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Report C

Advances in neurodegenerative diseases

The situation in Spain

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Production process

Reports C are brief documents on subjects chosen by the Bureau of the Congress of Deputies that contextualise and summarise the available scientific evidence on the analysed subject. They also inform about areas of agreement, disagreement, unknowns, and ongoing discussions. The preparation process for these reports is based on an exhaustive bibliographical review, complemented with interviews of experts in the field who subsequently conduct two review rounds of the text. Oficina C conducts this process in collaboration with the management team of the Spanish Parliament's Lower House Documentation, Library and Archive service.

To produce this report the C Office referenced 273 documents and consulted 21 experts in the subject. Of this multi-disciplinary group, 33.3% come from the field of social sciences (psychology, economics), 61.9% are from life sciences (biochemistry, medicine and nursing) and 4.8% are from engineering. 90.5% work in Spanish institutions or centres, whereas 9.5 % have affiliations abroad.

Oficina C is responsible for publication of this report.

RSV has received personal payments in the last 3 years for participation on advisory boards for Lilly, Novo-Nordisk, Grifols-Araclon, Aviadobio, Prevail, Wave Pharmaceuticals and Pfizer on products under research that are not currently approved or on the market.
MSC has undertaken consultation and advisory roles for Roche Diagnostics International Ltd and Grifols S.L. He was awarded a project funded by Roche Diagnostics International Ltd. All of the fees were aid to his institution (BBRC). Through his institution he has received support in kind for research for the following companies: ADx Neurosciences, Roche Diagnostics International Ltd, Avid Radiopharmaceuticals, Inc. Eli Lilly and Janssen Research & Development. He has participated in symposia sponsored by Almirall, Eli Lilly, Novo Nordisk, Roche Diagnostics and Roche Farma.

Summary C

The report in 5 minutes

Relevance

Neurodegenerative diseases involve the nervous system, are incapacitating and, to date, incurable. Between 1 and 1.5 million people are affected by these diseases, which entail a high personal, social and financial cost. In addition, the risk of suffering Alzheimer's, Parkinson's or amyotrophic lateral sclerosis (ALS) multiply with age, which means that increased life expectancy implies a very significant increase in cases. Conversely, other diseases included in this report such as Huntington's or multiple sclerosis present at an earlier age. Their earlier onset results in the difficulties typical of these life stages, such as a loss of productivity, extends the duration of the disease, and multiplies possibilities of being discriminated against and stigmatised.

There is still no European plan for these diseases, the Spanish National Health System's Neurodegenerative Diseases Strategy dates from 2016, and the National Plan on Alzheimer's and other dementias finishes this year. Experts have voiced their concern about the urgent need to plan public, social and healthcare policies that guarantee the protection of this most vulnerable sector of the population.

This report provides a summary of current knowledge about the most prevalent neurodegenerative diseases, and includes information about their causes, risk factors, current state of diagnosis and treatments, in addition to describing adaptations of social services and the healthcare system necessary to face the challenge.

Neurodegenerative diseases

Except for multiple sclerosis, which is related to inflammatory processes mediated by the immune system, it is believed that neurodegenerative diseases have their origin in dysfunctional proteins that accumulate over many years, causing diverse problems of toxicity and death in brain and spinal cord neurons.

Neural cell death brings a progressive loss of cognitive and motor functions. Each disease follows a different course because each affects different types of neurons. But in all of these diseases, mild onset symptoms worsen as neural deterioration progresses. In some instances, like Alzheimer's and the majority of Parkinson's cases, cognitive deterioration manifests in the final phase of the disease, presenting a set of symptoms known as dementia.

With the exception of Huntington's and cases of familial origin for which the causes are exclusively genetic, in most cases the risk of developing these diseases is influenced by the interaction of genetic, environmental and lifestyle factors over time, although we still do not know all of the aspects involved.

Focal point

As neurodegenerative diseases take years to evolve, changing some lifestyle habits or reducing the risk factors at given stages of life may reduce the risk of developing this kind of disease. It is estimated that over a third of all dementia cases could be preventable.

When symptoms appear, these diseases are not usually detected at an early stage. Although the diagnosis can be a serious setback for the patient and their family, there are also many medical and social advantages, if the necessary support is available from the start to manage the negative feelings that arise and obtain resources to cope with the disease.

Although there are no specific techniques for all neurodegenerative diseases, Alzheimer's can be diagnosed with lumbar puncture (spinal tap) or positron emission tomography whereas Huntington's is confirmed with genetic testing. Researchers have recently developed a highly effective technique to detect Parkinson's during its early stages using samples of cerebrospinal fluid. In the future, detection of Alzheimer's and other diseases could be based on a simple blood test.

There are highly effective treatments that hold back multiple sclerosis, stopping inflammation before the onset of neural damage. The most incapacitating symptoms of Parkinson's disease can be controlled using pharmacological therapies (levodopa and others), and surgical (deep brain stimulation) or non-invasive treatments such as high-intensity focused ultrasound. However, effective treatments are still necessary for Huntington's disease, ALS, Alzheimer's and other causes of dementia. To achieve this aim, we need to improve the transfer of outcomes in research into these diseases to clinical practice.

Although new drugs that can hold back the progression of Alzheimer's for some months are a great step forward, Europe is debating their benefit risk ratio.

Some experts also question the safety and effectiveness of certain psychopharmaceuticals for people with dementia.

Imagen FOTCIENCIA. Pensando en Plata © Raquel Martín Baquero

On the other hand, cognitive stimulation therapies have the support of scientific evidence and are cost-effective, although there is not equal access to them throughout Spain. Other therapies such as physiotherapy, speech and language therapy, occupational therapy or early access to palliative care can improve the quality of life of people with neurodegenerative diseases, although access to these services is not the same in each autonomous community.

On the horizon

To improve equality, medical professionals highlight the need for a distribution of resources to achieve sufficient regional coverage, and the advisability of establishing robust inter-hospital referral systems. They also suggest that planning would be made easier with patient registries and emphasise the importance of training for primary care professionals in these diseases, in addition to increasing the number of specialist personnel.

On the other hand, social costs are higher than those of medical care and this increases with the severity and length of the disease. It is families that bear most of the burden, which highlights the need to develop a system of sustainable, professional specialist care.

The current stance is to foster the social inclusion of patients, allowing them to remain at home for as long as possible with the support of technologies and carers. However, when people with dementia cannot live at home anymore, alternatives exist, such as unidades de convivencia ("coexistence units") and other options already firmly established in other European countries. Associations representing ALS and Huntington's call for the creation of care centres specialised in these diseases.

The comprehensive care requires greater coordination between the social and healthcare sectors to improve the inclusion and well-being of patients and their families

Advances in neurodegenerative diseases

Introduction

The most notably prevalent neurodegenerative diseases are Alzheimer's and other disorders that cause cognitive deterioration and dementia. These are followed by Parkinson's, multiple sclerosis (of autoimmune origin) amyotrophic lateral sclerosis (ALS) and Huntington's disease.

All of these diseases cause neural cell death, with consequent cognitive and motor disability. They reduce the life expectancy of patients and are, to date, incurable.

The term neurodegenerative diseases covers over 600 different disorders; however, among the most notable due to their prevalence and severity, are Alzheimer's and other causes of dementia, Parkinson's, multiple sclerosis, amyotrophic lateral sclerosis (ALS), and Huntington's[1] (**Key Point 1**). The risk of suffering one of these diseases rises exponentially with age, which is why increased life expectancy will bring a rise in the number of cases. Thus, the worldwide population with dementia is expected to have practically tripled by the year 2050, whereas projections for Spain estimate an 83% increase, which will mean 1.5 million cases[2]. Moreover, for reasons that are still unknown, Parkinson's is probably the neurodegenerative disease whose incidence has most increased in recent decades[3] and its figures are expected to duplicate by 2030[4]. It is calculated that the number of ALS patients will have risen 69% worldwide by 2040[5].

What all of these diseases have in common is that they are chronic, and their progression brings a gradual dysfunction of the nervous system[1]. Brain and spinal cord neurons undergo changes that cause their abnormal functioning and, ultimately, cell death[6]. Each disease is characterised by initially affecting different types of neurons, which causes different symptoms[1]. Although their onset occurs in a specific region, as time passes, they gradually spread throughout the whole nervous system[7]. During early phases, the symptoms are usually mild and go unnoticed. However, as neural deterioration progresses, they become more severe, generating disability[6]. Currently, these diseases are incurable and reduce the life expectancy of the people who have them[6]. Indeed, they are a source of concern for most of the Spanish population, who consider them to be a serious or very serious health problem[8]. These disorders were also the most common cause for people to request and undergo euthanasia (117 deaths) in 2022. Within this group, 41.9% had ALS, 11.1% multiple sclerosis and 8.5% Parkinson's[9].

In this context, experts have voiced the urgent need to plan public policies that adapt the health and social welfare systems to this silent epidemic[2]. However, to date there is no European plan covering this area. In Spain, the National Health System's Neurodegenerative Diseases Strategy, which dates from 2016, is currently under review[1]. Experts note that the National Plan on Alzheimer's and other dementias, which finishes this year[10], lacks both funding and impact.

· Prevalence: the total number of people within a population who have or had a disease.
· Incidence: the number of new cases of a disease.

Although the definition of neurodegenerative diseases refers to disorders involving the central nervous system, other disorders cause cell death in the peripheral nervous system, muscles or sensory organs. Another type are transmissible neurodegenerative diseases caused by prions.

Key point 1. Other neurodegenerative diseases

Although the classic definition of neurodegenerative diseases includes those that involve the central nervous system, in other cases, degeneration affects different cell types, such as the peripheral nervous system (this is the case of neuropathies of the Charcot-Marie-Tooth disease group of conditions or familial amyloid polyneuropathy) the neuromuscular junction (myasthenia gravis) myocytes (muscular dystrophies such as Duchenne muscular dystrophy, limb-girdle muscular dystrophies, Steinert disease or congenital myopathies)[11]. These are rare conditions, but there are around 60,000 people in Spain[12] who have them. These diseases are hereditary and affect children and young people the most[13–17].

There are also disorders where degeneration may occur in sensory organs like eyes or ears. Some examples are retinitis pigmentosa, diabetic retinopathy or age-related macular degeneration, which is the main cause of geriatric blindness worldwide and affects some 700,000 people in Spain[18,19].

Another type of neurodegenerative disorders are human transmissible spongiform encephalopathies, like Creutzfeldt–Jakob disease[20]. They are caused by infectious agents called prions and, although uncommon, are categorised as reportable and are always fatal[20]. Animals that may be their focus of transmission are monitored by the Spanish Ministry of Agriculture, Fisheries and Food[21].

The most prevalent neurodegenerative diseases

The risk of having a neurodegenerative disease increases with age.

The symptoms of multiple sclerosis and Huntington's disease, which is hereditary, first appear in younger people.

Description of the diseases

Alzheimer's disease and other dementias

Figures for Spain in 2019 estimated between 734,000 and 937,000 cases of dementia[2]. This is the most frequent neurodegenerative disorder, affects more women than men[2] and its incidence exponentially increases from 65-70 years of age, although it may appear in younger people[1].

The term dementia is used to refer to a group of symptoms that include difficulties with memory or language, and the loss of problem-solving skills to an extent that prevents the patient having an autonomous or independent life[22].

Diseases that produce the cognitive deterioration and behavioural symptoms that lead to dementia in their final stages include Alzheimer's, which is the most frequent cause; however, there are other related disorders, like the degeneration of frontal and temporal lobes (that initially produces behavioural or language symptoms) or Lewy body dementia (that affects the frontal cortex causing cognitive, behavioural and motor symptoms)[22].

Alzheimer's is responsible for 60-80% of dementia cases[1,22]. It initially presents as everyday, persistent forgetfulness of recently learned things, in addition to subtle problems related to language or thought[22]. Progression may occur at different speeds[23] until reaching a stage of dementia that causes increasing difficulties for independent living, may result in confusion, agitation, changes in personality and character, difficulties in recognising family members, incontinence and, during the most severe stages, difficulties in moving or swallowing and the need for continuous care[22].

· Central nervous system: the part of the nervous system composed of the brain and spinal cord.
· Prions: a misfolded infectious protein that induces others of its type to adopt abnormal structures and extend the infection.

Parkinson's disease

Parkinson's is the second most common neurodegenerative disorder, with a significant number of undetected cases[24]; estimations place the number of patients in Spain between 150,000 and 300,000[25–27]. There are double the number of cases in men, who also experience an earlier onset, than in women[1,3,26]. Although prevalence increases from the age of 70[25], 25% of patients are younger than 65, and 5-10% are under the age of 50[3].

There are various types of Parkinson's, and its presentations are heterogeneous but, in general, it is characterised by a combination of resting tremor, slowness of movement, reduced facial expressions and muscle rigidity that are initially limited to one part of the body[29]. Among the first symptoms, particularly in more elderly patients, there may be other disorders, such as constipation, loss of smell, restless sleep, apathy or depression[30]. Although the speed at which the disease develops varies in each person, and treatments can improve the symptoms, the progression of this disorder over decades make it a chronic process affecting multiple systems[31]. It can result in speech problems, postural instability and gait dysfunctions, sleep disorders and ultimately cognitive disorders and dementia, with other complications related to the patient's ageing process itself[32].

Amyotrophic lateral sclerosis (ALS)

Amyotrophic lateral sclerosis (ALS) is the third most common of this type of disease, after dementias and Parkinson's[1], with 1.71-1.89 cases per 100,000 people in Europe and North America[33] and a prevalence in Spain of 6.1 cases per 100,000 inhabitants[34]. Calculations for Spain estimate that 900 new cases are diagnosed each year[35]. Given the low life expectancy, figures for ALS patients are not as high as those for other diseases, but it is calculated that between 4,000 and 4,500 people live with this disease[35]. Although there are cases among young people, on average it presents at 65 years[34] and more frequently in men[33,36]. The disease is characterised by progressive muscular weakness that can result in paralysis, affecting limbs, swallowing, the ability to cough, communication and breathing, although the senses and eye muscles function normally[37].

It can also cause cognitive deterioration and dementia in some patients[38]. Most patients die between 3 to 5 years after the onset of symptoms due to respiratory failure, although 10-20% of patients survive more than 10 years[39].

Huntington's disease

Another of the most prevalent serious neurodegenerative diseases is Huntington's. In Canada and other populations of European ancestry its prevalence is around 12 people per 100,000[40–42]. Although there are no studies for Spain, it is estimated that over 4,000 people are affected and 15,000 people are at risk of having inherited the mutation from a parent[43,44]. Onset usually occurs between 30 and 50 years of age, with unspecific, heterogeneous symptoms such as feeling clumsier or being more irritable[45]. Progression is inexorable[46], with a development over time of motor, cognitive and psychiatric symptoms, involuntary or imprecise movements (chorea), problems with planning and concentration, and behavioural changes that can result in frustration, apathy, depression and rage[47]. More care is required at advanced stages and new symptoms may appear, such as rigidity, difficulty swallowing, weight loss, difficulty in communication and dementia[45].

Multiple sclerosis

Although multiple sclerosis has its origin in the dysregulation of some immune system cell types, it also induces neurodegeneration, which is the reason it is included in the Neurodegenerative Diseases Strategy and in this report[1].

The average age of onset for this disease is 32 years and it affects twice as many women as men[48,49]. In Spain, over 58,000 people have the disease, with a prevalence of 123 patients per 100,000 inhabitants[49]. It is known as the disease of a thousand faces due to its heterogeneity of symptoms and progress, although some of the most representative manifestations are problems of sight, loss of strength in limbs or half of the body, pins and needles, difficulty walking, dizziness, lack of coordination, problems controlling sphincters and fatigue[50].

Pathology: what happens to the neurons of diseased people.

With the exception of multiple sclerosis, the neurodegenerative diseases in this report originate in dysfunctional proteins that accumulate, causing diverse problems of toxicity and death in neurons of the nervous system.

