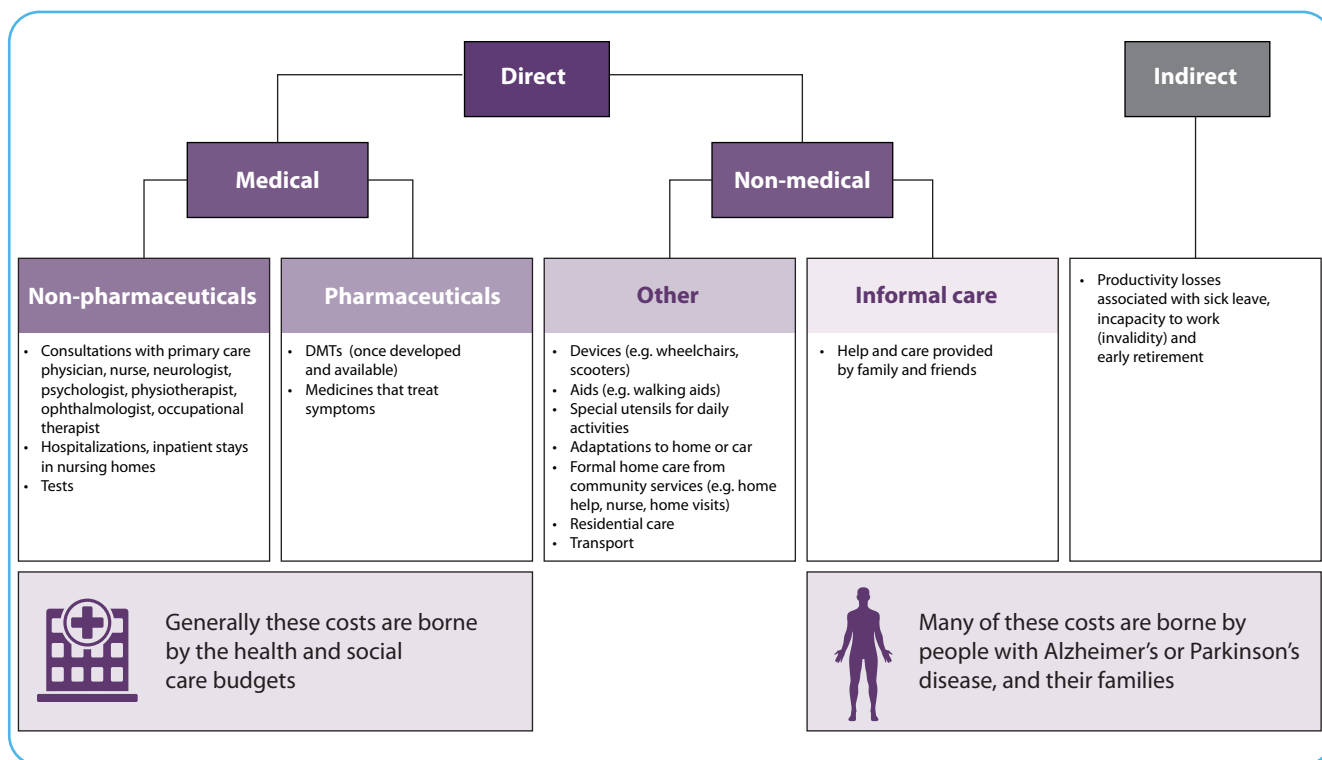
Figure 2. The total societal costs of neurodegenerative diseases are borne mainly by people with neurodegenerative diseases and their families.
DMT, disease-modifying therapy. Modified with permission from MS Brain Health report.[35]

Owing to the availability of the data, economic statements are given regarding dementia rather than AD specifically. The global costs of dementia increased from US$604 billion in 2010 to US$818 billion in 2015.[27,36] Of this, US$331 billion was for the cost of informal care by family and friends, equating to approximately 40% of all dementia-related costs.[27,37]

The cost of neurodegenerative diseases is not just financial. Many people with neurodegenerative diseases report a deterioration in their HRQoL because cognitive, behavioural and functional symptoms increase with disease progression.[15,38] These symptoms eventually reduce a person's ability to perform normal daily activities and can result in depression, loss of independence and lack of interaction with the wider world.[39]

The World Health Organization (WHO) has estimated that, by 2030, AD and other dementias will be responsible for 1.2% of the total deterioration in HRQoL.[40] Similarly, it is estimated that PD will be responsible for 0.2% of the global deterioration in HRQoL by 2030.[40] People with PD and their carers both report a lower HRQoL than the general population.[41]

"

Stefan received his diagnosis of PD at the age of 46. After diagnosis, he was not permitted to continue in his profession within the service sector. His job required high levels of precision and attention, and he held responsibility for human lives. Owing to his symptoms, such as tremor, he couldn't find a permanent job. After several short-term jobs, a period of sick leave and unemployment, he was forced to apply for a disability pension at the age of 51. The official disability pension and the later retirement pension depend on the amount of money contributed during employment years. Given these circumstances, it was difficult to maintain the household and raise two children. The dream to own his own house was no longer possible. Stefan's family still depends on additional support from social assistance.

Stefan's story

Jung & Parkinson/Die Selbsthilfe e.V.

"

2   The course of neurodegeneration

Key points

- The continuum of neurodegeneration begins many years before symptoms appear.[42]
- This means that AD and PD are often not diagnosed clinically until relatively late in the disease course.[33,43]
- Fear of emotional and practical challenges or of stigma may prevent people from seeking an early diagnosis.
- A public health campaign that encourages people to discuss brain health and educates them about reducing their personal risk could increase the opportunities for early intervention.
- A 10–20-year window of opportunity exists in midlife during which an individual may reduce his or her own risk of developing neurodegenerative disease and/or delay the progression of its signs and symptoms; this window is a key public health target.[55]

Neurodegeneration starts long before symptoms develop

The underlying pathology of neurodegenerative diseases generally occurs slowly and progressively, and begins many years before symptoms appear.[42] This makes it difficult to identify the **presymptomatic phase** (when no symptoms are present) and to differentiate this from the **prodromal phase** (when symptoms are present but insufficient for diagnosis).[42]

Neurodegenerative diseases exist as a continuum of progressive deterioration, as defined in **Table 1**. **Figure 3** shows the course of disease progression.

Table 1. Definitions of the course of neurodegenerative disease.

| Phase	Description
At-risk	The individual does not have the disease but may have been exposed to initiating events
Presymptomatic	Neurodegeneration and pathology have begun, but there are no signs or symptoms of disease
Prodromal	There are signs or symptoms reflecting the underlying pathology, but these are insufficient for diagnosis
Clinical	The threshold for diagnosis has been met; disease may or may not be diagnosed
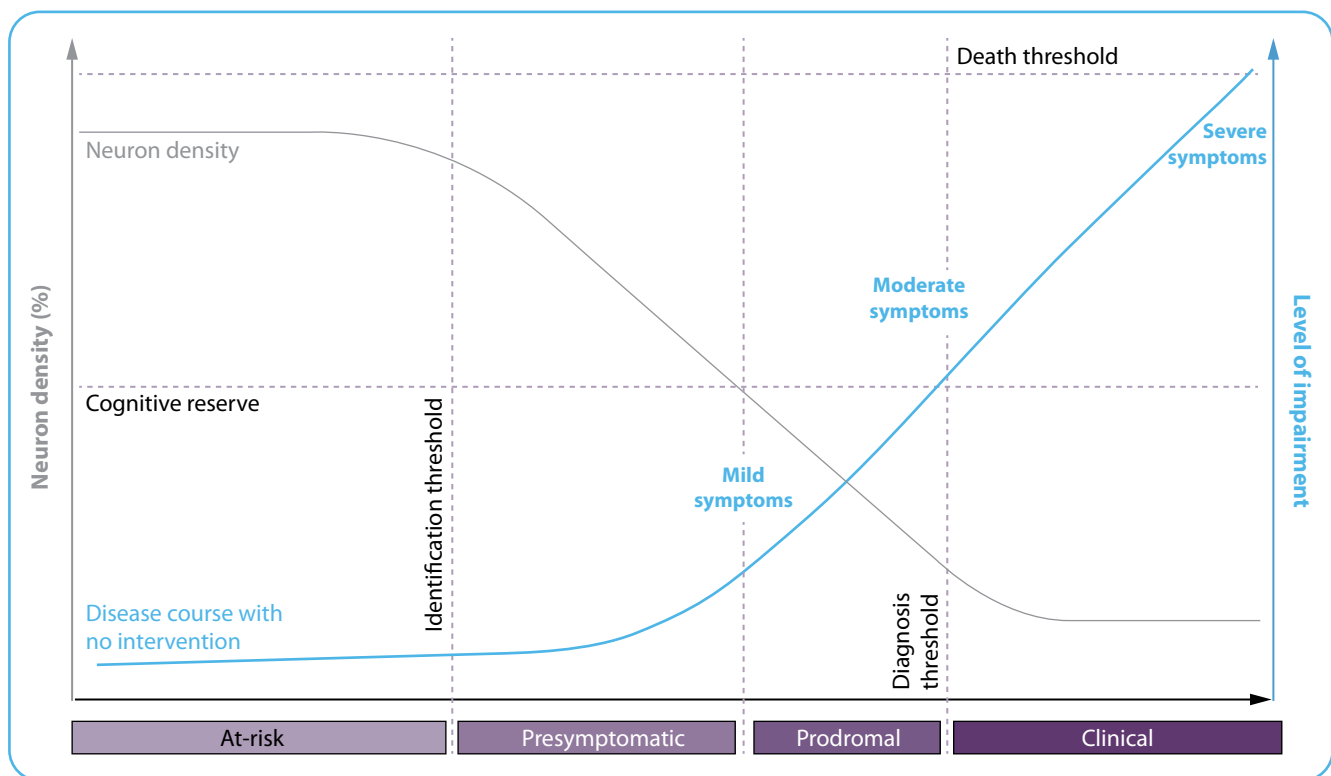
Figure 3. Simplified schematic representation of neurodegenerative disease progression over time.