It is often complicated to understand which dysfunctions influence a disease's mechanism, and which arise first.

In all of these disorders, different dysfunctions occur at cellular level that are still the subject of research (**see Key point 2**).

Huntington's disease

Has its origin in the mutation of a single gene, huntingtin[51]. If a person inherits a copy of the mutated gene from one of their parents, the disease is always triggered. The mutation generates a pathological protein that is longer than normal, where a single amino acid is repeated a minimum 36 times[46]. This mutant protein cannot achieve the usual structure, and aggregates, which causes the death of striatum neurons, and later atrophies other regions of the brain[46]. The children of parents with this disorder have a 50% probability of developing the disease, regardless of their sex[40].

Parkinson's disease

One of the proteins involved is alpha-synuclein (**see Key point 2**), which forms aggregates alongside other proteins (Lewy bodies) causing toxicity and cell death, particularly in the substantia nigra neurons that produce dopamine[28]. Low levels of this neurotransmitter can cause problems in synaptic transmission and a disconnection between the brain and other parts of the body, which causes loss of movement control and other difficulties. The spread of this disease to other regions of the brain is associated with other symptoms, including dementia[22,52].

Alzheimer's disease

To date, the most commonly accepted mechanism explaining **Alzheimer's** is the amyloid hypothesis[53], which postulates the disease is triggered by aggregates of beta-amyloid protein[54] (**see Key point 2**). Outside the neurons, aggregates disrupt the neural connections, forming damaged structures of a larger size, such as fibrils and ultimately, plaques[53]. In an attempt to clean the plaques and remains of dead neurons, immune cells congregate around the affected neurons, liberating inflammatory substances that may contribute to loss of synapsis[53] and establishing chronic inflammation[22]. A later event is the tangle aggregation of another misfolded protein, Tau, inside neurons[53]. Although neuronal loss of Alzheimer's first affects regions involved in memory, like the hippocampus, it goes on to affect the neocortex, which is responsible for language, reasoning and social behaviour. Later, the damage spreads to other areas, causing the brain to shrink[55].

Amyotrophic lateral sclerosis

The causes of ALS are still being researched. To date, scientists have observed the aggregation of different proteins, among which are TDP-43 and SOD1, which can spread damage from one cell to another[7,56]. These mainly damage motor neurons, but also affect other nervous system cells[7].

· Striatum: The part of the brain that regulates, among others, voluntary movements and coordination of some aspects of behaviour.
· Dopamine: Key neurotransmitter in motor function.
· Synapsis: Neural structure that allows transmission of the nerve signal between neurons.

Multiple sclerosis

This is a disease of the central nervous system mediated by aberrant activation of the immune system: white blood cells enter the brain, inducing an inflammatory cascade that results in the loss of myelin and damage, with neural cell death that increases over the years[57]. The result is scarring (sclerotic plaques) and problems in transmitting nerve impulses[58].

The connection with ageing, the processes that lead to neurodegeneration, or the role of the microbiota are some of the research topics common to all neurodegenerative diseases.

Key point 2. Cutting edge research

Ageing represents the biggest risk of the factors common to all neurodegenerative diseases. Researchers are attempting to make it possible to modify this factor, which has so far been inexorable, by means of cellular rejuvenation[31,59,60]. Along these lines, investigators are currently exploring the possibility of biochemically reprogramming neurons to erase the marks of the past and rejuvenate them[61].

In addition, neurodegeneration follows convergent paths in different diseases and such overlaps have also attracted scientific interest[62].

On the other hand, Spain's State Reference Centres undertake research into health and social welfare, knowledge and information management, preparation of guidelines, dissemination of good practices and professional training nationally[63].

For subjects specific to each disease, part of the Alzheimer's research community proposes alternatives to the amyloid hypothesis[54]. As an extension of the amyloid hypothesis, some scientists indicate that tau deposits cause more damage than the amyloid itself and highlight the advisability of combating both[54]. Others suggest focussing on the inflammation and the processes that induce neural death[64], which are more active at later stages of the disease. Meanwhile, a minority theory points to microorganisms as trigger agents of amyloid accumulation: this postulates that the amyloid has antimicrobial functions and would aggregate to trap virus or bacteria[54].

Other scientists defend the stance that amyloid plaques and tau tangles are harmful and accelerate the disease, but rather than being the cause are one of the consequences of a pathological cascade that begins with an imbalance in cellular metabolism of cholesterol[65].

In Parkinson's, some researchers also question whether aggregation of the alpha-synuclein protein is the cause or consequence of neurodegeneration[66]. Another major subject is research into inflammation in the process[66], and approaches with gene therapy to introduce a growth factor into the brain that can restore neural connectivity[31].

In addition to a vaccine against the Epstein Barr virus, research in the field of multiple sclerosis is looking into how to achieve the remyelination of damaged areas, and the role of intestinal microbiota[67-70], a topic that is also of interest in Parkinson's and Alzheimer's[71-73].

As Huntington's disease is caused by defects in a single gene, one of the main strategies against this disease is aimed at counteracting the expression of the mutant gene with short chains of nucleotides that specifically block production of the protein[74]. Various therapies are already the subject of clinical trials, one of the most notable involves small molecules capable of crossing the blood-brain barrier; these molecules process the gene incorrectly before translation to protein, causing its degradation[74].

In ALS, the genetics of Spanish patients are being extensively characterised[75,76] and antibodies against abnormal mutant proteins are being tested. Likewise, work is underway in the development of strategies based on gene therapy for the most frequent mutations[33]. Another avenue of research is the role of skeletal muscle in the onset of this disease, as damage could be a primary event involved in the degeneration of motor neurons[77].

· Myelin: The insulating layer (sheath) that protects the extensions of nerve cells enabling the quick transmission of nerve impulses.

Causes and risk factors

Most cases are classified as sporadic, with causes derived from four relevant factors: genetics, environment, lifestyle and their interaction over time. Conversely, in a small percentage of cases, classified as familial origin, specific genetic variants are responsible for the disease.

In most cases, which are sporadic, the causes of neurodegenerative disease are a cocktail of four important factors: genetics, environment, lifestyle and the interaction of these factors over time[3,33,78]. Whereas the genetic component is to a large extent stable, environment and lifestyle are continuously changing. Due to this and to the difficulty in accessing the brain, it is currently difficult to determine the potentially causal or protective environmental factors that had an effect at a given time, or which accumulated over the years, interacting with each person's genetics[3]. The following sections review the current state of knowledge about the role of these variables in the risk of developing neurodegenerative diseases.

Although most cases are sporadic, for some diseases, such as Alzheimer's, Parkinson's or ALS, specific genetic variants are responsible for a small percentage of cases, classified as familial origin, which affect younger people.

Genetic factors

Except for Huntington's, caused by mutations in a single gene, the genetic causes of neurodegenerative diseases are complex, and not fully understood.

For sporadic cases, genetics only represents a small percentage of the risk of developing the disease.

Except for Huntington's, which is caused by mutations in a single gene, the genetic causes of neurodegenerative diseases are complex, and not fully understood[51].

Alzheimer's disease

Currently, there are 75 genes known to influence the risk of suffering sporadic Alzheimer's and other related dementias, although they do not necessarily mean that the disease will develop[78]. Among the variants, the most important is in gene *APOE E4*, which is not expressed in neurons but in other cells of the nervous system; it multiplies the risk of developing the disease between 3 and 12 times[22,79,80].

Familial Alzheimer's is passed from parents to children, generates memory problems, earlier onset dementia[81,82] and has a different genetic origin that usually directly affects nerve cells[83]. Although less than 1% of patients suffer familial Alzheimer's, one of the largest affected populations is in Colombia[81]. Studies of this population helped find two protective genetic combinations that delay the onset of the disease up to 20 years in people who carry the abnormal mutations[82,84]. Research hopes to find new genetic variants that confer resilience to cognitive decline and dementia, developing treatments that also enable transfer of this protection to people affected by sporadic Alzheimer's[85].

Parkinson's disease

There are 90 known genetic variants that only explain 16-36% of the risk of suffering sporadic Parkinson's, which gives a clear indication of the knowledge gap about the causes of this disease[86]. On the other hand, mutations in a handful of genes are directly responsible for familial Parkinson's, which only account for 3-5% of all cases[3,87-90]. These hereditary mutations mean an early onset of symptoms, typically among people under the age of 40 years[3].

Amyotrophic lateral sclerosis

It is believed that cases of familial ALS only account for 10-20% of the total, so the majority of patients have no family history of this disease[33]. We know that there are more than 40 genes that can induce familial ALS, and that they also play a role as risk factors in sporadic forms of this disease[33].

Multiple sclerosis

The weight of genetics in the risk of developing multiple sclerosis is 25%[91]. Currently, there are 236 variants identified as increasing the risk of suffering multiple sclerosis. Although none of them is sufficient, or necessary, to cause the disease, all of them contribute to the risk of developing it[92]. In addition, a new genetic variant has been identified that is associated with the most severe forms of the disease[93].

Environmental factors

Certain environmental and lifestyle factors are associated with variations in the risk of developing neurodegenerative diseases.

Timely intervention in these factors could lead to fewer cases.

Although evaluating the weight of environmental factors and their interaction with the genetics of each patient is complicated and still requires further study[3], certain environmental and lifestyle factors are associated with a reduced risk of developing these diseases. Conversely, the main non-modifiable risk factor is age, although neurodegenerative diseases are not a normal consequence of ageing [60].

Alzheimer's disease and other dementias

Lesions characteristic of Alzheimer's begin to develop in the brain some 20 years before the onset of symptoms[94], which offers a window of opportunity to influence the course of the disease and delay its onset[22].

An international commission of experts in dementia prevention, intervention and care identified 12 potential modifiable factors to which 40% of risk is attributable[22]. The ones that have the largest body of scientific evidence are (in parenthesis, percentage of reduction in the prevalence of dementia if this factor is eliminated): lower educational attainment at early stages of life (7%), loss of hearing (8%), traumatic brain injuries (3%), high blood pressure (2%), obesity (1%) or excessive alcohol consumption in middle-aged people (1%), smoking (5%), suffering from depression (4%), social isolation (4%), diabetes (1%) physical inactivity (2%) or being exposed to air pollution 96 at later stages of life (2%)[95].

These associations do not imply causality and some experts indicate that changes in lifestyle do not always bring the expected results[97]. Nevertheless, other intervention studies have had successful outcomes[98] and are being repeated in different countries around the world[99]. Moreover, the incidence of dementia seems to have decreased in richer countries in recent years, which is attributed to higher educational attainment and better control of cardiovascular risk[22,95]. This evidence suggests that some of the variables identified may be the cause of dementia rather than just an association[95].

Experts indicate that, although further research is necessary, addressing the lifestyle factors associated with dementia and not delaying recommendations are positive steps that also bring benefits for other areas of health[95]. They also highlight the need to implement specific programmes with concrete instructions about diet, physical and mental exercise, both to increase adherence to recommendations and so that the patient knows how to put them into practice. They also note the importance of controlling high blood pressure during intermediate stages of life.

In this sense, a simulation model estimates that modifying habits related with cardiovascular factors could lead to a 9% reduction of the prevalence of dementia in Spain, which would translate into 100,000 fewer cases and savings of 4,900 million euros by 2050[100].

· Causality: The possibility of establishing a cause-effect relationship between a risk factor and development of a disease.

Parkinson's disease

For Parkinson's, the association with the greatest weight, which has even served to establish animal models of the disease[101], is exposure to environmental pollutants[96] such as the herbicide paraquat, the pesticide rotenone, or trichloroethylene, which is used to clean metals[3,30]. Additionally, the unintentional consumption of the neurotoxin MPTP, produced accidentally during the clandestine synthesis of opioids, was found to be the direct, sudden cause of substantia nigra lesions that mimic Parkinson's disease[29,102]. Conversely, smoking seems to be a protective factor against the disease[28,103] and is associated with a later onset of symptoms[104]. At the same time, tobacco consumption correlates with greater severity of some symptoms that are also associated with age and the long progression of Parkinson's[105]. On the other hand, drug-induced parkinsonism, caused by some antipsychotics, antidepressants or prokinetic agents, is reversible when medication is suspended[106]. According to experts, there would be savings in specialist resources if the situation were detected in primary care. Finally, it is important to note that Parkinson's has also been associated with traumatic brain injury[3,107,108].

Amyotrophic lateral sclerosis

The consumption of tobacco can double the risk of developing ALS compared to non-smokers[109-112]. There is also contradictory evidence: some studies indicate extenuating physical activity[113] and cholesterol in blood as risk factors[109] in addition to pollutants[33].

Huntington's disease

In the case of a known family history of this disease, the only way to avoid it is by selecting embryos that do not carry the mutation[114,115].

Multiple sclerosis

In 2022, a study monitoring over 10 million soldiers in the American forces over a 20-year period detected that infection by the Epstein-Barr virus, the cause of infectious mononucleosis, gave a risk of developing multiple sclerosis that was 32 times higher[116]. Although infection by this virus is very common in the general population and not a cause of major problems, its presence may be necessary to trigger multiple sclerosis in people with a genetic predisposition[117]. Two vaccines are currently being worked on[118,119] but experts believe we need a better understanding of how the infection triggers the disease. Other factors that seem to increase the risk of multiple sclerosis are a deficit of vitamin D, smoking or juvenile obesity[120,121]. On the other hand, a higher level of educational attainment seems to be a protective factor[93].

Diagnosis

Patients of neurodegenerative diseases rarely receive an early diagnosis. Although diagnosis can be a serious setback for the patient and their family, it also opens the door to many medical and social advantages.

Infradiagnosis

Patients of neurodegenerative diseases do not often receive an early diagnosis.

It is estimated that 75% of dementia sufferers worldwide have not received a diagnosis[122], due to a lack of awareness about this syndrome, or to social stigma, a lack of specialists or healthcare resources[123,124], among other reasons. A study of the Spanish population found that only 30% of people with dementia had previously been diagnosed by healthcare services[125]. Although these data are old, the Spanish Society of Neurology estimates that currently, over 50% of mild cases remain undiagnosed[126], a figure that could be as high as 90%[10]. Other studies find that, at the time of diagnosis, most patients are already at a moderate stage of dementia[10] but the medical community notes that this aspect has improved in recent years.

· Prokinetic agents: Drugs that interfere with receptors of dopamine or serotonin which are used to improve bowel transit because they stimulate the contraction of smooth muscle.

It is often difficult to detect ALS at an early stage since the onset can be confused with other, more common, diseases, which means that patients are not referred to a neurologist[33]. Something similar occurs with Parkinson's because current diagnosis is based on clinical assessment, which highlights the importance of evaluation by a specialist[3]. Although medical professionals indicate that the situation in Spain is better, a survey in the United Kingdom found that 26% of Parkinson's patients had received a misdiagnosis[127].

Although receiving the diagnosis of a neurodegenerative disease for which there is currently no cure represents a serious setback for the patient and their family[122], neurologists highlight the advantages of early diagnosis. One of the main benefits is access to effective treatments that can improve symptoms and to non-pharmacological interventions or, in the case of multiple sclerosis, being able to hold back the disease (**see the section on Treatmen**t). Treatments are more effective if they are applied at the best time during the disease's progression[121,128]. Diagnosis also provides a patient with answers, avoids extra visits and can help with a better prognosis of the disease's course. For instance, the mild cognitive deterioration caused by some psychoactive drugs, vascular problems etc. (not in the case of Alzheimer's) can be halted or reversed[22,129]. Diagnosis of these disorders before they lead to dementia can save costs in healthcare and long-term care which are calculated at 7 billion dollars for the USA[22]. Diagnosis also opens the door to participation in clinical trials offering new therapeutic opportunities and a more effective evaluation of treatments[130]. It also enables long-term organisation of care and legal preparation for when patients reach the most advanced stages of the disease[122].

Diagnostic methods

The exploration and judgment of the medical specialist can be complemented in the case of Alzheimer's, Huntington's disease, and multiple sclerosis with diagnostic tests not yet available for Parkinson's disease and ALS. The diagnosis of the latter two also relies on complementary tests.

In order to detect cognitive deterioration, a full medical history and neuropsychological evaluation are conducted; this includes tests of memory, attention, orientation, language and problem solving[131]. These tests help detect cognitive deterioration and behavioural alterations in an objective way, can indicate which regions of the brain are more involved, and suggest a cause[131]. The work of a neurophysiologist is also essential alongside that of other professionals to design a personal care plan[132].

Diagnosing the cause of cognitive deterioration requires a very detailed study. Some complementary tests, such as blood tests or neuroimaging help rule out secondary or potentially treatable causes of cognitive deterioration (B12 deficiency, tumours, vascular lesions, infectious diseases, etc. that are also the cause of cognitive deterioration)[123]. Likewise, neuroimaging can inform about patterns of brain atrophy and suggest the origin of the cognitive symptoms[133].

If the suspected cause of cognitive deterioration is **Alzheimer's**, it can be diagnosed after a medical examination with lumbar puncture to extract cerebrospinal fluid and analyse various biomarkers that are signs of the disease's presence in the brain[134,135]. This technique is simple, cheap and causes very few side effects but requires specialist personnel and organisation[123,133]. Another option is positron emission tomography (amyloid PET) a non-invasive technique that also provides an effective diagnosis[133] although it is a more expensive test[123].

The prognosis of **Parkinson's** and **ALS** is clinical but corroborated with complementary tests[3,33,138].

For **Huntington's** disease, diagnosis consists of genetic testing to check for the presence of abnormal mutant variants in the patient's DNA.

In **multiple sclerosis** there is a need for clinical diagnosis and tests that enable other conditions with similar symptoms to be ruled out. One of the tests that helps in this process is cerebrospinal fluid testing, which detects markers of underlying inflammation[139,140]. Magnetic resonance imaging (MRI) is another, more sensitive, technique to identify lesions that are characteristic of the disease, which offers information about its possible development[48,139]. Early diagnosis is key to start anti-inflammatory therapies as soon as possible and avoid the disability derived from neural damage[121].

The future of diagnosis

Expectations are that diagnosis of Alzheimer's will be possible with a simple blood test.

A new technique promises effective early detection of Parkinson's from samples of cerebrospinal fluid.

Analysis of Alzheimer's biomarkers in blood is minimally invasive, accessible, scalable and cheap, is already successfully used in research, and envisioned to reach clinical practice in the near future[123]. It does, however, require more sensitive testing since concentrations of biomarkers in blood are lower than in cerebrospinal fluid[141]. There are currently several valid biomarkers in blood to distinguish Alzheimer's from other neurodegenerative diseases[142–144]. A negative result could rule out Alzheimer's and avoid the patient undergoing other diagnostic tests, such as lumbar puncture[123]. In future, it is hoped that blood tests will be enough to diagnose Alzheimer's and follow-up the disease. Even so, experts indicate that more clinical practice experience with more heterogeneous populations is still necessary, as is standardisation of measurements to ensure transfer and reproducibility in different laboratories[123].

It is possible to detect biomarkers in blood even before cognitive symptoms appear. So, this type of testing is a useful tool to select participants in clinical trials. In this context, although detection at an early stage does not imply that the disease will develop[130] it is necessary to inform the patient of the significance of knowing the results of testing[123].

For Parkinson's, a recently published study reported detection of alpha-synuclein aggregates in cerebrospinal fluid with 88% effectiveness for diagnosis at early stages, even before motor symptoms present[145]. Work is also underway on diagnosis using blood samples in this and other diseases[146,147].

Support after diagnosis

Both patients and their carers need counselling from diagnosis to help manage the negative feelings it triggers, combat barriers such as discrimination or stigma, and obtain resources to cope with the disease.

Both patients and their families may experience anticipatory grief from the time of diagnosis, with feelings of uncertainty and loss of hopes and dreams for the future[122].

To better cope with the disease and combat these feelings of shock, desperation, powerlessness, frustration, fear and anxiety, neurodegenerative disease patients need professional support from the moment of diagnosis[122]. In the case of ALS, understanding the disease and expediting processes is particularly important because of its rapid progression to disability[148]. ALS patients therefore call for the accreditation of dedicated units so that diagnosis comes with automatic recognition of a 33% degree of disability[149].

In Alzheimer's and other related diseases, support after diagnosis promotes personal autonomy, and delays access to long-term care[150] (**see Key point 3**). In Spain, the majority of dementia patient carers who answered a survey stated that they had received very limited or no information about key aspects of the disease and have very little knowledge about the healthcare and social welfare resources available[10,151]. Based on this situation, one of the objectives of the National Plan on Alzheimer's and other dementias[10] is to inform, train and provide counselling after diagnosis.

Key point 3. Support after diagnosis of dementia in other countries.

Different countries adopt different approaches to post-diagnosis support. In South Korea, there is a network of local centres that combine aspects of healthcare and social welfare. This strategy has increased the number of people with dementia who continue to live in their communities and reduced the medical costs of long-term care[122].

The Scottish model (United Kingdom) is considered the best example of post-diagnostic support in the world and has helped thousands of patients since 2013[122]. Patients recently diagnosed with dementia receive support for at least one year from a case manager called a *link worker* who has training in this disease[122,125]. With a person-based approach, the link worker serves to guide patients and their families through this disease: helping them understand the dementia, manage symptoms and increase resilience to maintain independence for as long as possible[152]. The worker also connects patients with the services they need, helps plan care, and provides advice on making informed legal decisions, ensuring that the services have the patient's consent[152]. The link worker also connects patients with other people with dementia who collaborate so that the patient can maintain their social network and obtain support to keep participating in activities they enjoy[152].

As Huntington's disease is hereditary, it generates anxiety in families because the descendants, who may have seen the disease in one of their parents, have a 50% probability of also developing it in the future. In this sense, they can benefit from psychological support to prepare themselves, decide whether to undergo genetic testing, and help in dealing with the diagnosis[153].

People who receive a diagnosis when they are young adults, as is the case of multiple sclerosis, or a get a positive result in genetic testing for Huntington's disease, face their own challenges. For instance, a study of people who had tested positive for Huntington's but were still asymptomatic found that many of them became more aware of the passing of time and speeded up their life events; it also influenced their thoughts about having children or not[154]. They also indicated the challenge represented by revealing their genetic status to potential partners or in the work environment, for fear of discrimination[154]. For instance, research undertaken in the 2000s found that women who received a diagnosis of multiple sclerosis were 6 times more likely to divorce or separate than male patients[155]. Patients also face multiple barriers at work, and it is more likely that they will require adjustments to carry out their functions[156]. Indeed, it has been found that the numbers of people with multiple sclerosis who are employed is 20% less than the general population and that the disease affects the productivity of 72% of those who have a job[157]. Invisible symptoms such as fatigue, cognitive difficulties or mood disorders can have a great impact on the capacity to work[157].

Treatment

To date, neurodegenerative diseases have no cure. However, treatments exist that can hold back multiple sclerosis or control the most incapacitating symptoms of Parkinson's.

To date, there are no cures for neurodegenerative diseases. However, treatments exist that can hold back multiple sclerosis[121] or control the most incapacitating symptoms of Parkinson's disease[3]. In different conditions, many of the symptoms, which vary over the years, can be treated with drugs or specific interventions[1].

Medical and pharmacological interventions

Parkinson's disease

When symptoms begin to make the activities of daily living difficult, the most effective, best-tolerated first-line treatment is levodopa, alongside other drugs such as dopamine antagonists[3,158]. Levodopa contributes to restoring correct levels of dopamine and improves tremors, muscle rigidity and slowness of movement[159]. Although patients fear this medicine will accelerate the progression of Parkinson's, there is no evidence that it changes the course of the disease[160]. For some patients it can cause an increase in involuntary movements[161,162], but their frequency and severity have reduced in recent years thanks to better dose control[162].

· Dopamine antagonists: Drug that limits the effects of dopamine in the brain.

Levodopa can be combined with other medications and, as a second line, use sustained-release devices[162]. This maintains stable levels of the substance, which are more similar to the physiological ones, avoiding the oscillations in dopamine levels derived from metabolism of the drug, which may be responsible for the adverse effects[162].

All neurodegenerative diseases have treatments to alleviate symptoms, with varying degrees of efficacy. Except for multiple sclerosis, the other conditions do not have treatments that significantly slow down the progression of the disease.

Over the years, the deficit of dopamine increases due to nerve cell degeneration, and medication may not be sufficient to cover it. In that case, the patient can be treated with deep brain stimulation[163]. This consists of the placement of a programmable device to block the neural activity of specific problematic areas of the brain using continuous high-frequency electrical currents[164]. Although surgery has risks, this procedure reduces the symptoms that respond to levodopa in patients with advanced Parkinson's for several years, as well as eliminating or reducing the adverse effects derived from pharmacological treatments[165,166].

On the other hand, a new, non-invasive treatment called high-intensity focused ultrasound (HIFU) can reduce the main signs (slowness of movement, resting tremor, rigidity) immediately and without the complications of a surgery[167,168]. Its mechanism of action is based on ultrasound, which precisely eliminates the areas responsible for the motor signs using heat[167]. A recent study suggests that its application may be beneficial at early stages[169].

Alzheimer's disease and other dementias

Following the success of restoring dopamine levels in Parkinson's, attempts are being made to recover the normal activity of certain neurotransmitters in the symptomatic treatment of Alzheimer's or Lewy bodies diseases[122]. Although they are not as effective as their equivalents in Parkinson's, and have side effects to consider, these medicines have proved effective in numerous clinical trials and the patients, their families and physicians perceive benefits from their use[122].

However, some professionals are questioning the use of psychopharmaceuticals to treat neuropsychiatric symptoms such as agitation, aggression or psychosis in patients with Alzheimer's or other dementias[122]. There is no conclusive evidence for the effectiveness of all the drugs in use to treat dementias and only some of them have modest benefits for certain symptoms in a small percentage of patients[170–173]. Along the same lines, some studies find a 1.8 times higher risk of mortality and other adverse effects associated with this type of drug[170–173], highlighting the need to consider risks versus benefits when prescribing them, and proposing that this should occur on a case by case basis[122]. The Spanish Society of Geriatrics and Gerontology has also requested the legal prohibition of chemical restraint, i.e., the non-therapeutic use of psychopharmaceuticals in order to restrict mobility or control behaviour for reasons of organisational convenience rather than for a patient's benefit[174].

In the last 20 years, there have been no new drugs to alleviate the symptoms of Alzheimer's or other types of cognitive deterioration[122], but the United States Food and Drug Administration (FDA) has just approved the first drug that can modify Alzheimer's disease[90]. In the EU, the European Medicines Agency could authorise its use in the near future, although its cost-benefit ratio is still under discussion[137,175]. After the failure of other medications, and although it is far from being a cure, this new drug is considered a major step forward[137]. It is an antibody that, for the first time, has managed to reduce amyloid plaques and cognitive deterioration in 25% of patients with early stages of the disease[176]. Estimates are that it delays progression of the disease some 6 months[137] although the pharmaceutical company's projections estimate a delay of up to 3 years, which it has not yet been possible to prove[177].

Some estimates calculate that 5.4 million patients in the 27 countries of the EU could be eligible to use this medication[137]. If its price, which has not yet been fixed, were similar to that of the United States, treating all of the possible patients would cost the equivalent of half of the total EU spending on pharmaceuticals, which experts consider to be exorbitant[137]. In addition to this expense, we would have to add the cost of adapting the healthcare system to diagnose Alzheimer's, periodic administration of the drug and monitoring of the first phases of treatment[137,178]. On the other hand, we need to consider that delaying the disability of patients is a saving, since the social costs of care can be three times the costs of healthcare[179]. Another issue to consider is that estimates applying clinical trial inclusion criteria calculate an eligibility for these emerging treatments which is very much lower than the 5.4 million patients mentioned above[180]. Finally, there is another antibody that has offered very promising results in new clinical trials[181].

Amyotrophic lateral sclerosis

There is only one drug that holds back the progression of ALS, which was approved in the mid-1990s and gives some extra months of life for certain groups of patients[33,182]. Nevertheless, evidence indicates that it only prolongs life at more advanced stages of the disease when the patient has a lower quality of life[183]. According to medical professionals, its all-round contribution is poor and the short-term prognosis for this disease is fatal for the majority of patients.

Patients can also receive treatments for symptoms such as excessive salivation or muscle rigidity, in addition to other medical interventions such as non-invasive ventilation and gastrostomy to improve nutrition[33].

Huntington's disease

There is currently no treatment that modifies the course of this disease[74]. Despite the hopes of patients, a phase III clinical trial whose target was to reduce the amount of pathological protein, was cancelled some years ago due to the drug's lack of effectiveness[184,185]. Recently, however, a review of the data has reopened the trial with younger patients[185].

There are drugs to treat chorea which also improve other motor and psychiatric aspects, although some of these therapies may exacerbate depression and suicidal thoughts[186]. A new drug to improve chorea has shown good results in a phase III clinical trial[187].

Multiple sclerosis

Effective treatments for multiple sclerosis have increased over the last two decades[121]. Although not all patients respond, various treatments are able to modify the course of the disease, which in some cases can stop flare-ups, hold up progression of the disease and avoid the appearance of new active lesions[188]. One of the most effective, safe and tolerable are antibodies against B cells, which appear to be dysfunctional and pro-inflammatory in these patients[121,189]. So, due to their good benefit risk ratio, there has been a transition from escalating these treatments step by step to, in many cases, prioritising high effectiveness from the start, preventing inflammation reaching the central nervous system and triggering neurodegeneration[121].

Although the disease is the same, progressive forms of multiple sclerosis (without flare-ups) follow a different clinical course, with the same abnormal mutant characteristics and different degrees of expression, according to genetic or environmental determinants[91]. Despite advances, for these patients there is only one treatment that can hold back the disease, which is not always effective[121]. Meanwhile, several molecules that are able to simultaneously inhibit different immune cells and attack the disease on several fronts are being tested, which could also be a successful therapy for progressive forms[190].

· Chorea:The involuntary, uncoordinated movements that Huntington's disease causes.
· B cells: The white blood cells that produce antibodies .

There are also treatments for symptoms like muscular tension, fatigue, pain, sphincter control, cognitive deterioration and others[188].

Improving the transfer of research to practice

To enhance the effectiveness of clinical trials testing drugs targeting neurodegenerative diseases, experts recommend using experimental models that better replicate human diseases, developing new biomarkers or improving existing ones, and reducing heterogeneity in participant samples.

Between 2002 and 2012, 99.6% of the clinical trials testing new therapies for Alzheimer's failed[6,191] and the situation was similar for other neurodegenerative diseases[6]. One of the reasons is that the animal models used in these contexts, such as mice, cannot fully reproduce the human disease so the results obtained are often not reproducible in patients[6].

Although mice can be a good initial model, as they are manageable and their genetics are well known, some researchers propose using animals that are more similar to human beings, such as miniature pigs[192] or non-human primates[193]. Other suggestions include intermediate approaches, such as implanting human nerve cells in a mouse brain[64]. Many recent studies use human cells that are genetically reprogrammed to differentiate them from neurons, which can also be cultured in three dimensions and form cerebral organoids. However, such models are still undergoing a standardisation optimisation process[6].

To improve the results of translational research and achieve treatments that can modify the course of these diseases, the scientific community also highlights the need to discover new biomarkers or improve existing ones to track both the disease's progression and the effectiveness of drugs. Another improvement would be to personalise treatments, whether by means of cerebrospinal fluid or blood plasma analysis[31,194,195].