In practice, this means that AD and PD are often not diagnosed clinically until a relatively late stage in the disease course, when symptoms are advanced, and substantial neuronal damage and loss have already taken place.[33,43] AD starts insidiously, with damage occurring via a complex set of cellular processes that affect many cell types, and the prodromal phase may span at least a decade.[44] The rate of AD progression varies widely and cannot be reliably predicted for each individual.[45]

The prodromal phase of PD is estimated to last between 10 and 20 years.[46–48] By the time PD has been diagnosed, approximately 30–50% of neurons involved in the transmission of dopamine have died.[42,47]

Diagnosis of neurodegenerative disease may not be straightforward

In some people, distinguishing AD from the forgetfulness associated with normal old age and from other forms of dementia may be hard.[49,50] By the time that help is sought and a diagnosis is made, the disease may already be far advanced.[51,52] Clinical diagnosis of AD involves individuals visiting a healthcare professional and raising concerns about their health. Tests are subsequently conducted and, when necessary, a referral is made to a specialist, who may or may not be based in a memory clinic. Although there is no simple clinical test for diagnosing AD, recommended and validated screening instruments can be used in practice to indicate the extent of a patient's cognitive impairment.[53] These include a range of memory tests and evaluations to eliminate other common causes and help to confirm diagnosis.

Some people may be averse to seeking a diagnosis or to admitting that they have a neurodegenerative disease, for fear of the emotional and practical challenges they may face[54,55] or for other reasons, including perception of limited treatment options and language barriers.[51] Perceived stigma can further contribute to a delay or failure to seek diagnosis or management.[54] If the general public was more aware of neurodegenerative diseases, this could help to challenge the associated stigma. Increased awareness of the disease course may provide incentives to seek help early and to identify sources of help. A greater awareness of the numbers affected by disease and its underlying mechanisms may help to dispel any fear of being 'abnormal'. Both of these concepts present opportunities for earlier intervention.[55]

Similarly, an individual concerned about PD may visit a healthcare professional and will be referred to a specialist if disease is suspected. A diagnosis of PD is likely if a patient has two of the three symptoms commonly associated with

PD,[56,57] such as slowness of movement, shaking or tremor that only occurs at rest and/or muscle stiffness (rigidity), as well as some of the non-motor symptoms already mentioned. For some individuals, the diagnosis may be a relief after uncertainty about their symptoms. However, no clinical test can conclusively show that an individual has PD.[33]

> **Why does getting an early diagnosis matter?**
>
> **If cognitive difficulties are mistakenly put down to 'a midlife crisis', or alcohol use, or any of the other excuses people come up with, there is no support, no sick pay, no benefits. People resign, get divorced, are made redundant or sacked. It would be very different if they had a heart attack or a stroke, but those things are immediately recognizable. An earlier diagnosis would mean at least we could deal with the behavioural changes associated with dementia.**
>
> *Helen's story*

Society needs to understand and talk more about brain health

The long period of deterioration seen with many neurodegenerative diseases provides a window of opportunity during which healthcare intervention could benefit patients and their families. However, public understanding of these progressive diseases is generally poor. Even though awareness may be growing, societal willingness to discuss brain ill health is limited. Health systems are not yet equipped to manage large numbers of people who are potentially at high risk of long-term neurodegenerative conditions.

To maximize the potential of early intervention, the general public needs to understand the risk factors that can affect their brain health and what can be done to maintain it.[55] For example, dementia is not an inevitable part of ageing, but in a large-scale survey of 2361 adults in the UK, one in five adults surveyed believed that it is,[55] and only one in five adults surveyed in the European Union believed that dementia could be prevented.[55] Approximately 35% of dementia cases are attributable to a large number of modifiable risk factors;[1] however, only 34% of respondents to the UK survey thought that it was possible to reduce their risk of developing dementia (**Figure 4**).[55]

Despite this low awareness of risk factors for AD, the same report indicated that three out of four UK adults surveyed want to receive information in midlife from a doctor about their personal risk of developing dementia in later life.[55] A further study has shown, however, that people's desire to learn about their risk of developing AD decreases when they realize that **biomarkers** for the disease are currently inconclusive and that there is little or no information about how to reduce that risk.[58]

Irrespective of how many individuals want more information about neurodegenerative diseases, there is a strong rationale for the general public to understand risk better. A public health campaign to improve knowledge about risk reduction strategies could maximize the scope for prevention and early intervention.

Alongside this, knowledgeable individuals, such as specialists and primary care physicians, must learn how to share this information effectively. With increasing shared decision-making in healthcare, there is a growing pool of individuals who are keen to know their risk or who have sought out their risk using private screening methods.[59] Therefore, more research is needed to understand how best to communicate to individuals the potentially complex results of screening. Healthcare professionals and others may need appropriate training for this and to help them to encourage behavioural changes that reduce an individual's risk of disease.

Which, if any, of the following health conditions do you think it's possible for people to reduce their risk of developing?

Diabetes
81%

Heart disease
77%

Stroke
60%

Cancer
52%

Dementia
34%

34%
of respondents think it is possible for people to reduce their risk of developing dementia

None of these
3%

Don't know
2%
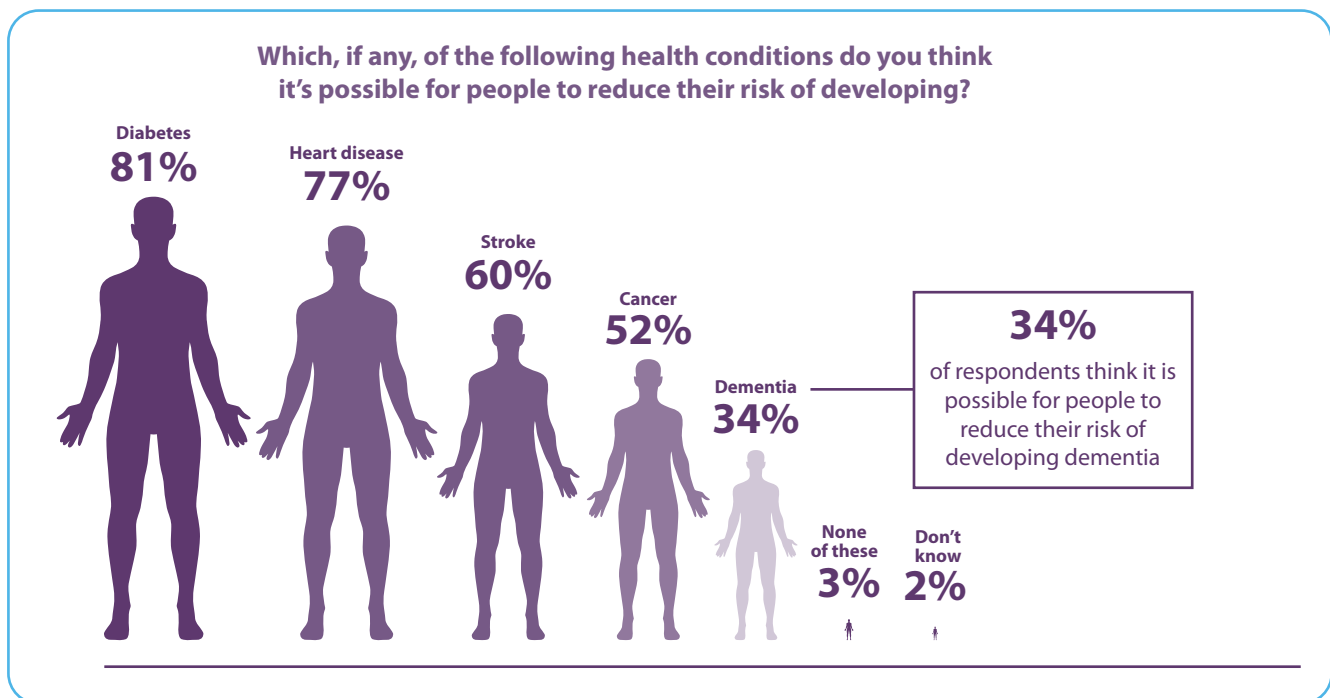
Figure 4. Do people think that they can reduce their risk of developing dementia? Public perceptions from a UK-based survey.
Modified with permission from Alzheimer's Research UK.[55]

The survey results of 2361 adults in the UK[55] support the need for personalized approaches to increase awareness of risk factors and to encourage behavioural and lifestyle modification.[60] Guidelines recommend raising public awareness of the fact that common unhealthy behaviours can increase the risk of neurodegenerative disease.[61,62] For instance, the UK National Institute for Health and Care Excellence (NICE) has advised that public health campaigns should explain the risks of smoking, lack of physical activity and obesity, and their associations with neurodegenerative disease.[61] A recent study has found that a healthy lifestyle was associated with a lower risk of dementia among participants with high genetic risk.[60]

> Dementia is a terrible condition, where you slowly witness the loss of a loved one's memories and personality – it's like they drift away from you and become harder and harder to recognize.
>
> Having witnessed the effects of dementia on my mum, I know how important it is to spread the message that there are things we can do to reduce our risk of dementia.
>
> Running helped me cope with the stress and heartbreak of losing my mum to dementia; keeping my brain healthy through exercise and diet is definitely something that motivates me now.
>
> *Andy's story*

The WHO has recently published guidance about reducing the risk of developing dementia. This includes recommendations to:

- increase physical activity
- improve nutrition
- maintain cognitive activities
- manage weight
- control diabetes
- minimize depression

- cease tobacco smoking
- reduce alcohol use
- increase social activity
- reduce blood pressure
- control dyslipidaemia (high levels of lipids in the blood)
- minimize hearing loss.[62]

No equivalent guidelines for PD prevention have yet been developed.

Accepted strategies exist for disease prevention

The WHO has defined three levels of prevention strategies. Standard definitions are provided below.[63]

- **Primary prevention**: avoiding the onset of a disease. This is done by preventing or reducing exposure to risks and behaviours, providing information and offering clinical prevention services such as vaccination of children and adults.[63]
- **Secondary prevention**: early detection of disease, leading to a better chance of positive health outcomes. This is mainly done by evidence-based population screening programmes.[63]
- **Tertiary prevention**: improving HRQoL and reducing the symptoms of a disease, once diagnosed, by means of symptomatic treatments and support services.[63]

There is a window of opportunity for change

The public is generally unaware that a 10–20-year window of opportunity exists in midlife, during which one may be able to reduce the risk of developing neurodegenerative disease before signs and symptoms appear, and to delay the progression of signs and symptoms that mark the onset of the clinical phase.[55]

Primary prevention strategies are the first priority, particularly in the absence of approved **disease-modifying therapies** (**DMTs**); however, successful secondary prevention strategies in neurodegenerative diseases could slow the progression of disease and/or reduce symptom development (see **Chapter 4**). This 10–20-year window is therefore a key public health target.

If research were able to characterize the prodromal phase of a disease accurately, develop valid and accurate screening tests (see **Chapter 4**), and identify effective and cost-effective interventions (see **Chapter 5**), the pressure of neurodegenerative disease on healthcare systems could be alleviated.

Recommendations

- Protect and provide the public health budgets to improve public understanding of how to promote brain health and promote a positive approach that helps to prevent neurodegenerative diseases.

- Conduct research to improve our understanding of the underlying molecular mechanisms of the at-risk and presymptomatic phases of neurodegenerative disease.

3 Risk factors for neurodegeneration

Key points

- Some characteristics, such as age and genetic factors, cannot be changed to reduce the risk of developing neurodegenerative diseases.
- Several factors that increase the risk of dementia relate to lifestyle choices (e.g. poor diet, lack of exercise, smoking, alcohol consumption);[61,64,65] modifying these behaviours may help to delay the onset of disease symptoms.
- Lifestyle factors that may increase the risk of PD include low physical activity, head injury and pesticide exposure.[66]
- 'Big data' is helping to identify associations between brain diseases and some of their causative factors. This could speed up the development of drug therapy targets.[67]

Some risk factors influence the likelihood of developing neurodegenerative disease more than others.[1,68] Research needs to determine the key areas for focus. Brain health can be affected by **genetic factors**, environmental influences and lifestyle choices.[1,61,64–66,69–73] This chapter summarizes the role of these influences in AD and PD (**Figure 5**) and the expanding role of '**big data**' in improving the understanding of an individual's risk of developing neurodegenerative disease and the factors that may affect progression.
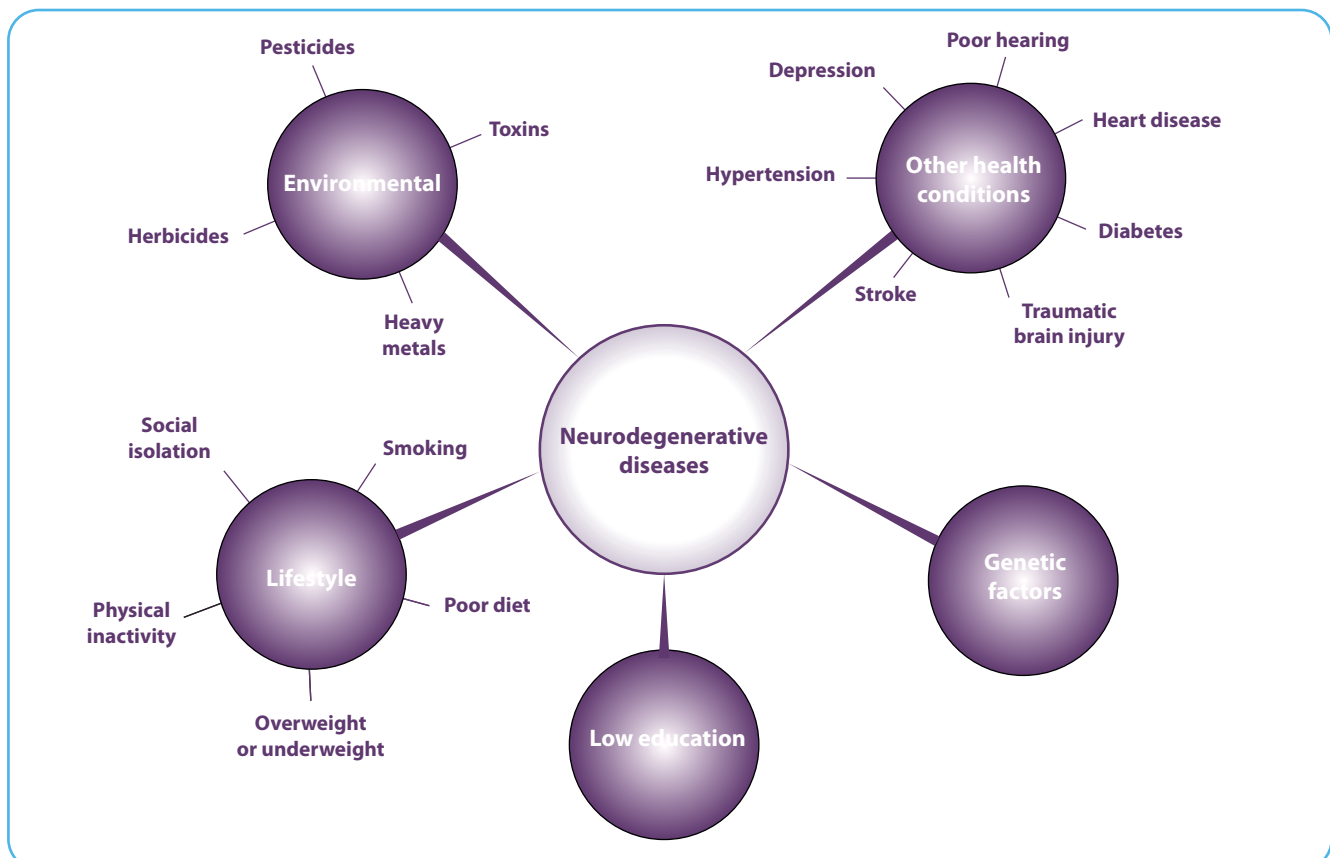

Figure 5. Risk factors associated with neurodegenerative diseases.

Some risk factors are modifiable

There has been a substantial increase in studies investigating potential risk factors for the development of neurodegenerative diseases.[42,61,64–66,69,73–75] Many of the identified lifestyle factors are modifiable, meaning that they can be changed to help to alleviate risk. For AD, modifiable factors include physical inactivity, poor diet, excessive alcohol consumption, **hypertension**, smoking and obesity.[61,64,65] It has also been shown that conditions such as heart disease, stroke, **cardiovascular diseases** (**CVDs**), depression and diabetes are risk factors for neurodegenerative diseases and cognitive decline.[65,69,73]

Multiple modifiable and lifestyle factors identified by large-scale studies have been included in recommendations for delaying or preventing the onset of dementia and disability.[61] Livingston and colleagues listed nine risk factors for dementia that are modifiable. These collectively contribute to 35% of the variation in disease (**Table 2**).[1] In other words, interventions focusing on these risk factors may reduce or delay the onset of dementia symptoms.

Table 2. Risk factors for dementia across the life course. If one or more of the risk factors listed below are removed, then an individual's overall risk of developing dementia falls by the respective contribution(s) to overall risk shown on the right of the table.

Factors for dementia		Contribution to overall risk (%)
Modifiable factors		
Early life	Low education	8
Midlife	Hearing loss	9
	High blood pressure	2
	Obesity	1
Late life	Smoking	5
	Depression	4
	Physical inactivity	3
	Social isolation	2
	Diabetes	1
Total contribution of modifiable risk factors		**35**
Non-modifiable factors		
	ApoE4 gene	7
Other factors		
	Unknown genetic and environmental factors	58
Total contribution of non-modifiable and unknown risk factors		**65**

ApoE4, apolipoprotein E4. Adapted from Livingston *et al. Lancet* 2017;390:2673–734.[1]

High education levels are correlated with **cognitive reserve**, which delays the appearance of cognitive symptoms.[1] It should be noted that diabetes and depression are **biological risk factors**, not lifestyle risk factors. However, lifestyle interventions focused on these factors could reduce the risk of dementia and are therefore included in **Table 2**.

The term 'cognitive reserve' can be viewed as the ability of the brain to process tasks and to compensate actively for physical damage. All other things being equal, people with neurodegenerative diseases who have a high cognitive reserve lose less cognitive function than those with a low cognitive reserve, for the same amount of physical damage.[76,77]

Risk factors for PD include both modifiable and non-modifiable elements. Male sex, occupational exposure to solvents, pesticides and other organophosphates, lack of physical activity, type 2 diabetes and head injury are associated with increased risk of PD.[46,66] Surprisingly, drinking coffee has been correlated with a 30% lower risk of PD than not drinking coffee.[78] Also surprising is the observation that smoking tobacco has been correlated with a 60% lower risk of PD than not smoking.[78] However, these correlations do not necessarily mean that exposing people to smoking or coffee will reduce risk, and smoking could never be advocated as a protective strategy, owing to the other health risks it poses.[79]

Most of these health recommendations[61,62] are consistent with previous health policies that have been made for other therapy areas, such as CVD or diabetes. Nonetheless, it is important to raise awareness that these lifestyle changes and risk-reducing behaviours can help to promote brain health too.

Some risk factors are non-modifiable

Some characteristics, such as age and genetic factors, cannot be changed to reduce the risk of developing neurodegenerative diseases. These are termed non-modifiable risk factors. Although nothing can be done about non-modifiable risk factors, it is still important to understand the overall risk that they pose.