Focussing clinical trials on specific populations of patients, stratified by symptoms and according to the molecular subtype of the disease presented can also contribute to success as the heterogeneity of the sample decreases[195]. Other approaches aim to increase the effectiveness and reduce the cost of clinical trials by testing several molecules at the same time[196].

Another consideration is that the blood-brain barrier is very selective and only allows certain substances to pass through so as to protect the brain from infections and other toxic agents. An important area of research into neurodegenerative diseases is how to cross the barrier, enabling treatments to access the brain and gain effectiveness[197,198].

Patients could also benefit from advances in neuroimaging methods, such as specific markers for positron emission tomography or structural and functional MRI that enable the *in vivo* study of a patient[31].

With this panorama, experts point out the advisability of improving the capacity of Spain's science system to transfer knowledge on these and other diseases to the industrial sector and ensure returns that contribute to the system's sustainability.

Non-pharmacological interventions

Patients can improve their condition with interventions like taking exercise, better nutrition, physiotherapy, psychological care, speech and language therapy or occupational therapy.

As disease progresses, the situation of a patient worsens and new symptoms appear that require a comprehensive care approach[1,122]. As well as medication, most patients can benefit from one or several non-pharmacological interventions at some time during the course of their disease. These are defined as any intervention that is not based on medication, has a theoretical basis, is focussed and reproducible for a patient or the carer, and potentially capable of achieving relevant benefit[199].

For instance, there is evidence that aerobic exercise has positive cognitive effects and improves mental function in people with mild cognitive deterioration, Alzheimer's and different dementias[122,200,201]. High-intensity aerobic exercise is safe for early Parkinson's patients and is expected to improve or even hold back both motor and non-motor symptoms[31,202]. Studies also report improvements in the physical state and walking endurance of Huntington's patients[203]. And, although further long-term research is necessary, evidence seems to indicate that exercise is also beneficial for multiple sclerosis patients[204].

There are different types of physiotherapy available for all of the diseases described in this report, to reduce rigidity, improve the quality of movement, postural control, stability, breathing, etc.[24,43,188,199,205].

Likewise, psychological attention is beneficial (in the case of dementias, it is more indicated at early and moderate stages), speech and language therapy if there are disorders of speech or swallowing, interventions to improve nutrition, and occupational therapy that can help patients and carers carry out activities of daily living, by modifying either the task or the environment[24,122,188,199,205-207].

Along the same lines, people with dementia who join in activities aimed at improving cognition experience varying degrees of progress (**see Key point 4).**

People with Alzheimer's and other related diseases experience improvement with therapies such as cognitive training, interventions using art, and group cognitive stimulation.

Group cognitive stimulation has very positive effects and is also cost effective.

Key point 4. Cognitive interventions

Cognitive training consists of the formal practice of skills and processes like memory, processing information, attention and executive functions by means of repeating increasingly difficult tasks[122]. There is evidence that people with moderate or mild dementia experience small or moderate cognitive improvement in the short and medium terms, above all, in semantic verbal fluency, language and short-term memory[122,208,209]. Although further study is necessary, there is also an association between cognitive training and a delay in disease progression, as well as a reduction in the carer's burden when treatment ends[208]. However, there is no evidence that this improves quality of life, the functional capacity to perform activities of daily living or behaviour patterns, although it is known that there are no negative effects[122,208,209].

For their part, cognitive stimulation therapies consist in performing group activities with patients who have mild to moderate dementia in order to strengthen their memory, executive functions and language in addition to improving their wellbeing and avoiding psychiatric complications[122]. Among other activities, these include word or physical games, questions, categorising objects or talking about current affairs[122]. Although there is a demand for more rigorous studies[210] evidence indicates that this therapy improves cognition, quality of life, language and the social interaction of participants, and can even have more effect than some medicines[211-214]. It seems that the benefit the group generates is important and it may be an advantage that the facilitator is not a family member[122,215]. Calculations estimate that offering cognitive stimulation to all the dementia patients in England would be a cost-effective intervention[122,216].

Likewise, for people with dementia, interventions that use art (poetry, narrative, theatre, dance, painting, pottery and music) can help to reduce stress, anxiety, depression or behavioural disorders, as well as improving social and cognitive aspects[122,217,218]. They can also be therapeutic for carers[219]. Experts indicate that further studies should define certain parameters such as what is the key to the success of an intervention or how long the effects should last for a therapy to be considered beneficial[122,220-222].

Again, some studies indicate inequality of access to non-pharmacological therapies in Spain, and there are no data that report the number of patients who use them[10,136].

On the other hand, it is important that people with neurodegenerative diseases and their families have access to up-to-date, truthful information, and the resources to avoid disinformation or access to fraudulent therapies, which are financially burdensome and serve no purpose; this is a risk for patients' health and can delay access to effective treatments[123,223-225].

Palliative care

Attending a palliative care consultation at an early stage seems to improve the quality of life of neurodegenerative disease patients, although access to this service is not the same countrywide.

The goal of palliative care is to guarantee the quality of life of patients with a serious disease who face the physical, psychological, social or existential problems inherent to a potentially fatal disease[226,227]. The focus here is on three dimensions: addressing the symptoms, environmental support, and planning treatment and care in accordance with the patient's preferences[228,229].

Early access to a palliative consultation reduces hospital admissions for dementia patients[22,230] improves the quality of the care they receive in their last 14 days of life, reduces the possibility of them receiving pointless treatments or interventions[122,231]; it also lowers the costs of the last month of life[122,231]. Early access to palliative care is also considered beneficial for other neurodegenerative diseases. On one hand, it ensures that the care is person-centred, as it helps in drawing up a shared care plan and the possibility of preparing an advance healthcare directive (also called a living will)[232,233]. On the other, treatments are personalised to control symptoms. This can include strategies for difficulties swallowing (changing textures in the diet or improving nutrition), problems with catheters such as deciding where to place or when to remove them, the need to begin mechanical ventilation, reduce dribbling or constipation, treat psychological and cognitive problems, combat pain, help with sleep and end-of-life assistance. This aspect also includes support for the carer and in the grieving process[10,227,232,234,235].

Only 10% of medical faculties and 48% of nursing faculties offer specific obligatory courses in palliative care that guarantee basic capacity building in these skills[236]. Neurologists note the need for more training and call for the creation of specific protocols for each condition to make health care more uniform[237,238].

In terms of access to palliative care, the European Association for Palliative Care recommends that there should be two palliative care services for every 100,000 inhabitants, one home-based and the other in-hospital[236]. However, Spain is at the bottom of the list of European countries, with 0.6 services for every 100,000 inhabitants[236]. Although some specialist units have palliative care professionals, for instance, some ALS units, this is not a common situation. Indeed, healthcare professionals indicate that for other neurodegenerative diseases palliative care is deficient[237]. Access to this service is unequal, with different resources and organisation in each autonomous community[238]. To improve the situation, the National Palliative Care Strategy was updated in 2011 and healthcare professionals want to promote a palliative care law that sets minimums to guarantee better equality of access[239,240].

Adaptation of the National Health System

To adapt to the foreseeable increase in the number of neurodegenerative disease cases, the medical community recommends more health and social welfare coordination, the creation of a patient registry, training for primary care staff, more specialist physicians and the creation of a professional role specialised in patients with dementia.

In light of the challenge presented by neurodegenerative diseases and a foreseeable increase in the number of cases, medical professionals highlight the need to undertake the following adaptations of the healthcare system:

Data and coordination of health and social welfare

To prepare a response to the increase in the number of cases of certain neurodegenerative diseases like Alzheimer's and other dementias, it would be very useful to have a periodically updated accurate patient registry[10,241] like the Dementias Platform UK or the Swedish registry for cognitive/dementia disorders[10]. According to the medical community, this information would help organise not only clinical trials but also enable more precise estimates of the drug requirements for medicines that can modify the course of diseases like Alzheimer's if approval is given[10].

Likewise, experts mention the need to coordinate social services and healthcare to the benefit of patients and the effectiveness of the system[10,242]. For instance, it would be advisable

to have data about social services categorised in greater detail about neurodegenerative diseases, such as how many of the people living in residential care facilities, or who need care, have dementia.

Distribution of resources

There are currently eight Reference Centres, Services and Units (Spanish acronym, CSUR) designated to perform surgery for movement disorders in the autonomous communities of Catalonia, Madrid, Valencia, Galicia, Basque Country and the Principality of Asturias[243]. There are also six reference centres for rare diseases that present movement disorders, which would include Huntington's disease, in the autonomous communities of Andalusia, Catalonia, Valencia and Madrid. The twelve CSUR for multiple sclerosis are located in Aragon, Catalonia, the communities of Madrid and Valencia, Galicia, the Region of Murcia and the Basque Country[243]. Neuromuscular diseases CSUR (in Andalusia, Catalonia, the autonomous communities of Madrid, Valencia and the Basque Country) treat ALS patients[243] although the reference centres are not specifically for ALS, and medical professionals consider that at advanced stages these patients require care close to home.

The way that healthcare professionals are organised in hospitals is also important. For instance, the treatment of patients in multi-disciplinary units consisting of different specialists (medical and nursing professionals, case managers, psychologists, social workers, rehabilitation and palliative care staff) improves both the survival and quality of life of ALS patients, in addition to reducing the number of hospital admissions[244-246].

On the other hand, medical professionals highlight the need to distribute resources and achieve sufficient regional cover, and the advisability of setting up permanent inter-hospital referral systems that make the whole process quicker both for users and for hospitals to recover funding[1].

Healthcare professionals

Experts recommend training in and improved awareness of neurodegenerative diseases for primary care professionals to facilitate early diagnosis and improve coordination with specialist services[10,24].

Within Spain, 18% of healthcare professionals believe that more neurologists are needed, and 67.3% think there is a lack of psychiatrists[247]. Another need is to expand access to rehabilitation programmes.

On the other hand, as dementias are so prevalent, it is increasingly common to find patients admitted to acute care hospitals, where they are at greater risk of suffering negative consequences[248]. To improve patient care and that of carers during hospital stays, the United Kingdom has created a specialist nursing corps, *Admiral Nurses*[248]. In addition to providing person-centred holistic care for the patient they provide support for families and also train other health and social welfare professionals to promote evidence-based best practices[248].

Assistance and care

Social services face the challenge of adapting to the increasing number of people who will presumably need more complex care and are more vulnerable in critical situations, such as the recent pandemic.

The care of people with neurodegenerative disease mostly falls to the family, with the consequent social and personal cost. Forecasts indicate the need to develop a sustainable system of professional, specialised care.

Healthcare and social services face the challenge of adapting to the increasing number of people who will presumably need more complex care[249] and are more vulnerable in critical situations, such as during the recent pandemic[250].

There are three basic pillars in the healthcare of people with neurodegenerative diseases:

Carers

Forecasts predict the need to train carers and staff specialised in the looking after people with dementia and chronic diseases[59,249]. However, in Spain, it is the family that mainly provides care for these patients.

Neurodegenerative diseases represent an economic burden for patients and their families. For instance, based on available data, in southern European countries, it is calculated that the cost of dementia is around 36,000 euros per year per patient[251], although other studies give the most conservative estimates as 42,336 euros[252]. What is known is that cost of the social welfare component is higher than that of healthcare and increases with the severity and duration of the disease[179,251,253]. Calculations are that 60% of the total cost of care corresponds to non-paid or informal care, usually provided by family members[254], which could involve financial risk, only 30% of which is mitigated by the public protection system[255]. This is very important in terms of the population since, according to the INE (Spanish Statistical Office) Survey on Disability, Personal Autonomy and Dependency Situations, the number of people who receive informal care in their homes increased more than 40% between 2008 and 2021[256]. A preliminary study estimates that in Spain, the medical cost of substituting the informal care of Alzheimer's patients with professional carers could be as high as 70,000 euros per patient per year[257].

Changes in work schedules (a reduction in working hours or leaving paid employment, since sometimes availability needs to be round-the-clock, every day of the year) in order to care for family members implies lower incomes for families, a difficulty in combining care with employment, and complications when it comes to re-joining the workforce for carers, who are mostly women, when the patient dies[10]. Social changes, such as smaller families, higher participation of women in the labour market or raising the age of retirement, reduce the availability of adult children for this type of task, which highlights the importance of developing a sustainable, professional, specialised care system[249]. For the time being, in addition to benefits and dependency services, one resource that helps keep potential carers in employment are adult day care centres, where patients can also receive therapeutic help[10,59].

Although caring for a family member can give a feeling of pride and a sense of purpose, it can also be a source of stress and other negative feelings, like loneliness and isolation, guilt or regret over decisions about the future of the sick relative[122,258]. For instance, 54% of dementia patient carers state that they often or always feel under stress[122]. Others, particularly women, have health problems, difficulty enjoying leisure or problems related with their professional activity[259,260]. As the burden increases in step with disease progress and the loss of patient autonomy, the costs of the carer losing their job[261] can lead to depression and a loss of quality of life[262]. If these obstacles are not overcome, exhaustion of the carer often leads to the patient being admitted[262].

Inclusion of Alzheimer's patients in the community

Social inclusion in the community is essential to empower Alzheimer's patients and other related diseases. This is fostered if they are considered when designing the environment and receive support from technological resources supervised by carers.

Social inclusion in the community is essential for the empowerment of people with Alzheimer's. This is made easier if the environment is designed with adaptations like good signage, accessibility, awareness and training of people who work in shops or services[263]. Access to outdoor areas is a right of people with dementia, and activities in natural surroundings increase the wellbeing of patients and their carers[264]. Gardens provide a multi-sensory experience with similar benefits, and they can be designed along similar lines as mentioned above, with the inclusion of areas to rest, shade, plants that feel pleasant to touch or that evoke the seasons, etc.[265]. One of the main pillars of Spain's National Plan on Alzheimer's is transformation of the environment by raising sensitivity to and awareness of the disease[10].

In Spain and other countries, the aim is for older adults to receive support in their home environment enabling them to live as long as possible at home[59,266]. There are objects that can help people stay at home with a good quality of life and the support of their carer. Such devices include the digital watch that also shows the date and day of the week, touch lamps to help prevent falls, whiteboards to write down the week's activities or reminders not to forget the house keys[267]. Technology can also come in the shape of care robots, geolocation devices, telehealth services, virtual therapies or communication tools, although their success depends on the patient's profile and access to the technology[59,242].

Alternative accommodation

When people with Alzheimer's or other dementias can no longer live at home, alternatives include "coexistence units" and other options already firmly established in other European countries.

Associations representing ALS and Huntington's call for the creation of centres that specialise in their diseases.

Due to limitations in the design of conventional homes and the difficulty of finding specialised accommodation, despite support, many people with dementia cannot maintain an acceptable quality of life in their own homes when the disease reaches an advanced stage[268].

When this occurs, one of the alternatives to traditional residential care facilities are what is known in Spain as a *unidad de convivencia* ("coexistence unit"). These are home-like places, with private and community areas, where a reduced number of people live, with continuous attention organised on a small scale[59,269,270]. The pilot projects put into practice in Spain have met with high degrees of satisfaction from residents, professionals and families[59,269].

In the Netherlands, the *dementia village* project reproduces the areas of a small village (squares, streets, gardens, supermarket, restaurant) so that its inhabitants, 150 people with dementia, can participate in daily activities in freedom and safety[270]. Six or seven people live in each independent terraced house, grouped by preferences and interests, accompanied by permanent teams of professionals[270]. The success of this closed community project has meant that it has been copied in countries like France, Canada, Switzerland and Denmark[270].

The United Kingdom has set up specialised *extra care housing* projects for older adults. These are similar to the community cohousing projects that already exist in Spain to promote the autonomy of older adults, where inhabitants live in independent apartments with access to shared utilities (laundry, restaurant, gym, hairdresser) and activities designed to liven up community living. They also offer residents the possibility of contracting the degree of care that adapts to their increasing needs over time[59,268]. These alternatives also have the potential to improve a dementia patient's quality of life and cover their different needs as their condition changes. For instance, support for the dementia patient increases because living with their partner is possible, and the carer's quality of life improves because they gain social contacts and independence. Experts recommend thinking about the specific needs of people with cognitive deterioration when it comes to designing and managing this type of project[268].

In the case of ALS patients, the rapid progression of this disease leads them to need continuous care, so they call for financial support for home care or a place in a specialist public residential care facility[271] where there are staff trained in specific care, such as cleaning tracheostomy tube components or reacting to emergency situations to prevent suffocation[272]. There is currently only one such centre planned, and a day care centre in Madrid[273]. There are no specialist centres for other diseases such as Huntington's.

Key concepts

- **Neurodegenerative diseases cause neural cell death, disability, dependency, significantly shorten life expectancy and are, to date, incurable. In Spain, it is calculated that they affect between 1 and 1.5 million people.**
- **Increased life expectancy goes hand in hand with a very significant increase in the cases of diseases like Alzheimer's, Parkinson's and amyotrophic lateral sclerosis (ALS), which has an impact on both planning and budgets for public policies in healthcare and social welfare.**
- **The risk of developing these diseases is influenced by genetic factors, the environment, lifestyle and the interaction of these factors over time, although the weight of each one is still not fully understood. Changing lifestyle or reducing risk factors that can be modified during determined stages of life could reduce the risk of developing these diseases. By doing this, it is estimated that over a third of all dementia cases could be prevented or have a delayed onset.**
- **These disorders are often not detected at early stages. Although early diagnosis is a serious setback for the patient and their family, it can also bring many medical advatanges (more effective early interventions to alleviate or hold back symptoms) and social (medical, legal and care planning) if the necessary support exists. Techniques currently exist for the specific diagnosis of Alzheimer's disease and multiple sclerosis, although access to these services is different in each of Spain's autonomous communities. In the near future, conditions like Alzheimer's disease could be detected with a simple blood test.**
- **Treatments already exist that can hold back multiple sclerosis or control the most incapacitating symptoms of Parkinson's disease. For different diseases many of the symptoms, which vary or accumulate over years, can be treated with drugs or specific interventions. Although emerging treatments can hold back the progression of Alzheimer's for some months and represent a step forward, the cost-benefit ratio is not clear in terms of patient autonomy, so Europe is debating their approval and funding by National Health Systems.**
- **Social costs are higher than those of medical care and increase with the severity and length of these diseases. In most cases it is the family who has to cope, which highlights the need to develop a sustainable, specialist professional care system. Comprehensive healthcare requires greater coordination between the social welfare and healthcare fields to improve the inclusion and wellbeing of both patients and their families.**

Bibliography:

1. Ministerio de Sanidad, Servicios Sociales e Igualdad. Estrategia en enfermedades neurodegenerativas del Sistema Nacional de Salud. https://www.sanidad.gob.es/organizacion/sns/planCalidadSNS/pdf/Est_Neurodegenerativas_APROBADA_C_INTERTERRITORIAL.pdf (2016).
2. Nichols, E. et al. Estimation of the global prevalence of dementia in 2019 and forecasted prevalence in 2050: an analysis for the Global Burden of Disease Study 2019. The Lancet Public Health 7, e105–e125 (2022) https://doi.org/10.1016/S2468-2667(21)00249-8.
3. Bloem, B. R., Okun, M. S. & Klein, C. Parkinson's disease. The Lancet 397, 2284–2303 (2021) https://doi.org/10.1016/S0140-6736(21)00218-X.
4. Dorsey, E. R. et al. Projected number of people with Parkinson disease in the most populous nations, 2005 through 2030. Neurology 68, 384–386 (2007) https://doi.org/10.1212/01.wnl.0000247740.47667.03.
5. Gowland, A. et al. Predicting the future of ALS: the impact of demographic change and potential new treatments on the prevalence of ALS in the United Kingdom, 2020–2116. Amyotrophic Lateral Sclerosis & Frontotemporal Degeneration 20, 264–274 (2019) https://doi.org/10.1080/21678421.2019.1587629.
6. Joint Research Centre (European Commission). Advanced non-animal models in biomedical research. Neurodegenerative diseases. https://publications.jrc.ec.europa.eu/repository/handle/JRC124723 (2021).
7. Cicardi, M. E., Marrone, L., Azzouz, M. & Trotti, D. Proteostatic imbalance and protein spreading in amyotrophic lateral sclerosis. The EMBO Journal 40, e106389 (2021) https://doi.org/10.15252/embj.2020106389.
8. AECC Observatorio. Oncobarómetro. Datos de 2020. https://observatorio.contraelcancer.es/informes/oncobarometro#percepcion (2021).
9. Instituto Nacional de Estadística. Defunciones según la causa de muerte. Año 2022 (datos provisionales). https://www.ine.es/prensa/edcm_2022.pdf (2023).
10. Ministerio de Sanidad, Consumo y Bienestar Social. Plan integral de Alzheimer y otras demencias. 2019-2023. https://www.sanidad.gob.es/profesionales/saludPublica/docs/Plan_Integral_Alhzeimer_Octubre_2019.pdf (2019).
11. ELA y otros trastornos neuromusculares | CIBERNED. https://www.ciberned.es/programas-de-investigacion/ela-y-otros-trastornos-neuromusculares [14/09/2023].
12. Garcés, M., Crespo Puras, C., Finkel, L. & Arroyo Menéndez, M. Estudio sobre las enfermedades neurodegenerativas en España y su impacto económico y social. Universidad Complutense y Neuroalianza. (2016).
13. Roberts, T. C., Wood, M. J. A. & Davies, K. E. Therapeutic approaches for Duchenne muscular dystrophy. Nature Reviews Drug Discovery 1–18 (2023) https://doi.org/10.1038/s41573-023-00775-6.
14. Center for Drug Evaluation and Research. Duchenne muscular dystrophy and related dystrophinopathies: Developing drugs for treatment guidance for industry. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/duchenne-muscular-dystrophy-and-related-dystrophinopathies-developing-drugs-treatment-guidance (2018).
15. Libberecht, K., Vangansewinkel, T., Van Den Bosch, L., Lambrichts, I. & Wolfs, E. Proteostasis plays an important role in demyelinating Charcot Marie Tooth disease. Biochemical Pharmacology 216, 115760 (2023) https://doi.org/10.1016/j.bcp.2023.115760.
16. Pisciotta, C. & Shy, M. E. Chapter 25 - Hereditary neuropathy. Handbook of Clinical Neurology (ed. Younger, D. S.) vol. 195 609–617 (Elsevier, 2023).
17. Lasa-Elgarresta, J., Mosqueira-Martín, L., Naldaiz-Gastesi, N., Sáenz, A., López de Munain, A. & Vallejo-Illarramendi, A. Calcium mechanisms in limb-girdle muscular dystrophy with CAPN3 mutations. International Journal of Molecular Sciences 20, 4548 (2019) https://doi.org/10.3390/ijms20184548.
18. Flores-Bellver, M. et al. Extracellular vesicles released by human retinal pigment epithelium mediate increased polarised secretion of drusen proteins in response to AMD stressors. Journal of Extracellular Vesicles 10, e12165 (2021) https://doi.org/10.1002/jev2.12165.
19. Degeneración Macular Asociada a la Edad (DMAE). Barcelona Macula Foundation: Research for Vision https://barcelonamaculafound.org/es/patologias/dmae-degeneracion-macular-asociada-la-edad/ [13/09/2023].
20. Instituto de Salud Carlos III. Protocolo de vigilancia de las encefalopatías espongiformes transmisibles humanas. (2022).
21. Ministerio de Agricultura, Pesca y Alimentación. Resultados de la vigilancia de las encefalopatías espongiformes transmisibles en España. (2022).
22. Alzheimer's Association. 2023 Alzheimer's disease facts and figures. The patient journey in an era of new treatments. Alzheimer's & Dementia 19, 1598–1695 (2023) https://doi.org/10.1002/alz.13016.
23. Ward, A., Tardiff, S., Dye, C. & Arrighi, H. M. Rate of conversion from prodromal Alzheimer's disease to Alzheimer's dementia: a systematic review of the literature. Dementia and Geriatric Cognitive Disorders Extra 3, 320–332 (2013) https://doi.org/10.1159/000354370.
24. Ministerio de Sanidad. Abordaje del Parkinson y parkinsonismos. Estrategia en enfermedades neurodegenerativas del Sistema Nacional de Salud. (2022).
25. García-Ramos, R., López Valdés, E., Ballesteros, L., Jesús, S. & Mir, P. The social impact of Parkinson's disease in Spain: Report by the Spanish Foundation for the Brain. Neurologia (Barcelona, Spain) 31, 401–413 (2016) https://doi.org/10.1016/j.nrl.2013.04.008.
26. Sociedad Española de Neurología. 11 de abril: día mundial del párkinson. Nota de Prensa. (2023).
27. Base de datos clínicos de Atención Primaria (BDCAP) del Ministerio de Sanidad. (2023).
28. Poewe, W. et al. Parkinson disease. Nature Reviews Disease Primers 3, 1–21 (2017) https://doi.org/10.1038/nrdp.2017.13.
29. Dorsey, R., Sherer, T., S. Okun, M. & R. Bloem, B. Ending Parkinson's disease: a prescription for action. (PublicAffairs, 2020). ISBN: 978-1-5417-2452-5.
30. Twist of fate: What happens when a top Parkinson's researcher gets the disease? https://www.science.org/content/article/twist-fate-what-happens-when-top-parkinson-s-researcher-gets-disease [05/07/2023].
31. Obeso, J. A., Monje, M. H. G. & Matarazzo, M. Major advances in Parkinson's disease over the past two decades and future research directions. The Lancet Neurology 21, 1076–1079 (2022) https://doi.org/10.1016/S1474-4422(22)00448-3.
32. Etapas del Parkinson | Parkinson's Foundation. https://www.parkinson.org/espanol/entendiendo-parkinson/que-es-parkinson/etapas [29/06/2023].
33. Feldman, E. L., Goutman, S. A., Petri, S., Mazzini, L., Savelieff, M. G., Shaw, P. J. & Sobue, G. Amyotrophic lateral sclerosis. The Lancet 400, 1363–1380 (2022) https://doi.org/10.1016/S0140-6736(22)01272-7.
34. Castro-Rodríguez, E., Azagra, R., Gómez-Batiste, X. & Povedano, M. La esclerosis lateral amiotrófica (ELA) desde la Atención Primaria. Epidemiología y características clínico-asistenciales. Atención Primaria 53, (2021) https://doi.org/10.1016/j.aprim.2021.102158.
35. Sociedad Española de Neurología. Nota de prensa. Unas 4.000-4500 personas padecen actualmente ELA en España. (2023).
36. Traxinger, K., Kelly, C., Johnson, B. A., Lyles, R. H. & Glass, J. D. Prognosis and epidemiology of amyotrophic lateral sclerosis. Neurology: Clinical Practice 3, 313–320 (2013) https://doi.org/10.1212/CPJ.0b013e3182a1b8ab.
37. La Enfermedad. Asociación Española de Esclerosis Lateral Amiotrófica. adELA https://adelaweb.org/la-ela/la-enfermedad/ [04/07/2023].
38. FYI: ALS, Cognitive Impairment & Dementia. The ALS Association https://www.als.org/navigating-als/resources/fyi-als-cognitive-impairment-dementia [10/07/2023].
39. Chio, A., Logroscino, G., Hardiman, O., Swingler, R., Mitchell, D., Beghi, E. & Traynor, B. G. Prognostic factors in ALS: A critical review. Amyotrophic lateral sclerosis: official publication of the World Federation of Neurology Research Group on Motor Neuron Diseases 10, 310–323 (2009) https://doi.org/10.3109/17482960802566824.
40. Bates, G. P. et al. Huntington disease. Nature Reviews Disease Primers 1, 1–21 (2015) https://doi.org/10.1038/nrdp.2015.5.
41. Fisher, E. R. & Hayden, M. R. Multisource ascertainment of Huntington disease in Canada: Prevalence and population at risk. Movement Disorders 29, 105–114 (2014) https://doi.org/10.1002/mds.25717.
42. Evans, S. J., Douglas, I., Rawlins, M. D., Wexler, N. S., Tabrizi, S. J. & Smeeth, L. Prevalence of adult Huntington's disease in the UK based on diagnoses recorded in general practice records. Journal of Neurology, Neurosurgery & Psychiatry 84, 1156–1160 (2013) https://doi.org/10.1136/jnnp-2012-304636.
43. Raffelsbauer, D. Enfermedad de Huntington. Preguntas y respuestas para los que desean saber más. European Huntington's disease network. (2009).
44. Enfermedad de Parkinson, Huntington y otros trastornos motores degenerativos | CIBERNED. https://www.ciberned.es/programas-de-investigacion/enfermedad-de-parkinson-huntington-y-otros-trastornos-motores-degenerativos [17/08/2023].
45. What is Huntington's disease? Huntington's Disease Association https://www.hda.org.uk/information-and-support/huntingtons-disease/what-is-huntingtons-disease/ [04/07/2023].
46. Tabrizi, S. J., Flower, M. D., Ross, C. A. & Wild, E. J. Huntington disease: new insights into molecular pathogenesis and therapeutic opportunities. Nature Reviews Neurology 16, 529–546 (2020) https://doi.org/10.1038/s41582-020-0389-4.
47. Huntington's disease symptoms. Huntington's Disease Association https://www.hda.org.uk/information-and-support/huntingtons-disease/huntingtons-disease-symptoms/ [04/07/2023].
48. Brownlee, W. J., Hardy, T. A., Fazekas, F. & Miller, D. H. Diagnosis of multiple sclerosis: progress and challenges. The Lancet 389, 1336–1346 (2017) https://doi.org/10.1016/S0140-6736(16)30959-X.
49. King, R. Atlas de la esclerosis múltiple. Federación Internacional de Esclerosis Múltiple. https://www.msif.org/wp-content/uploads/2020/10/Atlas-Epidemiology-report-Sept-2020-Final-ES.pdf (2020).
50. Síntomas de la Esclerosis Múltiple en los diferentes tipos | FEM. Fundación Esclerosis Múltiple https://www.fem.es/es/esclerosis-multiple/sintomas-de-la-esclerosis-multiple/ [04/07/2023].
51. Saft, C. Huntington's disease: disappointments and new beginnings. The Lancet Neurology 21, 582–584 (2022) https://doi.org/10.1016/S1474-4422(22)00189-2.
52. Latif, S. et al. Dopamine in Parkinson's disease. Clinica Chimica Acta 522, 114–126 (2021) https://doi.org/10.1016/j.cca.2021.08.009.
53. Drew, L. An age-old story of dementia. Nature 559, S2–S3 (2018) https://doi.org/10.1038/d41586-018-05718-5.
54. Makin, S. The amyloid hypothesis on trial. Nature 559, S4–S7 (2018) https://doi.org/10.1038/d41586-018-05719-4.
55. NIHAging. What happens to the brain in Alzheimer's disease? National Institute on Aging https://www.nia.nih.gov/health/what-happens-brain-alzheimers-disease [06/07/2023].