Environmental factors, such as exposure to toxins (e.g. pesticides, herbicides and heavy metals) are also classed as non-modifiable at an individual level.[71] However, this classification has been challenged at the public health level, inasmuch as changes to legislation could compel manufacturers and local authorities to operate within stricter limits and thus help to reduce some environmental risks.[80] It could also be effective to educate the public about individual interventions that can be made at the lifestyle or behavioural level. Evidence from people working on plantations, or in industries in which heavy metals are regularly used, shows that exposure to these toxins and materials is associated with an increased risk of developing PD.[66]

In most individuals with PD, there is no clear cause: hence, the disease is described as **idiopathic** (i.e. it occurs spontaneously).[66,81] However, genetic causes or risk factors are increasingly recognized as having key roles in the development of PD. Evidence from twin studies and other genetic studies suggests that approximately 27% of the risk of developing PD is due to genetics and can be inherited.[82,83] The largest genetic study to date identified more than 90 independent genetic variants that modify PD risk, although most variants were only associated with small contributory effects toward the risk of developing PD.[75,83] A family history of PD has also been associated with a high risk of the disease. A study conducted in 2012 found that individuals with a first-degree relative with PD had more than twice the risk of having PD compared with individuals without a first-degree relative with PD.[84] In general, the genetic contribution to PD is greater in patients with an earlier age of onset or diagnosis (50 years or younger).[72] A study conducted in 2015 suggested a new approach to diagnosing PD, using both genetic and clinical markers.[85]

More than 20 genetic variants are significantly associated with AD, but these only contribute to a small proportion of the genetic risks; this indicates that more genes are yet to be identified.[86] *ApoE* is the gene that is the most important and established cause of susceptibility for late-onset AD.[86] The presence of a single *ApoE* ε4 **allele** (**Table 2**) is associated with a 2–3-fold increase in the risk of AD, and individuals with two copies of this allele have a fivefold increase in risk of AD.[87]

> " I am in my early 60s and found out my ApoE status during the screening part of a clinical study. The study team did a great job of explaining what this meant about my personal risk of developing Alzheimer's disease and putting all this into context of other risk factors.
>
> When we spoke about this together as a family, we did discuss the lifestyle risk factors that we can do something about. I was surprised to find out that having a healthy lifestyle had such a big impact on the risk of developing dementia! I try to exercise regularly and eat healthily and will keep up with this.
>
> I have also been telling my friends about my experience, to make them think about how they could change their risk of developing dementia too.
>
> *Tracey's story* "

Big data can shed light on genetic and biological risk factors

The term '**big data**' refers to large data sets, often of many measurements from large populations. These data sets can be analysed for trends, patterns and associations relating to behaviours and genetics. Big data is playing an increasing role in the identification of biomarkers and risk factors associated with neurodegenerative diseases. This is because the large sample sizes allow detection of small effects and can lead to unintended discoveries. The discovery of new associations between genes and disease helps to speed up the development of drug therapy targets.[67]

The main contributors to big data have been the ever-decreasing cost of **DNA** sequencing and gene analysis. These have increased the ease with which individuals can obtain information about their own genetic profile and agree for it to be documented in online databases. Big data can aid future research into identifying people at risk of developing these diseases.[75,88]

More than half of clinical studies that investigate potential new treatments for neurodegenerative diseases fail, owing to lack of treatment efficacy.[89] Drugs that include genetic evidence among the predefined methods for assessing outcomes in their development programmes may have 2–3-fold increased odds of ultimately being approved by regulatory bodies that approve drugs for use in humans (e.g. the European Medicines Agency and the US Food and Drug Administration).[89]

What's good for your heart is generally good for your brain

Given that neurodegenerative disease originates long before symptoms are apparent, consideration and adjustment of modifiable lifestyle factors in early- to midlife may help to reduce the risk in later life. Such lifestyle changes are known as **primary prevention**.

Interventions at an early stage can change the course of disease, potentially reducing the likelihood of progression.[90] There is also potential for lifestyle modification at a later stage, once a diagnosis of AD or PD has been received, which may also slow the progression of the disease symptoms. However, early intervention is likely to be more effective, in comparison.

Lifestyle changes may include introducing a healthy diet, stopping smoking, increasing exercise, **cognitive training** and monitoring, and management of diseases of the heart and circulatory system.[1,60,64] A multidomain approach that incorporates all these aspects could improve or maintain cognitive function in at-risk individuals. Regular exercise has important physical and mental health benefits (including improved **executive functioning** and reduced risk of depression) and it has been shown to reduce the risk of CVD.[91]

The WHO guidelines recommend exercise as a potential intervention at any age to reduce the risk of non-communicable diseases,[62] which reflects the philosophy that "what's good for your heart is good for your brain".[92,93] As well as recommending increased physical activity, the WHO advises additional health interventions, as mentioned in **Chapter 2**.[62]

Healthy diets, as described by WHO recommendations,[94] are endorsed for physical and mental well-being, but research suggests that a healthy diet can also reduce the risk of developing dementia, especially in combination with physical exercise and cognitive training.[1,60,61,64,65] There is some evidence for associations between consuming specific foods or drinks, such as coffee, and a lower risk of cognitive decline.[95,96] However, none of these factors has been shown to prevent damage to nerve cells or the nervous system.[95,97–99]

A key approach for risk reduction and primary prevention of diseases is to raise awareness of risk factors (particularly modifiable ones) and to educate the general population about what they can do to reduce these risks.[60,61] Policymakers can of course help to create a 'supportive environment', by legislating at the population level (e.g. by taking steps to reduce consumption of sugar). However, benefits will only be seen if individuals make healthy choices. If public health campaigns and primary care physicians can instigate a movement in the general population to adopt brain-healthy lifestyles, then disease progression could look like the 'primary prevention' pathway as shown in **Figure 6**, potentially reducing the risk factors[100] and the likely progression to a disease diagnosis.
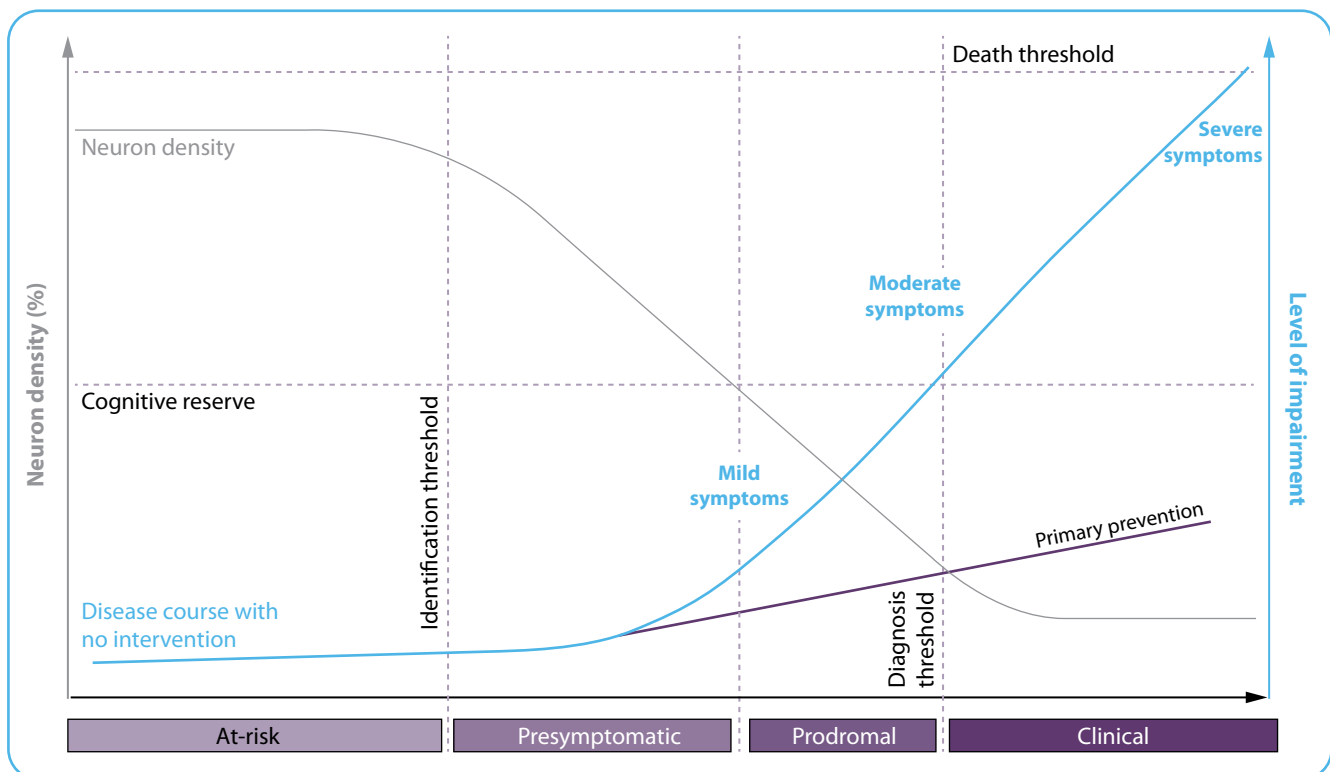

Figure 6. Likely change in the disease progression pathway if primary prevention interventions were implemented.

Many modifiable risk factors associated with neurodegenerative disease contribute to the overall risk, ranging between 1% and 9% of the total.[1,68] However, not all risk factors are of equal weighting: some probably influence the likelihood of developing the disease more than others.[1,68] Evidence on this is emerging. Recently, a large study has shown that a favourable lifestyle (including currently not smoking, regular physical activity, healthy diet and moderate alcohol consumption) was associated with a reduced dementia risk in this group.[60] For people with a high genetic risk of dementia, an unfavourable lifestyle was associated with the highest risk of dementia, whereas a favourable lifestyle reduced the risk.[60] In a separate study, the effects of a favourable lifestyle on reducing the risk of dementia were lower in people with a high genetic risk of dementia than in those with a low or intermediate genetic risk.[101] This reinforces the concept that there is an interplay of risk factors, whether modifiable (lifestyle) or non-modifiable (genetic), that contribute to the overall risk of dementia.

However, further research is needed to establish exactly which lifestyle factor modifications would bring about the greatest reduction in the risk of neurodegenerative diseases.

Recommendations

- Encourage behaviours at all ages that help to improve brain health, such as healthy eating and taking adequate exercise.

- Provide a supportive environment, including national guidance and legislation when appropriate, that empowers individuals to make important lifestyle changes.

- Prepare for the likely growth in the demand for genetic testing by people who want to understand their risk of a neurodegenerative disease. This should involve establishing rigorous support systems and processes, including training healthcare professionals to counsel individuals who have undergone testing and to share their test result in an ethical and regulated way.

Research is needed to achieve the aims listed below.

- Increase our understanding of diagnostic and progression markers, particularly during the presymptomatic and prodromal phases, to help to track the disease course and severity.

- Identify the effectiveness and cost-effectiveness of interventions to promote brain health.

- Assess the relative weight of different risk factors (e.g. lifestyle, genetic and molecular factors) and the interactions between them, so that decision-makers can decide how to prioritize them and address them.

- Understand the extent to which an individual's awareness that he or she has strong risk factors for a neurodegenerative disease may motivate them to change their behaviour, and how best to support that behaviour change.

- Investigate the risk and protective factors involved in specific neurodegenerative diseases and neurodegeneration in general, at both the individual and societal level (e.g. by improving infrastructure and social capital).

4   Strategies to identify people at risk of disease

Key points

- Population screening programmes have been used successfully in diseases for which effective treatments exist, such as breast cancer[102] and cardiovascular disease.[103]
- Neurodegenerative diseases do not currently meet established, standardized criteria for setting up population screening programmes;[104] two of these criteria are the existence of accurate diagnostic tools and effective DMTs.[104–107]
- A diagnostic tool for widespread use in population screening needs to be non-invasive and cost-effective.
- In the past few years, blood-based biomarkers have been identified that can differentiate individuals in the early stages of AD[108] and PD[107,109] from healthy individuals; these can be used as a step in selecting those who do or do not need further testing for diagnosis.
- Several DMTs tested for AD may have been unsuccessful because participants joined the studies too late in the disease course.[110–114] If clinical trials could include individuals at an earlier (presymptomatic or prodromal) stage who are shown by diagnostic tests to be at high risk for the disease, it may be possible to demonstrate a disease-modifying effect.[115]

We have already outlined the necessity for better methods and tools to detect neurodegenerative diseases. Currently, diagnosis comes too late for effective intervention. There is also a significant lack of awareness of protective strategies for brain health among the general public. Importantly, **what's good for your heart is generally good for your brain**, and this is a key message to deliver to the public.

We now discuss some of the secondary prevention principles that are used in healthcare and consider how population screening programmes might be applied to neurodegenerative diseases in future. However, these can only be implemented when there is sufficient evidence to meet strict screening criteria (discussed below) to ensure that such a programme would be beneficial at a population level.

Population screening can be used for treatable diseases

Population screening is the process of identifying people who are currently healthy, but may have an increased chance of developing a disease or condition, and offering a test to diagnose that disease rapidly and easily. If the results indicate that intervention is desirable, the screening provider then offers information, further tests and treatment. The initiative for detailed research into the requirements for a potential screening programme will need to come from governments and healthcare systems, rather than from the general population.

Population screening is a public health tool and is known as **secondary prevention**.[63] If a programme successfully detects disease, it can allow earlier intervention (assuming suitable treatments are available) and management to alter disease progression and prolong life, as shown in **Figure 7**.
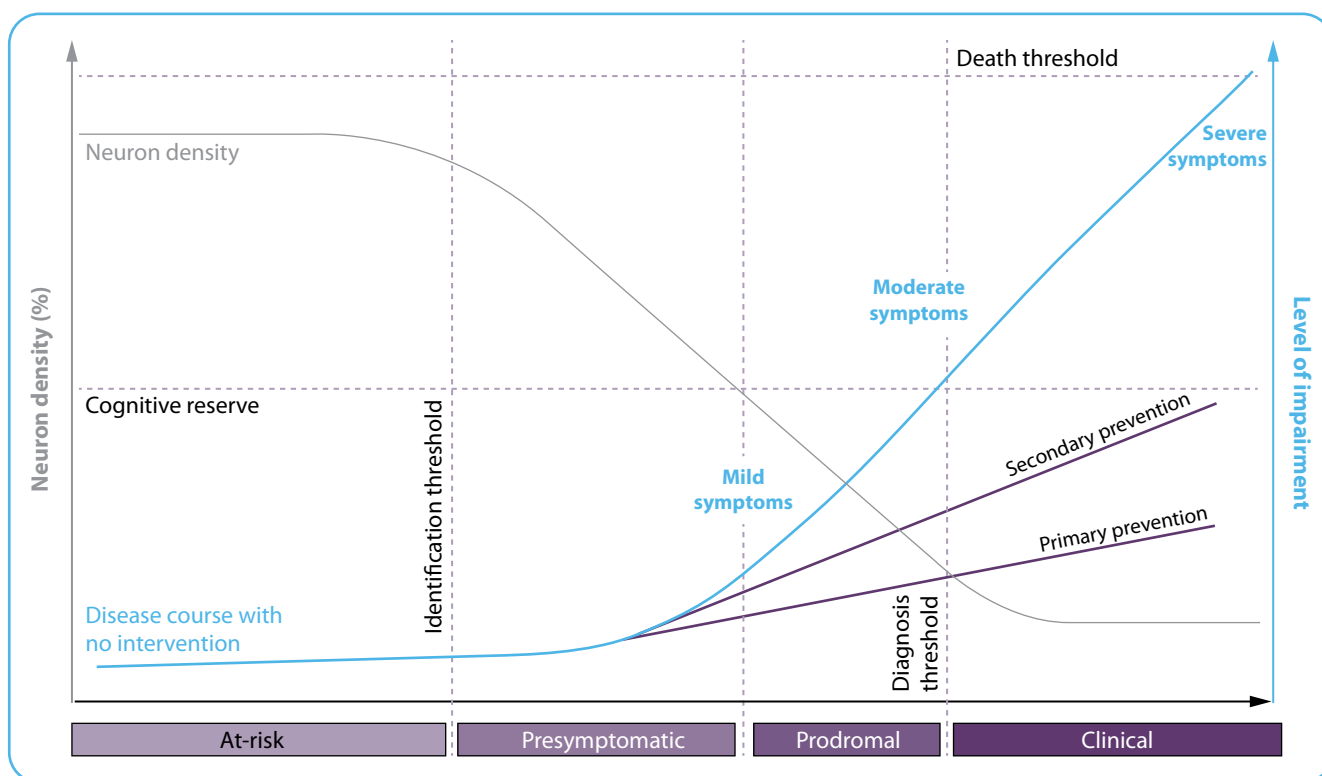
Figure 7. Secondary prevention programmes can potentially halt or slow disease progression.

Population screening programmes have been used successfully in other diseases for which there are effective treatment options.[103,116] For example, the hearing and heel prick blood spot tests in the first few days of life have helped to identify severe health problems and, potentially, to reduce the number of deaths.[116,117] There are screening programmes for many types of cancer; in the UK, women between 50 and 70 years of age are offered breast cancer screening every 3 years.[102] These programmes may have contributed to a reduction in premature death rates by the early detection of disease and early access to treatments, for example, in cervical cancer.[106] Furthermore, in cardiovascular medicine, the aortic aneurysm screening programme has helped to prevent a considerable number of potential cardiac events.[103]

Strict criteria exist for population screening

The design and management of national screening programmes rely on a series of core foundations. These are based on the Wilson and Jungner criteria used by the WHO, a well-established, standardized set of requirements. Key elements include those listed in the box below.[104]

- Identification and invitation of a population that is currently healthy and eligible to be screened for the condition.
- Good understanding of the natural history of the disease, including the prodromal phase.
- A precise screening test that is acceptable to the population.
- An efficient and effective follow-up and referral pathway.
- Availability of diagnostic tools that are accurate, accessible and affordable.
- A readily available and effective treatment, which is offered if the condition is diagnosed.[104]

Screening programmes need careful consideration

Anyone invited for a population brain health-check programme must have sufficient information to make an informed decision about participating.[104,105] For some people, participating in screening causes anxiety or worry about the test itself, or the possible outcomes.[118,119] In 2018, a study of dementia screening found that, based on the currently available tests, 12% of people would have falsely positive test results (i.e. a result that wrongly suggests that they may have dementia).[120] This can lead to **overtreatment**,[104] which means treating a person with a condition when not treating them would have made no significant difference to their disease course.

Having a coordinated, organized programme that meets the WHO criteria for screening can potentially help to reduce any stigma associated with undergoing a health check and to inform people of the associated potential benefits.[121]

Finally, programmes will need to be practical and of an acceptable cost so that healthcare services can provide **equitable access** to the whole population.[104] It must be noted that this list of key criteria is not exhaustive. If, in the future, a screening programme is considered for AD or PD, additional factors will be relevant to the discussion.[104]

Could equivalent checks be considered for brain health one day?

The National Screening Committee criteria outline the scenarios in which screening is appropriate and ethical, using the Wilson and Jungner criteria referred to above.[104] Two key requirements are that both accurate diagnostic tests and effective DMTs exist.

Although neurodegenerative diseases currently do not meet these criteria, it is essential that work begins now so that when diagnostic tests and DMTs do become available, they can be utilized in a timely manner to minimize the impact of disease in affected individuals.

Diagnostic tools must be sufficiently accurate[104] to minimize the risks of:

- incorrectly telling someone that they have the disease (overdiagnosis)
- incorrectly telling someone that they do not have the disease (false reassurance)
- identifying and treating a suspected disease, when leaving the disease untreated would have made no significant difference to their disease course (overtreatment).[105]

The balance of the potential benefits and risks of a screening or health-check programme for neurodegenerative diseases is therefore dependent on the development of accurate diagnostic tests and effective treatments.[104–106] There is ongoing research into the pathological processes involved in neurodegeneration.[109,122] In the near future, this is expected to lead to the identification of novel DMTs and the development of techniques to quantify the risk of disease and to diagnose it at presymptomatic or prodromal phases.[123,124]

Of course, an individual may prefer not to know they have a neurodegenerative disease because of the possible effects on their mental well-being, their relatives, their health insurance and their employment.[104,125] Guidelines and laws must account for this and prepare for the situation in which identification of future health risk becomes commonplace.