56. Zufiría, M. et al. ALS: A bucket of genes, environment, metabolism and unknown ingredients. Progress in Neurobiology 142, 104–129 (2016)
https://doi.org/10.1016/j.pneurobio.2016.05.004.
57. Lubetzki, C. & Stankoff, B. Demyelination in multiple sclerosis. Handbook of Clinical Neurology 122, 89–99 (2014)
https://doi.org/10.1016/B978-0-444-52001-2.00004-2.
58. Esclerosis múltiple España. Qué es la esclerosis múltiple.
https://esclerosismultiple.com/esclerosis-multiple/que-es-la-esclerosis-multiple/ [07/07/2023].
59. Oficina de Ciencia y Tecnología del Congreso de los Diputados (Oficina C). Informe C: Envejecimiento y bienestar. (2023)
https://doi.org/10.57952/q3ze-2c39.
60. Hou, Y., Dan, X., Babbar, M., Wei, Y., Hasselbalch, S. G., Croteau, D. L. & Bohr, V. A. Ageing as a risk factor for neurodegenerative disease. Nature Reviews Neurology 15, 565–581 (2019)
https://doi.org/10.1038/s41582-019-0244-7.
61. Avila, J. Brain aging, epigenetic changes, tau and neurodegeneration. Aging Brain 1, 100004 (2021)
https://doi.org/10.1016/j.nbas.2020.100004.
62. Gan, L., Cookson, M. R., Petrucelli, L. & La Spada, A. R. Converging pathways in neurodegeneration, from genetics to mechanisms. Nature Neuroscience 21, 1300–1309 (2018)
https://doi.org/10.1038/s41593-018-0237-7.
63. Centros de referencia estatal (CRE). Instituto de Mayores y Servicios Sociales
https://imserso.es/centros/centros-referencia-estatal-cre [17/10/2023].
64. Balusu, S. et al. MEG3 activates necroptosis in human neuron xenografts modeling Alzheimer's disease. Science 381, 1176–1182 (2023)
https://doi.org/10.1126/science.abp9556.
65. Area-Gomez, E. & Schon, E. A. On the pathogenesis of Alzheimer's disease: The MAM hypothesis. The FASEB Journal 31, 864–867 (2017)
https://doi.org/10.1096/fj.201601309.
66. Blesa, J., Foffani, G., Dehay, B., Bezard, E. & Obeso, J. A. Motor and non-motor circuit disturbances in early Parkinson disease: which happens first? Nature Reviews Neuroscience 23, 115–128 (2022)
https://doi.org/10.1038/s41583-021-00542-9.
67. Berer, K. et al. Gut microbiota from multiple sclerosis patients enables spontaneous autoimmune encephalomyelitis in mice. Proceedings of the National Academy of Sciences of the United States of America 114, 10719–10724 (2017)
https://doi.org/10.1073/pnas.1711233114.
68. Jangi, S. et al. Alterations of the human gut microbiome in multiple sclerosis. Nature Communications 7, 12015 (2016)
https://doi.org/10.1038/ncomms12015.
69. Yokote, H., Miyake, S., Croxford, J. L., Oki, S., Mizusawa, H. & Yamamura, T. NKT cell-dependent amelioration of a mouse model of multiple sclerosis by altering gut flora. The American Journal of Pathology 173, 1714–1723 (2008)
https://doi.org/10.2353/ajpath.2008.080622.
70. Cantoni, C. et al. Alterations of host-gut microbiome interactions in multiple sclerosis. eBioMedicine 76, (2022)
https://doi.org/10.1016/j.ebiom.2021.103798.
71. Kiani, L. Early microbiome changes in neurodegenerative disease. Nature Reviews Neurology 19, 458–458 (2023)
https://doi.org/10.1038/s41582-023-00848-5.
72. Ferreiro, A. L. et al. Gut microbiome composition may be an indicator of preclinical Alzheimer's disease. Science Translational Medicine 15, eabo2984 (2023)
https://doi.org/10.1126/scitranslmed.abo2984.
73. Palacios, N., Wilkinson, J., Bjornevik, K., Schwarzschild, M. A., McIver, L., Ascherio, A. & Huttenhower, C. Metagenomics of the gut microbiome in Parkinson's disease: Prodromal changes. Annals of Neurology 94, 486–501 (2023)
https://doi.org/10.1002/ana.26719.
74. Tabrizi, S. J. et al. Potential disease-modifying therapies for Huntington's disease: lessons learned and future opportunities. The Lancet Neurology 21, 645–658 (2022)
https://doi.org/10.1016/S1474-4422(22)00121-1.
75. García-Redondo, A. et al. Analysis of the C9orf72 gene in patients with Amyotrophic Lateral Sclerosis in Spain and different populations worldwide. Human Mutation 34, 79–82 (2013)
https://doi.org/10.1002/humu.22211.
76. Vázquez-Costa, J. F. et al. Characterizing SOD1 mutations in Spain: The impact of genotype, age and sex in the natural history of the disease. European Journal of Neurology 30, 861–871 (2023)
https://doi.org/10.1111/ene.15661.
77. Pikatza-Menoio, O. et al. The skeletal muscle emerges as a new disease target in Amyotrophic Lateral Sclerosis. Journal of Personalized Medicine 11, 671 (2021)
https://doi.org/10.3390/jpm11070671.
78. Bellenguez, C. et al. New insights into the genetic etiology of Alzheimer's disease and related dementias. Nature Genetics 54, 412–436 (2022)
https://doi.org/10.1038/s41588-022-01024-z.
79. Corder, E. H. et al. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. Science 261, 921–923 (1993)
https://doi.org/10.1126/science.8346443.
80. Belloy, M. E., Napolioni, V. & Greicius, M. D. A quarter century of APOE and Alzheimer's Disease: progress to date and the path forward. Neuron 101, 820–838 (2019)
https://doi.org/10.1016/j.neuron.2019.01.056.
81. Sepulveda-Falla, D., Glatzel, M. & Lopera, F. Phenotypic profile of early-onset familial Alzheimer's disease caused by presenilin-1 E280A mutation. Journal of Alzheimer's disease: JAD 32, 1–12 (2012)
https://doi.org/10.3233/JAD-2012-120907.
82. Vélez, J. I. et al. APOE*E2 allele delays age of onset in PSEN1 E280A Alzheimer's disease. Molecular Psychiatry 21, 916–924 (2016)
https://doi.org/10.1038/mp.2015.177.
83. Sepulveda-Falla, D. et al. A multifactorial model of pathology for age of onset heterogeneity in familial Alzheimer's disease. Acta Neuropathologica 141, 217–233 (2021)
https://doi.org/10.1007/s00401-020-02249-0.
84. Lopera, F. et al. Resilience to autosomal dominant Alzheimer's disease in a Reelin-COLBOS heterozygous man. Nature Medicine 29, 1243–1252 (2023)
https://doi.org/10.1038/s41591-023-02318-3.
85. Kriebs, A. Genetic protection from early-onset familial Alzheimer's disease. Nature Aging 3, 635–635 (2023)
https://doi.org/10.1038/s43587-023-00445-7.
86. Nalls, M. A. et al. Identification of novel risk loci, causal insights, and heritable risk for Parkinson's disease: a meta-analysis of genome-wide association studies. The Lancet Neurology 18, 1091–1102 (2019)
https://doi.org/10.1016/S1474-4422(19)30320-5.
87. Polymeropoulos, M. H. et al. Mutation in the -Synuclein gene identified in families with Parkinson's disease. Science 276, 2045–2047 (1997)
https://doi.org/10.1126/science.276.5321.2045.
88. Kitada, T. et al. Mutations in the parkin gene cause autosomal recessive juvenile parkinsonism. Nature 392, 605–608 (1998)
https://doi.org/10.1038/33416.
89. Zimprich, A. et al. Mutations in LRRK2 cause autosomal-dominant Parkinsonism with pleomorphic pathology. Neuron 44, 601–607 (2004)
https://doi.org/10.1016/j.neuron.2004.11.005.
90. Gorostidi, A., Ruiz-Martínez, J., Lopez de Munain, A., Alzualde, A. & Martí Massó, J. F. LRRK2 G2019S and R1441G mutations associated with Parkinson's disease are common in the Basque Country, but relative prevalence is determined by ethnicity. neurogenetics 10, 157–159 (2009)
https://doi.org/10.1007/s10048-008-0162-0.
91. Kuhlmann, T. et al. Multiple sclerosis progression: time for a new mechanism-driven framework. The Lancet Neurology 22, 78–88 (2023)
https://doi.org/10.1016/S1474-4422(22)00289-7.
92. Goris, A., Vandebergh, M., McCauley, J. L., Saarela, J. & Cotsapas, C. Genetics of multiple sclerosis: lessons from polygenicity. The Lancet Neurology 21, 830–842 (2022)
https://doi.org/10.1016/S1474-4422(22)00255-1.
93. Harroud, A. et al. Locus for severity implicates CNS resilience in progression of multiple sclerosis. Nature 1–9 (2023)
https://doi.org/10.1038/s41586-023-06250-x.
94. Gordon, B. A. et al. Spatial patterns of neuroimaging biomarker change in individuals from families with autosomal dominant Alzheimer's disease: a longitudinal study. The Lancet Neurology 17, 241–250 (2018)
https://doi.org/10.1016/S1474-4422(18)30028-0.
95. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission - The Lancet.
https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)30367-6/fulltext [12/06/2023].
96. Oficina de Ciencia y Tecnología del Congreso de los Diputados (Oficina C). Calidad del aire. (2023)
https://doi.org/10.57952/h3ye-1663.
97. Montero-Odasso, M., Ismail, Z. & Livingston, G. One third of dementia cases can be prevented within the next 25 years by tackling risk factors. The case "for" and "against". Alzheimer's Research & Therapy 12, 81 (2020)
https://doi.org/10.1186/s13195-020-00646-x.
98. Ngandu, T. et al. A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial. The Lancet 385, 2255–2263 (2015)
https://doi.org/10.1016/S0140-6736(15)60461-5.
99. Prevention and risk reduction of dementia. World Wide FINGERS
https://wwfingers.com/ [02/08/2023].
100. Soto-Gordoa, M., Arrospide, A., Moreno-Izco, F., Martínez-Lage, P., Castilla, I. & Mar, J. Projecting burden of dementia in Spain, 2010–2050: Impact of modifying risk factors. Journal of Alzheimer's Disease 48, 721–730 (2015)
https://doi.org/10.3233/JAD-150233.
101. Betarbet, R., Sherer, T. B., MacKenzie, G., Garcia-Osuna, M., Panov, A. V. & Greenamyre, J. T. Chronic systemic pesticide exposure reproduces features of Parkinson's disease. Nature Neuroscience 3, 1301–1306 (2000)
https://doi.org/10.1038/81834.
102. Langston, J. W., Ballard, P., Tetrud, J. W. & Irwin, I. Chronic Parkinsonism in humans due to a product of meperidine-analog synthesis. Science (New York, N.Y.) 219, 979–980 (1983)
https://doi.org/10.1126/science.6823561.
103. Domenighetti, C. et al. Mendelian Randomisation Study of Smoking, Alcohol, and Coffee Drinking in Relation to Parkinson's Disease. Journal of Parkinson's disease 12, 267 (2022)
https://doi.org/10.3233/JPD-212851.
104. Gabbert, C. et al. Coffee, smoking and aspirin are associated with age at onset in idiopathic Parkinson's disease. Journal of Neurology 269, 4195–4203 (2022)
https://doi.org/10.1007/s00415-022-11041-x.
105. Gabbert, C., König, I. R., Lüth, T., Kasten, M., Grünewald, A., Klein, C. & Trinh, J. Lifestyle factors and clinical severity of Parkinson's disease. Scientific Reports 13, 9537 (2023)
https://doi.org/10.1038/s41598-023-31531-w.
106. Shiraiwa, N., Tamaoka, A. & Ohkoshi, N. Clinical features of drug-induced Parkinsonism. Neurology International 10, 7877 (2018)
https://doi.org/10.4081/ni.2018.7877.
107. Camacho-Soto, A., Warden, M. N., Searles Nielsen, S., Salter, A., Brody, D. L., Prather, H. & Racette, B. A. Traumatic brain injury in the prodromal period of Parkinson's disease: A large epidemiological study using medicare data. Annals of Neurology 82, 744–754 (2017)
https://doi.org/10.1002/ana.25074.
108. Mackay, D. F., Russell, E. R., Stewart, K., MacLean, J. A., Pell, J. P. & Stewart, W. Neurodegenerative disease mortality in former professional soccer players. The New England journal of medicine 381, 1801–1808 (2019)
https://doi.org/10.1056/NEJMoa1908483.

109. Vasta, R., Chia, R., Traynor, B. J. & Chiò, A. Unraveling the complex interplay between genes, environment, and climate in ALS. eBioMedicine 75, (2022) https://doi.org/10.1016/j.ebiom.2021.103795.
110. Armon, C. Smoking is a cause of amyotrophic lateral sclerosis. High low-density lipoprotein cholesterol levels? Unsure. Annals of Neurology 85, 465–469 (2019) https://doi.org/10.1002/ana.25468.
111. Peters, S. et al. Effect modification of the association between total cigarette smoking and ALS risk by intensity, duration and time-since-quitting: Euro-MOTOR. Journal of Neurology, Neurosurgery & Psychiatry 91, 33–39 (2020) https://doi.org/10.1136/jnnp-2019-320986.
112. Wang, H. et al. Smoking and risk of amyotrophic lateral sclerosis: a pooled analysis of five prospective cohorts. Archives of Neurology 68, 207–213 (2011) https://doi.org/10.1001/archneurol.2010.367.
113. Julian, T. H. et al. Physical exercise is a risk factor for amyotrophic lateral sclerosis: Convergent evidence from Mendelian randomisation, transcriptomics and risk genotypes. eBioMedicine 68, (2021) https://doi.org/10.1016/j.ebiom.2021.103397.
114. Van Rij, M. C. et al. Preimplantation genetic diagnosis (PGD) for Huntington's disease: the experience of three European centres. European Journal of Human Genetics 20, 368–375 (2012) https://doi.org/10.1038/ejhg.2011.202.
115. Blancato, J. K., Wolfe, E. & Sacks, P. C. Preimplantation genetics and other reproductive options in Huntington disease. Handbook of clinical neurology 144, 107–111 (2017) https://doi.org/10.1016/B978-0-12-801893-4.00009-2.
116. Bjornevik, K. et al. Longitudinal analysis reveals high prevalence of Epstein-Barr virus associated with multiple sclerosis. Science 375, 296–301 (2022) https://doi.org/10.1126/science.abj8222.
117. Robinson, W. H. & Steinman, L. Epstein-Barr virus and multiple sclerosis. Science 375, 264–265 (2022) https://doi.org/10.1126/science.abm7930.
118. ModernaTX, Inc. A Phase 1, randomized, observer-blind, placebo-controlled, dose-ranging study of an Epstein-Barr virus (EBV) candidate vaccine, mRNA-1189, in 18- to 30-year-old healthy adults. NCT05164094 (2022).
119. National Institute of Allergy and Infectious Diseases (NIAID). Phase 1 study of the safety and immunogenicity of an Epstein-Barr Virus (EBV) gp350- ferritin nanoparticle vaccine in healthy adults with or without EBV infection. NCT04645147 (2022).
120. Soldan, S. S. & Lieberman, P. M. Epstein–Barr virus and multiple sclerosis. Nature Reviews Microbiology 21, 51–64 (2023) https://doi.org/10.1038/s41579-022-00770-5.
121. Cree, B. A. C., Oksenberg, J. R. & Hauser, S. L. Multiple sclerosis: two decades of progress. The Lancet Neurology 21, 211–214 (2022) https://doi.org/10.1016/S1474-4422(22)00040-0.
122. World Alzheimer Report 2022: Life after diagnosis: Navigating treatment, care and support. (2022).
123. International, A. D. & University, M. World Alzheimer Report 2021: Journey through the diagnosis of dementia. (2021).
124. Bernstein Sideman, A. et al. Facilitators and barriers to dementia assessment and diagnosis: perspectives from dementia experts within a global health context. Frontiers in Neurology 13, 769360 (2022) https://doi.org/10.3389/fneur.2022.769360.
125. Zunzunegui Pastor, M. V., del Ser, T., Rodríguez Laso, A., García Yébenes, M. J., Domingo, J. & Otero Puime, A. Demencia no detectada y utilización de los servicios sanitarios: implicaciones para la atención primaria. Atención Primaria 31, 581–586 (2003) https://doi.org/10.1016/S0212-6567(03)79220-8.
126. Sociedad Española de Neurología. Al menos un 30% de los casos de demencia en el mundo podrían ser prevenibles, sin embargo, menos de un 50% de la población española conoce cómo. 21 de septiembre: día mundial de la enfermedad de Alzhéimer. Nota de prensa. (2022).
127. Poll finds a quarter of people with Parkinson's are wrongly diagnosed. Parkinson's UK https://www.parkinsons.org.uk/news/poll-finds-quarter-people-parkinsons-are-wrongly-diagnosed [04/08/2023].
128. van der Flier, W. M., de Vugt, M. E., Smets, E. M. A., Blom, M. & Teunissen, C. E. Towards a future where Alzheimer's disease pathology is stopped before the onset of dementia. Nature Aging 3, 494–505 (2023) https://doi.org/10.1038/s43587-023-00404-2.
129. Canevelli, M. et al. Spontaneous reversion of mild cognitive impairment to normal cognition: A systematic review of literature and meta-analysis. Journal of the American Medical Directors Association 17, 943–948 (2016) https://doi.org/10.1016/j.jamda.2016.06.020.
130. Milà-Alomà, M. et al. Plasma p-tau231 and p-tau217 as state markers of amyloid-β pathology in preclinical Alzheimer's disease. Nature Medicine 28, 1797–1801 (2022) https://doi.org/10.1038/s41591-022-01925-w.
131. Chapman, R. M. et al. Diagnosis of Alzheimer's disease using neuropsychological testing improved by multivariate analyses. Journal of clinical and experimental neuropsychology 32, 793–808 (2010) https://doi.org/10.1080/13803390903540315.
132. Wegierek, A. M. J., Lesniak, K., Patel, S. & Bogdanovskaya, Y. A collaborative approach to treatment of Alzheimer's disease from a psychological perspective. Alzheimer's Disease (ed. Wisniewski, T.) (Codon Publications, 2019). ISBN: 978-0-646-80968-7.
133. National Institute of Aging. Biomarkers for dementia detection and research fact sheet. NIH Publication No. 18-AG-8044. (2020).
134. Alzheimer's Society. Having a lumbar puncture. https://www.alzheimers.org.uk/research/take-part-research/lumbar-puncture [03/08/2023].
135. Avila, J. & Perry, G. A multilevel view of the development of Alzheimer's disease. Neuroscience 457, 283–293 (2021) https://doi.org/10.1016/j.neuroscience.2020.11.015.
136. Martínez-Lage, P., Martín-Carrasco, M., Arrieta, E., Rodrigo, J. & Formiga, F. Mapa de la enfermedad de Alzheimer y otras demencias en España. Proyecto MapEA. Revista Española de Geriatría y Gerontología 53, 26–37 (2018) https://doi.org/10.1016/j.regg.2017.07.006.
137. Jönsson, L. et al. The affordability of lecanemab, an amyloid-targeting therapy for Alzheimer's disease: an EADC-EC viewpoint. The Lancet Regional Health – Europe 29, (2023) https://doi.org/10.1016/j.lanepe.2023.100657.
138. Pineda-Pardo, J. A., Sánchez-Ferro, Á., Monje, M. H. G., Pavese, N. & Obeso, J. A. Onset pattern of nigrostriatal denervation in early Parkinson's disease. Brain 145, 1018–1028 (2022) https://doi.org/10.1093/brain/awab378.
139. Llaneza González, M. Á., Meca Lallana, J., González Platas, M. & Oreja-Guevara, C. Manual de práctica clínica en esclerosis múltiple, NMO y MOGAD. Recomendaciones diagnóstico-terapéuticas de la SEN2023. (2023).
140. Hegen, H. et al. Cerebrospinal fluid kappa free light chains for the diagnosis of multiple sclerosis: A consensus statement. Multiple Sclerosis (Houndmills, Basingstoke, England) 29, 182–195 (2023) https://doi.org/10.1177/13524585221134217.
141. Delaby, C., Hirtz, C. & Lehmann, S. Overview of the blood biomarkers in Alzheimer's disease: Promises and challenges. Revue Neurologique 179, 161–172 (2023) https://doi.org/10.1016/j.neurol.2022.09.003.
142. Ashton, N. J. et al. Plasma p-tau231: a new biomarker for incipient Alzheimer's disease pathology. Acta Neuropathologica 141, 709–724 (2021) https://doi.org/10.1007/s00401-021-02275-6.
143. Palmqvist, S. et al. Discriminative accuracy of plasma phospho-tau217 for Alzheimer disease vs other neurodegenerative disorders. JAMA 324, 1–11 (2020) https://doi.org/10.1001/jama.2020.12134.
144. Karikari, T. K. et al. Blood phosphorylated tau 181 as a biomarker for Alzheimer's disease: a diagnostic performance and prediction modelling study using data from four prospective cohorts. The Lancet. Neurology 19, 422–433 (2020) https://doi.org/10.1016/S1474-4422(20)30071-5.
145. Siderowf, A. et al. Assessment of heterogeneity among participants in the Parkinson's Progression Markers Initiative cohort using α-synuclein seed amplification: a cross-sectional study. The Lancet Neurology 22, 407–417 (2023) https://doi.org/10.1016/S1474-4422(23)00109-6.
146. Liu, X. et al. Utility of serum neurofilament light chain and glial fibrillary acidic protein as diagnostic biomarkers of freezing of gait in Parkinson's disease. Brain Research 1822, 148660 (2024) https://doi.org/10.1016/j.brainres.2023.148660.
147. Koníčková, D. et al. Cerebrospinal fluid and blood serum biomarkers in neurodegenerative proteinopathies: A prospective, open, cross-correlation study. Journal of Neurochemistry 167, 168–182 (2023) https://doi.org/10.1111/jnc.15944.
148. Oh, J. & Kim, J. A. Supportive care needs of patients with amyotrophic lateral sclerosis/motor neuron disease and their caregivers: A scoping review. Journal of Clinical Nursing 26, 4129–4152 (2017) https://doi.org/10.1111/jocn.13945.
149. Grupo Parlamentario Ciudadanos. Proposición de Ley para garantizar el derecho a una vida digna de las personas con esclerosis lateral amiotrófica. (122/000180). XIV Legislatura. https://www.congreso.es/es/busqueda-de-iniciativas?p_p_id=iniciativas&p_p_lifecycle=0&p_p_state=normal&p_p_mode=view&_iniciativas_mode=mostrarDetalle&_iniciativas_legislatura=XIV&_iniciativas_id=122/000180 .
150. O'Shea, E., Keogh, F. & Heneghan, C. Post-diagnostic support for people with dementia and their carers. https://www.lenus.ie/handle/10147/623091 (2018).
151. Martínez-Lage Álvarez, P. Actitudes, dudas y conocimientos de los colectivos implicados en la atención del paciente con Alzheimer: resultados de la encuesta del proyecto kNOW Alzheimer. Farmacéuticos Comunitarios 7, 13–23 (2016) https://doi.org/10.5672/FC.2173-9218.(2016/Vol8).001.03.
152. Simmons, H. Getting post diagnostic support (PDS) right for people with dementia. Alzheimer Scotland. (2011).
153. Iruela, F. Mi realidad psicológica sobre la enfermedad de Huntington. Una guía práctica. (2019).
154. Gong, P., Fanos, J. H., Korty, L., Siskind, C. E. & Hanson-Kahn, A. K. Impact of Huntington disease gene-positive status on pre-symptomatic young adults and recommendations for genetic counselors. Journal of Genetic Counseling 25, 1188–1197 (2016) https://doi.org/10.1007/s10897-016-9951-z.
155. Glantz, M. J., Chamberlain, M. C., Liu, Q., Hsieh, C.-C., Edwards, K. R., Van Horn, A. & Recht, L. Gender disparity in the rate of partner abandonment in patients with serious medical illness. Cancer 115, 5237–5242 (2009) https://doi.org/10.1002/cncr.24577.
156. Vitturi, B. K. et al. Work barriers and job adjustments of people with multiple sclerosis: A systematic review. Journal of Occupational Rehabilitation 33, 450–462 (2023) https://doi.org/10.1007/s10926-022-10084-1.
157. Oreja-Guevara, C., Kobelt, G., Berg, J., Capsa, D., Eriksson, J., & European Multiple Sclerosis Platform. New insights into the burden and costs of multiple sclerosis in Europe: Results for Spain. Multiple Sclerosis (Houndmills, Basingstoke, England) 23, 166–178 (2017) https://doi.org/10.1177/1352458517708672.
158. NICE Guideline. Parkinson's disease in adults. What medicines might help? Information for the public. https://www.nice.org.uk/guidance/ng71/ifp/chapter/What-medicines-might-help [09/08/2023].
159. EMA. Levodopa/Carbidopa/Entacapone Orion. European Medicines Agency https://www.ema.europa.eu/en/medicines/human/EPAR/levodopa-carbidopa-entacapone-orion [09/08/2023].
160. Verschuur, C. V. M. et al. Randomized delayed-start trial of levodopa in Parkinson's disease. New England Journal of Medicine 380, 315–324 (2019) https://doi.org/10.1056/NEJMoa1809983.

161. Castela, I. et al. Selective activation of striatal indirect pathway suppresses levodopa induced-dyskinesias. Neurobiology of Disease 176, 105930 (2023) https://doi.org/10.1016/j.nbd.2022.105930.
162. Olanow, C. W., Calabresi, P. & Obeso, J. A. Continuous dopaminergic stimulation as a treatment for Parkinson's disease: current status and future opportunities. Movement Disorders: Official Journal of the Movement Disorder Society 35, 1731–1744 (2020) https://doi.org/10.1002/mds.28215.
163. Oficina de Ciencia y Tecnología del Congreso de los Diputados (Oficina C). Informe C: Avances en neurociencia: aplicaciones e implicaciones éticas. (2023) https://doi.org/10.57952/t6ry-4757.
164. Gardner, J. A history of Deep Brain Stimulation: Technological innovation and the role of clinical assessment tools. Social Studies of Science 43, 707–728 (2013) https://doi.org/10.1177/0306312713483678.
165. Deuschl, G. et al. A randomized trial of Deep-Brain Stimulation for Parkinson's disease. New England Journal of Medicine 355, 896–908 (2006) https://doi.org/10.1056/NEJMoa060281.
166. Bronstein, J. M. et al. Deep Brain Stimulation for Parkinson disease: An expert consensus and review of key issues. Archives of Neurology 68, 165 (2011) https://doi.org/10.1001/archneurol.2010.260.
167. Moosa, S., Martínez-Fernández, R., Elias, W. J., Del Alamo, M., Eisenberg, H. M. & Fishman, P. S. The role of high-intensity focused ultrasound as a symptomatic treatment for Parkinson's disease. Movement Disorders: Official Journal of the Movement Disorder Society 34, 1243–1251 (2019) https://doi.org/10.1002/mds.27779.
168. Arias-Pacheco, A., Polo-de-Santos, M. del M., Luengo-Matos, S., Hijas-Gómez, A. I., Rodríguez-Ortiz-de-Salazar, B. & Sánchez-Gómez, L. M. PP109 Efficacy and safety of high-intensity focused ultrasound In Parkinson's disease. International Journal of Technology Assessment in Health Care 38, S75–S75 (2022) https://doi.org/10.1017/S026646232200232X.
169. Martínez Fernández, R. et al. Unilateral focused ultrasound subthalamotomy in early Parkinson's disease: a pilot study. Journal of Neurology, Neurosurgery, and Psychiatry jnnp-2023-331211 (2023) https://doi.org/10.1136/jnnp-2023-331211.
170. Schneider, L. S., Dagerman, K. & Insel, P. S. Efficacy and adverse effects of atypical antipsychotics for dementia: Meta-analysis of randomized, placebo-controlled trials. The American Journal of Geriatric Psychiatry 14, 191–210 (2006) https://doi.org/10.1097/01.JGP.0000200589.01396.6d.
171. Ballard, C. & Waite, J. The effectiveness of atypical antipsychotics for the treatment of aggression and psychosis in Alzheimer's disease. The Cochrane Database of Systematic Reviews CD003476 (2006) https://doi.org/10.1002/14651858.CD003476.pub2.
172. Ballard, C. et al. Quetiapine and Rivastigmine and cognitive decline In Alzheimer's disease: randomised double blind placebo controlled trial. BMJ: British Medical Journal 330, 874–877 (2005).
173. Grossberg, G. T. et al. Efficacy and safety of Brexpiprazole for the treatment of agitation in Alzheimer's dementia: two 12-week, randomized, double-blind, placebo-controlled trials. The American Journal of Geriatric Psychiatry 28, 383–400 (2020) https://doi.org/10.1016/j.jagp.2019.09.009.
174. Sociedad Española de Geriatría y Gerontología. Cuidado sin sujeciones. (2023).
175. Commissioner, O. of the. FDA converts novel Alzheimer's disease treatment to traditional approval. FDA https://www.fda.gov/news-events/press-announcements/fda-converts-novel-alzheimers-disease-treatment-traditional-approval [03/08/2023].
176. van Dyck, C. H. et al. Lecanemab in early Alzheimer's disease. New England Journal of Medicine 388, 9–21 (2023) https://doi.org/10.1056/NEJMoa2212948.
177. EISAI's approach to U.S. pricing for LEQEMBITM (LECANEMAB), a treatment for early Alzheimer's disease, sets of forth our concept of 'societal value of medicine' in relation to 'price of medicine'. Eisai Newsroom https://media-us.eisai.com/2023-01-06-EISAIS-APPROACH-TO-U-S-PRICING-FOR-LEQEMBI-TM-LECANEMAB-,-A-TREATMENT-FOR-EARLY-ALZHEIMERS-DISEASE,-SETS-FORTH-OUR-CONCEPT-OF-SOCIETAL-VALUE-OF-MEDICINE-IN-RELATION-TO-PRICE-OF-MEDICINE [09/08/2023].
178. Lancet, T. Lecanemab for Alzheimer's disease: tempering hype and hope. The Lancet 400, 1899 (2022) https://doi.org/10.1016/S0140-6736(22)02480-1.
179. Wittenberg, R. et al. The costs of dementia in England. International Journal of Geriatric Psychiatry 34, 1095–1103 (2019) https://doi.org/10.1002/gps.5113.
180. Pittock, R. R. et al. Eligibility for anti-amyloid treatment in a population-based study of cognitive aging. Neurology 101, e1837–e1849 (2023) https://doi.org/10.1212/WNL.0000000000207770.
181. Sims, J. R. et al. Donanemab in early symptomatic Alzheimer disease: The TRAILBLAZER-ALZ 2 randomized clinical trial. JAMA 330, 512–527 (2023) https://doi.org/10.1001/jama.2023.13239.
182. Amyotrophic Lateral Sclerosis/Riluzole Study Group II, Lacomblez, L., Bensimon, G., Meininger, V., Leigh, P. N. & Guillet, P. Dose-ranging study of riluzole in amyotrophic lateral sclerosis. The Lancet 347, 1425–1431 (1996) https://doi.org/10.5555/uri:pii:S0140673696916803.
183. Fang, T., Khleifat, A. A., Meurgey, J.-H., Jones, A., Leigh, P. N., Bensimon, G. & Al-Chalabi, A. Stage at which riluzole treatment prolongs survival in patients with amyotrophic lateral sclerosis: a retrospective analysis of data from a dose-ranging study. The Lancet Neurology 17, 416–422 (2018) https://doi.org/10.1016/S1474-4422(18)30054-1.
184. Wadman, M. 'I feel so much hope'—Is a new drug keeping this woman's deadly Huntington disease at bay? Science AAAS - News Feature (2018).
185. GlobalData Healthcare. Roche to reassess Huntington's asset, reviving potential for younger patients. Clinical Trials Arena https://www.clinicaltrialsarena.com/comment/roche-tominersen-huntingtons-asset/ [11/08/2023].
186. Coppen, E. M. & Roos, R. A. C. Current pharmacological approaches to reduce chorea in Huntington's disease. Drugs 77, 29–46 (2017) https://doi.org/10.1007/s40265-016-0670-4.
187. Stimming, E. F. et al. Safety and efficacy of valbenazine for the treatment of chorea associated with Huntington's disease (KINECT-HD): a phase 3, randomised, double-blind, placebo-controlled trial. The Lancet Neurology 22, 494–504 (2023) https://doi.org/10.1016/S1474-4422(23)00127-8.
188. Thompson, A. J., Baranzini, S. E., Geurts, J., Hemmer, B. & Ciccarelli, O. Multiple sclerosis. The Lancet 391, 1622–1636 (2018) https://doi.org/10.1016/S0140-6736(18)30481-1.
189. Cencioni, M. T., Mattoscio, M., Magliozzi, R., Bar-Or, A. & Muraro, P. A. B cells in multiple sclerosis — from targeted depletion to immune reconstitution therapies. Nature Reviews Neurology 17, 399–414 (2021) https://doi.org/10.1038/s41582-021-00498-5.
190. Krämer, J., Bar-Or, A., Turner, T. J. & Wiendl, H. Bruton tyrosine kinase inhibitors for multiple sclerosis. Nature Reviews Neurology 19, 289–304 (2023) https://doi.org/10.1038/s41582-023-00800-7.
191. Cummings, J. L., Morstorf, T. & Zhong, K. Alzheimer's disease drug-development pipeline: few candidates, frequent failures. Alzheimer's Research & Therapy 6, 37 (2014) https://doi.org/10.1186/alzrt269.
192. Holm, I. E., Alstrup, A. K. O. & Luo, Y. Genetically modified pig models for neurodegenerative disorders. The Journal of Pathology 238, 267–287 (2016) https://doi.org/10.1002/path.4654.
193. Blesa, J., Trigo-Damas, I., Del Rey, N. L.-G. & Obeso, J. A. The use of nonhuman primate models to understand processes in Parkinson's disease. Journal of Neural Transmission (Vienna, Austria: 1996) 125, 325–335 (2018) https://doi.org/10.1007/s00702-017-1715-x.
194. Monreal, E. et al. Association of serum neurofilament light chain levels at disease onset with disability worsening in patients with a first demyelinating multiple sclerosis event not treated with high-efficacy drugs. JAMA Neurology 80, 397–403 (2023) https://doi.org/10.1001/jamaneurol.2023.0010.
195. Kiernan, M. C. et al. Improving clinical trial outcomes in amyotrophic lateral sclerosis. Nature Reviews Neurology 17, 104–118 (2021) https://doi.org/10.1038/s41582-020-00434-z.
196. HEALEY ALS Platform Trial. Massachusetts General Hospital https://www.massgeneral.org/neurology/als/research/platform-trial [26/09/2023].
197. Hang, Z., Zhou, L., Xing, C., Wen, Y. & Du, H. The blood-brain barrier, a key bridge to treat neurodegenerative diseases. Ageing Research Reviews 91, 102070 (2023) https://doi.org/10.1016/j.arr.2023.102070.
198. Blesa, J. et al. BBB opening with focused ultrasound in nonhuman primates and Parkinson's disease patients: Targeted AAV vector delivery and PET imaging. Science Advances 9, eadf4888 (2023) https://doi.org/10.1126/sciadv.adf4888.
199. Ministerio de Sanidad. Abordaje del Alzheimer y otras demencias. Estrategia en enfermedades neurodegenerativas del Sistema Nacional de Salud. https://www.sanidad.gob.es/organizacion/sns/planCalidadSNS/pdf/Abordaje_del_Alzheimer_y_otras_demencias_Accesible.pdf (2022).
200. Groot, C. et al. The effect of physical activity on cognitive function in patients with dementia: A meta-analysis of randomized control trials. Ageing Research Reviews 25, 13–23 (2016) https://doi.org/10.1016/j.arr.2015.11.005.
201. Jia, R., Liang, J., Xu, Y. & Wang, Y. Effects of physical activity and exercise on the cognitive function of patients with Alzheimer disease: a meta-analysis. BMC Geriatrics 19, 181 (2019) https://doi.org/10.1186/s12877-019-1175-2.
202. Schenkman, M. et al. Effect of high-intensity treadmill exercise on motor symptoms in patients with de novo Parkinson disease. JAMA Neurology 75, 219–226 (2018) https://doi.org/10.1001/jamaneurol.2017.3517.
203. Quinn, L. et al. Physical activity and exercise outcomes in Huntington's disease (PACE-HD): results of a 12-month trial-within-cohort feasibility study of a physical activity intervention in people with Huntington's disease. Parkinsonism & Related Disorders 101, 75–89 (2022) https://doi.org/10.1016/j.parkreldis.2022.06.013.
204. Proschinger, S., Kuhwand, P., Rademacher, A., Walzik, D., Warnke, C., Zimmer, P. & Joisten, N. Fitness, physical activity, and exercise in multiple sclerosis: a systematic review on current evidence for interactions with disease activity and progression. Journal of Neurology 269, 2922–2940 (2022) https://doi.org/10.1007/s00415-021-10935-6.
205. Ministerio de Sanidad, Consumo y Bienestar Social. Abordaje de la Esclerosis Lateral Amiotrófica. Estrategia en enfermedades neurodegenerativas del Sistema Nacional de Salud. https://www.sanidad.gob.es/organizacion/sns/planCalidadSNS/pdf/Abordaje_de_la_Esclerosis_Lateral_Amiotrofica_2017.pdf (2018).
206. Zaunbrecher, N. Non-drug treatments for Huntington's disease. Huntington's Disease News https://huntingtonsdiseasenews.com/non-drug-treatments-for-huntingtons-disease/ [14/08/2023].
207. Mar, J., Gorostiza, A., Ibarrondo, O., Larrañaga, I., Arrospide, A., Martinez-Lage, P. & Soto-Gordoa, M. Economic evaluation of supplementing the diet with Souvenaid in patients with prodromal Alzheimer's disease. Alzheimer's Research & Therapy 12, 166 (2020) https://doi.org/10.1186/s13195-020-00737-9.