Efforts to develop early diagnostic tools are progressing

In a survey of 2354 healthy adults, 91% reported that they would be willing to take an eye, blood, memory or cognitive test for AD.[55] The proportion of people willing to take a test decreases as the invasiveness of the test increases, with fewer than half of respondents (44%) willing to have a **lumbar puncture** investigation.[55]

Magnetic resonance imaging (MRI) or ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET) scans are used as diagnostic tests for AD (in addition to lumbar punctures) and may be useful as tests for early diagnosis.[126] However, the everyday usability of these scans may be impractical and expensive when rolled out to large numbers of the population,[53] which effectively limits their utility in a screening programme.

The International Parkinson and Movement Disorder Society (MDS) has developed flexible criteria that can incorporate any data for an individual (e.g. genetics, scans and survey responses) to predict the likelihood that he or she has

prodromal PD.[46,48] Follow-up studies of these criteria have shown that individuals with scores indicating a high risk of disease are indeed likely to go on to develop PD.[127] In the future, tools such as this may be used to identify PD at a much earlier stage than at present.

Biomarkers for diagnosing and monitoring brain diseases need further research

A **biomarker** is a biological marker that can be objectively measured to diagnose a disease, to monitor disease progression, to identify increased risk of disease or to monitor how well treatment is working. Different biomarkers are used for each category and, often, for each disease.

For example, a test to measure how red blood cells are affected by high levels of blood sugar can be used to aid diagnosis of diabetes.[128] To be useful, a biomarker needs to reflect the relevant disease process with, ideally, high **sensitivity** (by detecting the disease only when it is truly present) and high **specificity** (by correctly identifying people without the disease) or by using a combination of tests in parallel.[129] **Figure 8** illustrates an example calculation of sensitivity and specificity; high percentages indicate a test that has a high level of sensitivity and specificity to be an accurate test. A biomarker may be used in isolation or in combination with others to improve specificity and sensitivity.

However, success in identifying accurate biomarkers for neurodegenerative diseases has proven elusive.[123,130–132]

$$\text{Sensitivity} = \frac{\text{true positive}}{(\text{false negative} + \text{true positive})}$$

$$= \frac{\bigcirc}{(\bullet + \bigcirc)}$$

$$= \frac{8}{(2+8)} \times 100 = 80\%$$

$$\text{Specificity} = \frac{\text{true negative}}{(\text{false positive} + \text{true negative})}$$

$$= \frac{\bullet}{(\bigcirc + \bullet)}$$

$$= \frac{9}{(1+9)} \times 100 = 90\%$$

○ A person who has the disease and is correctly diagnosed with the disease

● A person who has the disease but is incorrectly not diagnosed with the disease

○ A person who does not have the disease but is incorrectly diagnosed with the disease

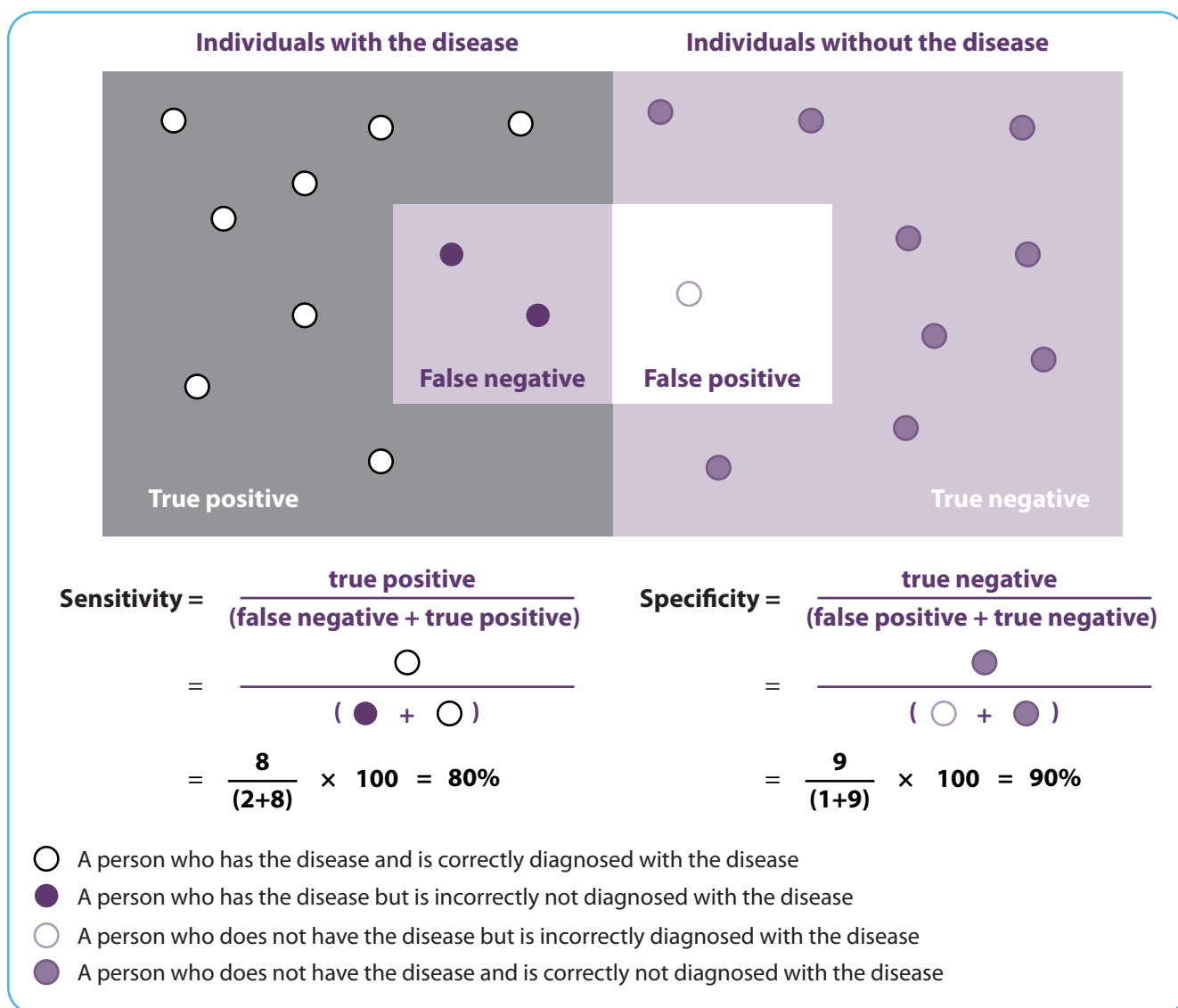● A person who does not have the disease and is correctly not diagnosed with the disease

Figure 8. Example results for people undergoing a screening test.
Some results are correct (e.g. a true positive result) and some are not (e.g. a false positive result). Below the figure are example calculations for sensitivity and specificity that indicate a useful test for screening.

Three main proteins (**t-tau**, **p-tau** and **amyloid-β 42**) have been implicated in AD. The presence of each in the fluid that surrounds the brain and spinal cord (cerebrospinal fluid) has been proposed as a biomarker for the disease, especially when used in combination with each other.[133] However, to obtain cerebrospinal fluid, a **lumbar puncture** is required, which is a procedure that is unlikely to be the basis of a population-wide health check.[134]

Detecting blood-based biomarkers would be a more realistic approach, and more acceptable to the public, than obtaining cerebrospinal fluid (CSF) biomarkers by a relatively intrusive lumbar puncture. Blood-based biomarkers for diagnosing AD and detecting progression include proteins (amyloid-β and tau) and genetic factors.[131,135] A blood-based biomarker to detect amyloid-β now appears able to differentiate individuals in the early stages of AD from healthy individuals, with a sensitivity of 75% and a specificity of 88%.[108] Another recent study used an automated assay of amyloid-β and tau in the blood to obtain accurate predictions of amyloid-β in the brain; this approach could be used to lower the costs and numbers of PET scans or lumbar punctures required to diagnose the disease[135] or act as a tool to pre-screen individuals for further diagnostic tests.[136]

Development of PD is associated with the misfolding of the α-synuclein protein. Measuring blood-borne forms of the misfolded α-synuclein protein is a promising diagnostic biomarker for PD, with good accuracy (sensitivity 75%, specificity 100%).[107,109] However, further studies are needed to replicate these results. During the past 10 years, research has suggested that a combination of CSF biomarkers has the greatest diagnostic accuracy in PD.[107] CSF-based biomarkers of PD progression include those used to assess progression in AD; amyloid-β 42 is a marker for future cognitive decline, and tau is a potential marker of motor progression in PD.[107]

The potential role of **microRNAs** (a type of genetic material) to detect AD and/or PD early has also been identified; further research is being conducted into the effectiveness of using blood-based biomarkers such as these to monitor disease progression.[132,137,138]

Effective biomarkers may support the further development of effective treatments

The introduction of treatments that slow or halt progression of disease is a prerequisite for introducing a population health-check programme for neurodegenerative diseases.[104,124,139] Independently, biomarkers that identify individuals at increased risk of disease may facilitate the discovery of effective DMTs, by enabling the selection of appropriate participants for clinical trials.[135]

In AD, between 25% and 50% of neurons in the brain may be lost by the time of diagnosis;[140–142] similarly, by the time PD is diagnosed, 30–50% of dopaminergic neurons have already been lost from the substantia nigra region of the brain.[42,47] Therefore, by the point of diagnosis, the window of opportunity for treatment may have already passed.[42,47] It may be that treatments tested for these conditions have generally been unsuccessful thus far because participants in these studies have joined at a stage when their disease is too advanced to be treatable.[110–114]

If clinical trials of DMTs included individuals who were known to be at risk for the disease (identified by genetics or biomarkers), rather than only suspected to be at risk, it may be possible to assess whether some drugs in development have a disease-modifying effect, if used early enough in the disease course.[115]

Despite the current barriers to adopting a screening programme, it is important to prepare for the eventual testing and introduction of novel DMTs.[26,124,143] Once effective DMTs are licensed, it will become more feasible, and therefore more urgent, to assess the benefits and drawbacks of screening for neurodegenerative diseases.[144]

We need to prepare our healthcare systems for the future

We should not, however, wait until diagnostic tools are validated and drug treatments are available before we investigate a framework for the potential advent of health screening in an at-risk population. It is advisable to make policy recommendations in parallel with conducting research: the below can be done *now* to pave the way.

- Conduct research to identify programmes acceptable to the public and define what these may look like.
- Agree on policy and recommendations about what happens to a tested individual.
  - What support would they receive before and after a brain health check and what treatment pathways would individuals with a diagnosis follow?
- Obtain evidence to ensure that the benefit from any potential health check would outweigh the potential physical and psychological harm from the testing procedure, diagnosis and treatment.
- Prepare quality assurance measures of the programme ahead of implementation.
- Plan research that helps with identifying at-risk individuals and trial-ready populations, to inform healthcare service design.
- Develop an infrastructure to regulate the sharing of research results in an ethical, trustworthy and sensitive way, to allow research to advance appropriately.
- Create a streamlined data system to utilize electronic health record data for research, monitoring and evaluation of any future programme that aims to reduce the burden of neurodegenerative diseases.

Policymakers and system administrators should prepare now, so that they can act on the findings of the research. This way, in the future, they will have a firm evidence base to put the following strategies in place to encourage early diagnosis and interventions, with the goal of changing the patient pathway and improving outcomes.[145]

- Engagement with multiple stakeholders (such as policymakers, researchers, government representatives, decision-makers, healthcare professionals and patients themselves) to obtain a wide range of opinions on a future proposal for health checks or screening.
- Investigation into all societal aspects involved in a screening programme, including location, process and invitation protocol.
- Development of an infrastructure for health checks (or screening) and treatments that is tailored at a policy level for different countries.
- Creation of health structures that will support early detection of neurodegenerative diseases at the population level.
- Clear communication to participants about the benefits and drawbacks of risk-profiling tools and/or disease treatment, to enable each individual to make an informed decision.

Recommendations

Research is needed to achieve the aims listed below.

- Increase our understanding of diagnostic and progression markers, particularly during the presymptomatic and prodromal phases, to help to track the disease course and severity.

- Identify which tests for disease detection and diagnosis have optimal accuracy, availability and affordability.

- Ensure that data from research are made publicly available and pooled to maximize their usefulness in developing the best diagnostic tools and treatments.

- Agree on policy and recommendations about the appropriate support required for a tested individual before and after a health check.

5 Management following neurodegenerative disease diagnosis

Key points

- Ideally, individuals diagnosed with a neurodegenerative disease should be referred to a specialist team for symptom management that can improve their HRQoL.
- Acetylcholinesterase inhibitors and *N*-methyl-D-aspartate (NMDA) receptor antagonists can alleviate symptoms in patients with mild to moderate AD[53] and have shown modest benefits on cognition (compared with a placebo).[1]
- There are a range of symptomatic treatments for PD.[33,146–148]
- Disease-modulating approaches under investigation for AD and PD include antibody therapies,[124] anti-inflammatory drugs,[30,149,150] iron chelation,[151] type 2 diabetes drugs[152] and statins.[153]
- The application of big data may inform the management of neurodegenerative diseases,[154] for example, by discoveries that promote neuroprotection.[155]
- Wearable technologies may help to track an individual's disease course by monitoring their daily activities and subtle symptoms.

People with a progressive neurodegenerative disease need specialist care

People with neurodegenerative diseases should be referred to and treated by specialist multidisciplinary teams – including specialist nurses, neurologists and other healthcare professionals – who have the experience, expertise and knowledge about how and where to obtain appropriate care. In many countries, there is often a significant waiting period for accessing specialized centres and/or experts, which contributes to the delay in diagnosis.[145] In many less-developed countries, however, there are no designated specialist services.[26]

Guidelines recommend a range of **non-pharmacological therapies** and lifestyle modifications to support drug treatment for individuals diagnosed with a neurodegenerative disease.[53,156,157] An effective approach to support ongoing management may involve **tertiary prevention** strategies, which aim to improve HRQoL and to provide effective symptom management for those with severe symptoms (**Figure 9**).
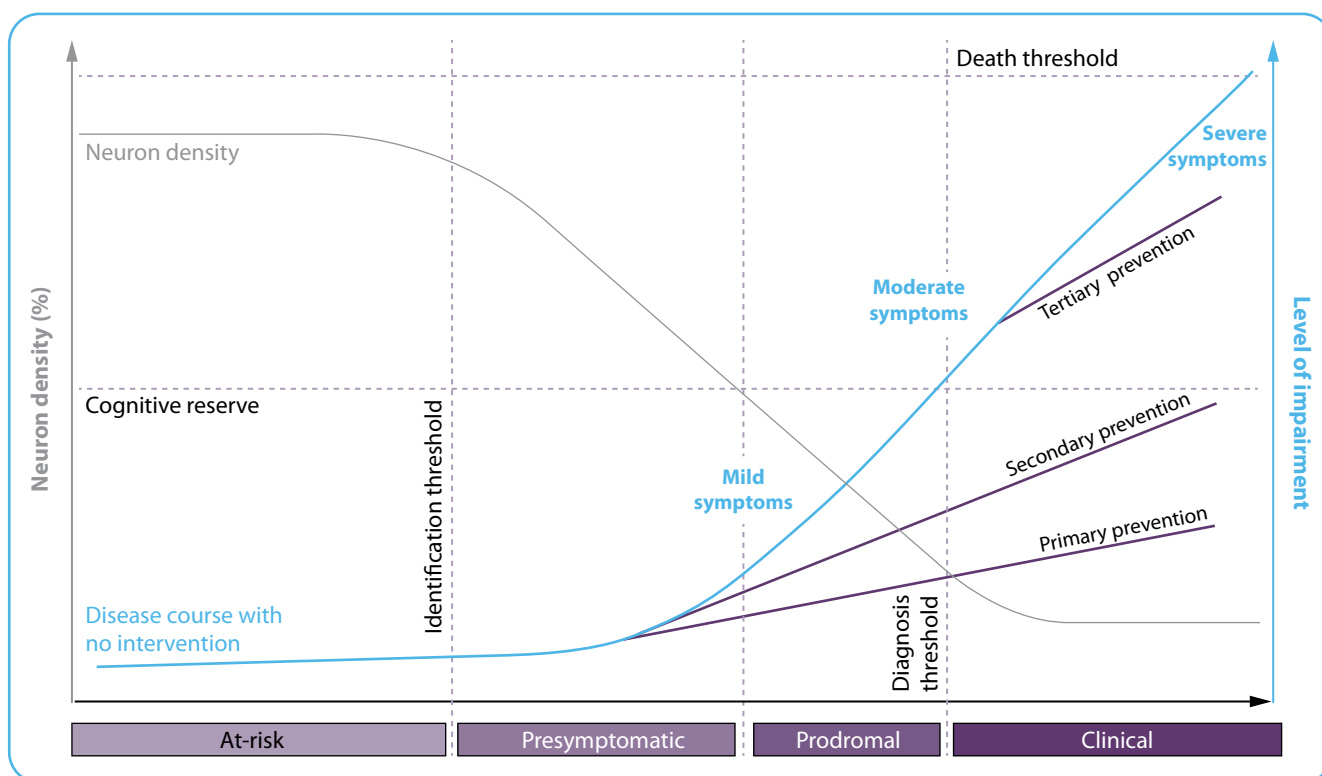
Figure 9. Alleviating symptoms with appropriate treatments can help to improve health-related quality of life; this is known as tertiary prevention.

Symptomatic treatments can help to improve health-related quality of life

Acetylcholinesterase inhibitors and *N*-methyl-D-aspartate (NMDA) receptor antagonists, which change signals between cells in the brain, are the most commonly used therapies to alleviate symptoms in patients with mild to moderate AD.[53] When used at the recommended doses, these drugs show modest, but detectable and effective benefits on cognition compared with a placebo (something that looks like the drug being tested but without any active ingredient).[1]

Well-established drug treatments available for PD alleviate movement symptoms but do not slow disease progression. Levodopa (L-dopa) is considered the most effective symptomatic therapy in PD.[33,158] Despite this, long-term use of L-dopa in high dosages is associated with involuntary movements (**dyskinesia**), which worsen as PD progresses and L-dopa is taken more frequently,[146,159] and motor fluctuations that drastically affect HRQoL.[160] Dopamine agonists (drugs that mimic the chemical dopamine in the brain) have demonstrated a mild to moderate improvement of PD movement symptoms.[56] Dopamine agonists are associated with several adverse events, including hallucinations and impulse control disorders (e.g. gambling or shopping addictions). Catechol-*O*-methyltransferase (COMT) inhibitors[147] and adamantanes[148] are sometimes beneficial in patients with fluctuating disease and are an alternative treatment. In early or mild PD, therapy may be initiated with a monoamine oxidase type B (MAO-B) inhibitor. These drugs are associated with fewer side effects than dopamine agonists but are less effective.[139]

The search continues for drugs that will modify progression in neurodegenerative diseases

Many of the drugs available for symptomatic treatment of AD and PD are associated with side effects after long-term use; further research is needed to identify alternatives that will modify disease progression. This is challenging, given that many studies of DMTs for AD and PD have failed.[110–114,160]

More recent disease-modulating approaches under investigation for AD and PD include antibody therapies,[124] anti-inflammatory drugs,[30,149,150] iron chelation,[151] type 2 diabetes drugs[152] and statins.[153] Clinical trials[151] and animal models[149] show that these types of treatment might be used for AD and PD in future.

Big data studies, such as those that seek to identify disease-associated genetic variants, may inform the treatment and management of neurodegenerative diseases.[154] For example, genetic studies have identified a mutation (called *LRRK2* p.G2019S) that is associated with the inheritance of PD;[161,162] 0.3% of people with predominantly European ancestry carry this mutation, which increases their lifetime risk of PD to about 25%.[161,163–168] A targeted approach that blocks or reverses the effects of this mutation may be useful to slow the pathological processes of PD.[161,162]

As technology advances, opportunities to promote **neuroprotection** (protecting brain health) will increase, assisted by the application of big data to subtyping patients and discovery of biomarkers.[155] AD and PD are conditions that can vary greatly among patients; therefore, one treatment might not help all patients. A personalized approach is therefore warranted to address the specific course of the individual's condition.

Wearable technologies can assist personalized treatment approaches

Measures based on the 'average' patient are commonly used in testing for early signs of neurodegeneration. Although useful, they make no allowance for the individuals who are '**high functioning**' (apparently coping well) and who potentially have substantial levels of cognitive reserve (for AD) or **motor reserve** (for PD). Therefore, a more personalized approach may be needed. Whenever possible, clinicians should compare an individual's current performance or symptoms with their abilities before the onset of disease, or measure their change in performance over time.[169] This could be done by using wearable technology to track an individual's disease course and monitor their brain health, as recommended earlier in this report.

The advent of wearable technology and mobile applications may allow better monitoring of daily activities and subtle symptoms of neurodegenerative diseases than using standard scales, such as the Unified Parkinson's Disease Rating Scale[170] or the Mini Mental State Examination (MMSE).[171] This brings several benefits.

- Wearable technology and mobile applications allow more frequent measurement than using the Unified Parkinson's Disease Rating Scale or the MMSE at medical appointments.
- Wearable technology allows the day-to-day variability to be smoothed out and to separate signal from 'noise' in the data.
- The data collected can be compared with the individual's previous data, rather than with an average population statistic.
- State-of-the-art machine learning algorithms (i.e. artificial intelligence) can be trained to give a score that is based on objectively measured variables, rather than on a physician's best judgement.[172]

Recommendations

- Provide access to available and effective treatments in a timely manner.

- Refer anyone with a suspected neurodegenerative disease to specialist, multidisciplinary services, if they are available.
- Provide follow-up to individuals, in the form of multidisciplinary services, to provide ongoing, widely accessible holistic care, including prevention information, treatment options and support.

- Research is needed to develop, validate and approve tests, tools and apps for monitoring brain health at an individual level, by working in collaboration with regulatory authorities and stakeholder groups, including researchers, clinicians and funding bodies.

6 Actions to avert a future crisis

Neurodegenerative diseases pose an enormous socioeconomic and individual burden, and this will continue to grow. What should we do to avert a crisis?

Now is the time for us all to act

- **Individuals** should start to look after their brain health now and to change their behaviour to improve their chances of healthy ageing.
- **Healthcare professionals** should educate the public about safeguarding their brain health.
- **Public authorities** should provide general health recommendations that include the benefits for brain health.
- **Administrators of healthcare systems** should ensure timely access to available interventions and services.
- **Budget holders** in relevant organizations should plan now to conduct research that will inform healthcare service design and delivery, so as to optimize disease diagnosis and management of people with or at risk of neurodegenerative diseases.
- **Researchers** should investigate the best ways for healthcare professionals to tell people the results of risk assessments or diagnoses in a timely and sensitive manner.
- **Researchers** should investigate further the most appropriate and effective biomarkers and treatments.

We can achieve more together than we can separately

All interested stakeholders need to work together for the common goal of improved healthcare for neurodegenerative diseases. The collaboration will involve:

- primary care physicians
- neurologists
- psychiatrists
- older person specialists (geriatricians)
- specialist nurses
- physiotherapists, occupational health therapists, speech and language therapists, dieticians
- pharmacists
- public health professionals
- caregivers
- patients and patient advocates
- policymakers
- researchers
- funding bodies.

The need for new policies to cover neurodegenerative diseases and more investment is clear.[143] Research into better methods of disease prevention and/or management would support improved HRQoL for those diagnosed with a neurodegenerative disease. Secondary prevention strategies to limit the impact of these diseases will only be possible once research has identified effective biomarkers and DMTs. When that moment comes, we need to be prepared. We should start to plan now, by gathering the evidence that is needed to make wise and transformative decisions – even if the implications are challenging, and potentially even disruptive.

Until then, primary prevention strategies offer the best opportunity to limit the harmful impact of these diseases on brain health. **What's good for your heart is generally good for your brain**. Let's continue to communicate this for as long as we need to!

Recommendations

- Provide a supportive environment, including national guidance and legislation when appropriate, that empowers individuals to make important lifestyle changes.

- Provide follow-up to individuals, in the form of multidisciplinary services, to provide ongoing, widely accessible holistic care, including prevention information, treatment options and support.

- Ensure that research results are provided, in a sensitive manner, to study participants, and that appropriate support is given.

- Ensure that data from research are made publicly available and pooled to maximize their usefulness in developing the best diagnostic tools and treatments.

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Glossary

Agnosia	Failure to recognize people or objects
Allele	A naturally occurring variant of an individual's genetic information, which may or may not associate with a disease
Alzheimer's disease	The most common form of dementia (a condition characterized by cognitive impairment that affects activities of daily living)
Amyloid-β	A protein that occurs in the brain and builds up to form plaques that are a sign of Alzheimer's disease
Aphasia	Impairment of language including the ability to comprehend or produce speech
ApoE	Apolipoprotein E, a protein that is involved in the development of Alzheimer's disease and is encoded by the gene *ApoE*
Apraxia	Inability to perform some movements but not owing to weakness or lack of understanding
At risk	Description of an individual who does not have a disease but may have been exposed to initiating events
Autonomic dysfunction	When the part of the nervous system that controls involuntary regulation (e.g. of the heart or pupils) does not function correctly
Big data	A term that refers to large data sets, often of many measurements from large populations
Biological risk factor	A risk factor that is modifiable but is related to a person's biology rather than lifestyle
Biomarker	A physical, chemical or imaging marker that reflects a naturally occurring molecule, gene or characteristic by which a disease can be identified
Bradykinesia	Slow voluntary movement
Brain atrophy	Loss of brain volume, implying loss of brain tissue, which may be localized in one area or affect the whole brain
Cardiovascular disease	Disease that affects the heart and circulatory system
Central nervous system	The brain and spinal cord
Clinical phase	When the threshold for diagnosis has been met; disease may or may not be diagnosed
Cognitive domain	A set of related functions that the brain performs and that relate to a specific region (or regions) of the brain
Cognitive impairment	A reduction of mental abilities or processes
Cognitive reserve	The brain's ability to adapt and resist disease resulting from loss of cells and changes to the brain and nerves
Cognitive training	A programme of regular mental activities to maintain or improve abilities such as memory

Direct healthcare cost	A cost directly paid by healthcare providers, such as for medication or for staying in a hospital for a procedure
Disease-modifying therapy	Treatment or intervention that affects the underlying processes of a disease and slows its course
DNA	Deoxyribonucleic acid, an individual's genetic information
Dyskinesia	Involuntary movements
Equitable access	A situation in which everyone has fair opportunity to access healthcare, to attain their full health potential
Executive function	Ability to organize, plan and conduct a set of plans in an efficient manner; one of the cognitive domains (see above)
Genetic factor	A factor (often inherited) that is encoded by DNA
Health-related quality of life	The impact of someone's health on their quality of life, which describes someone's physical, mental, emotional and social functioning
High functioning	A term used to describe individuals with neurodegenerative disease who appear to be coping well owing to the brain's ability to adapt (cognitive reserve)
Hypertension	High blood pressure
Hypokinesia	Small-sized movements
Hypomimia	Motionless face or a lack of facial expression
Idiopathic	Arising spontaneously or from an unknown cause
Indirect healthcare cost	A cost borne by anyone except healthcare providers (e.g. the cost to society or to a family or informal carers)
Lewy bodies	Abnormal aggregates of alpha-synuclein protein that develop in nerve cells. They are a sign of Parkinson's disease or Lewy body dementia
Lumbar puncture	A procedure in which a sample of the fluid from the spine (cerebrospinal fluid) is taken
Micrographia	Small handwriting
MicroRNA	A small piece of ribonucleic acid, which can be used as a biomarker
Motor control	Regulation of movement by the brain
Motor reserve	The brain's ability to adapt and resist disease resulting from loss of cells and changes to the brain and nerves that would otherwise affect the ability to move
Neurodegeneration	Deterioration in structure and/or loss of function of nerve cells
Neurodegenerative diseases	A varied group of diseases that are all characterized by progressive deterioration of the structure and function of the nervous system
Neuron	A specialized cell in the brain
Neuroprotective	Beneficial to the health of the nervous system
Non-pharmacological therapy	Therapy that does not involve drugs

Overtreatment	Treating for a disease that is not present, or treating when there is no benefit to doing so
Parkinson's disease	A progressive disease of the nervous system with motor, non-motor and cognitive manifestations
Pathological	Caused by a disease
Postural reflexes	The control of balance, posture and movement
Presymptomatic phase	A neurodegenerative process has started but there are no obvious symptoms
Primary prevention	Addressing and managing risk factors before the onset of disease
Prodromal phase	Symptoms have started to develop, but are not enough for diagnosis
Secondary prevention	Attempted reduction of disease progression or further events by early identification and intervention
Sensitivity	A measure of accuracy that assesses the degree to which a test detects a disease only when it is truly present
Specificity	A measure of accuracy that assesses the degree to which a test correctly identifies people without the disease
Substantia nigra	A structure in the upper part of the brainstem that is most affected in Parkinson's disease
Tau	A protein that is found in nerve cells and builds up to form tangles that are a sign of Alzheimer's disease
Tertiary prevention	Improved management of a disease to limit symptom severity or to prevent further advancement

Abbreviations

AD	Alzheimer's disease
ApoE	Apolipoprotein E
COMT	Catechol-*O*-methyltransferase
CVD	Cardiovascular disease
DMT	Disease-modifying therapy
DNA	Deoxyribonucleic acid
HRQoL	Health-related quality of life
L-dopa	Levodopa
MAO-B	Monoamine oxidase type B
MDS	The International Parkinson and Movement Disorder Society
NICE	National Institute for Health and Care Excellence
MRI	Magnetic resonance imaging
NMDA	*N*-methyl-D-aspartate
PD	Parkinson's disease
WHO	World Health Organization