208. AETSA. Efectividad del entrenamiento cognitivo en pacientes con demencia leve a moderada. Informes de evaluación de tecnologías sanitarias. (2020).
209. Bahar-Fuchs, A., Martyr, A., Goh, A. M., Sabates, J. & Clare, L. Cognitive training for people with mild to moderate dementia. The Cochrane Database of Systematic Reviews 2019, CD013069 (2019) https://doi.org/10.1002/14651858.CD013069.pub2.
210. Cafferata, R. M. T., Hicks, B. & von Bastian, C. C. Effectiveness of cognitive stimulation for dementia: A systematic review and meta-analysis. Psychological Bulletin 147, 455–476 (2021) https://doi.org/10.1037/bul0000325.
211. Spector, A., Thorgrimsen, L., Woods, B., Royan, L., Davies, S., Butterworth, M. & Orrell, M. Efficacy of an evidence-based cognitive stimulation therapy programme for people with dementia: Randomised controlled trial. The British Journal of Psychiatry 183, 248–254 (2003) https://doi.org/10.1192/bjp.183.3.248.
212. McDermott, O. et al. Psychosocial interventions for people with dementia: a synthesis of systematic reviews. Aging & Mental Health 23, 393–403 (2019) https://doi.org/10.1080/13607863.2017.1423031.
213. Lobbia, A., Carbone, E., Faggian, S., Gardini, S., Piras, F., Spector, A. & Borella, E. The efficacy of Cognitive Stimulation Therapy (CST) for people with mild-to-moderate dementia. European Psychologist 24, 257–277 (2019) https://doi.org/10.1027/1016-9040/a000342.
214. Justo-Henriques, S. I., Pérez-Sáez, E., Carvalho, J. O., Cavallo, M. & Sargaço, P. Home-based individualized Cognitive Stimulation (iCS) Therapy in Portuguese psychiatric patients: A randomized controlled trial. Brain Sciences 12, 1655 (2022) https://doi.org/10.3390/brainsci12121655.
215. Gibbor, L., Yates, L., Volkmer, A. & Spector, A. Cognitive stimulation therapy (CST) for dementia: a systematic review of qualitative research. Aging & Mental Health 25, 980–990 (2021) https://doi.org/10.1080/13607863.2020.1746741.
216. Knapp, M. et al. What are the current and projected future cost and health-related quality of life implications of scaling up cognitive stimulation therapy? International Journal of Geriatric Psychiatry 37, (2022) https://doi.org/10.1002/gps.5633.
217. Pérez-Sáez, E., Cabrero-Montes, E. M., Llorente-Cano, M. & González-Ingelmo, E. A pilot study on the impact of a pottery workshop on the well-being of people with dementia. Dementia 19, 2056–2072 (2020) https://doi.org/10.1177/1471301218814634.
218. Cernuda Lago, A., de Andrés Terán, A. L., Cernuda Lago, A. & de Andrés Terán, A. L. Beneficios del psicoballet cubano en el tratamiento de enfermos de Alzheimer. Validación psicométrica. Revista Información Científica 98, 171–183 (2019).
219. García-Valverde, E., Badia, M., Orgaz, M. B. & Gónzalez-Ingelmo, E. The influence of songwriting on quality of life of family caregivers of people with dementia: An exploratory study. Nordic Journal of Music Therapy 29, 4–19 (2020) https://doi.org/10.1080/08098131.2019.1630666.
220. de Medeiros, K. & Basting, A. "Shall I compare thee to a dose of Donepezil?": Cultural arts interventions in dementia care research. The Gerontologist 54, 344–353 (2014) https://doi.org/10.1093/geront/gnt055.
221. Windle, G., Gregory, S., Howson-Griffiths, T., Newman, A., O'Brien, D. & Goulding, A. Exploring the theoretical foundations of visual art programmes for people living with dementia. Dementia 17, 702–727 (2018) https://doi.org/10.1177/1471301217726613.
222. Cousins, E., Tischler, V., Garabedian, C. & Dening, T. A taxonomy of arts interventions for people with dementia. The Gerontologist 60, 124–134 (2020) https://doi.org/10.1093/geront/gnz024.
223. Robillard, J. M. The online environment: A key variable in the ethical response to complementary and alternative medicine for Alzheimer's disease. Journal of Alzheimer's Disease 51, 11–13 (2016) https://doi.org/10.3233/JAD-150641.
224. Office of Regulatory Affairs. Health fraud scams. FDA https://www.fda.gov/consumers/health-fraud-scams [16/08/2023].
225. Oficina de Ciencia y Tecnología del Congreso de los Diputados. Informe C: La desinformación en la era digital. (2023) https://doi.org/10.57952/j3p6-9086.
226. Cuidados paliativos. https://www.who.int/es/news-room/fact-sheets/detail/palliative-care [16/08/2023].
227. Kluger, B. M., Dolhun, R., Sumrall, M., Hall, K. & Okun, M. S. Palliative care and Parkinson's disease: Time to move beyond cancer. Movement Disorders 36, 1325–1329 (2021) https://doi.org/10.1002/mds.28556.
228. Brizzi, K. Outpatient neuropalliative care. Handbook of Clinical Neurology 191, 29–48 (2023) https://doi.org/10.1016/B978-0-12-824535-4.00002-1.
229. Muñoz Cobos, F., Espinosa Almendro, J. M., Portillo Strempell, J. & Benítez del Rosario, M. A. Cuidados paliativos: Atención a la familia. Atención Primaria 30, 576–580 (2002).
230. Miller, S. C., Lima, J. C., Intrator, O., Martin, E., Bull, J. & Hanson, L. C. Specialty palliative care consultations for nursing home residents with dementia. Journal of Pain and Symptom Management 54, 9-16.e5 (2017) https://doi.org/10.1016/j.jpainsymman.2017.03.005.
231. Miranda, R., Smets, T., De Schreye, R., Faes, K., Van Den Noortgate, N., Cohen, J. & Van den Block, L. Improved quality of care and reduced healthcare costs at the end-of-life among older people with dementia who received palliative home care: A nationwide propensity score-matched decedent cohort study. Palliative Medicine 35, 1701–1712 (2021) https://doi.org/10.1177/02692163211019321.
232. Mercadante, S. & Al-Husinat, L. Palliative care in Amyotrophic Lateral Sclerosis. Journal of Pain and Symptom Management S0885-3924(23)00574–2 (2023) https://doi.org/10.1016/j.jpainsymman.2023.06.029.
233. Ministerio de Sanidad. Registro Nacional de Instrucciones Previas. https://www.sanidad.gob.es/areas/profesionesSanitarias/rnip/home.htm [12/09/2023].
234. Lum, H. D. & Kluger, B. M. Palliative care for Parkinson disease. Clinics in geriatric medicine 36, 149–157 (2020) https://doi.org/10.1016/j.cger.2019.09.013.
235. Boersema-Wijma, D. J., van Duijn, E., Heemskerk, A.-W., van der Steen, J. T. & Achterberg, W. P. Palliative care in advanced Huntington's disease: a scoping review. BMC palliative care 22, 54 (2023) https://doi.org/10.1186/s12904-023-01171-y.
236. Arias-Casais, N. (Natalia) et al. EAPC Atlas of palliative care in Europe 2019. (2019).
237. Álvarez Saúco, M. et al. Manejo de la atención paliativa de los pacientes con enfermedad de Parkinson y otros trastornos del movimiento en España. Encuesta Nacional a neurólogos. Neurología S0213485321002577 (2021) https://doi.org/10.1016/j.nrl.2021.09.008.
238. Ministerio de Sanidad. Jornada de cuidados paliativos del Sistema Nacional de Salud. https://www.sanidad.gob.es/profesionales/excelencia/jornada/cuidadosPaliativos.htm [13/09/2023].
239. Casi 80.000 personas mueren cada año en España sin recibir cuidados paliativos – SID. https://sid-inico.usal.es/noticias/casi-80-000-personas-mueren-cada-ano-en-espana-sin-recibir-cuidados-paliativos/ [12/09/2023].
240. Ministerio de Sanidad, Política Social e Igualdad. Estrategia en cuidados paliativos del Sistema Nacional de Salud. Actualización 2010-2014. (2011).
241. Confederación Española de Asociaciones de Familiares de personas con Alzheimer y otras demencias. Censo de las personas con alzhéimer y otras demencias en España. Resultados y conclusiones de las jornadas virtuales para el intercambio de soluciones y propuestas. (2021).
242. Dawson, W. D. & Comas-Herrera, A. International dementia policies and legacies of the coronavirus disease 2019 pandemic. The Public Policy and Aging Report 32, 72–76 (2022) https://doi.org/10.1093/ppar/prac008.
243. Ministerio de Sanidad. Relación de centros, servicios y unidades de referencia (CSUR) del Sistema Nacional de Salud designados para la atención o realización de las patologías o procedimientos que se indican. (2022).
244. Hogden, A., Foley, G., Henderson, R., James, N. & Aoun, S. Amyotrophic lateral sclerosis: improving care with a multidisciplinary approach. Journal of Multidisciplinary Healthcare Volume 10, 205–215 (2017) https://doi.org/10.2147/JMDH.S134992.
245. Paipa, A. J. et al. Survival benefit of multidisciplinary care in amyotrophic lateral sclerosis in Spain: association with noninvasive mechanical ventilation. Journal of Multidisciplinary Healthcare 12, 465–470 (2019) https://doi.org/10.2147/JMDH.S205313.
246. Cordesse, V., Sidorok, F., Schimmel, P., Holstein, J. & Meininger, V. Coordinated care affects hospitalization and prognosis in amyotrophic lateral sclerosis: a cohort study. BMC Health Services Research 15, 134 (2015) https://doi.org/10.1186/s12913-015-0810-7.
247. Barber Pérez, P. & González López-Valcárcel, B. Informe oferta-necesidad de especialistas médicos 2021-2035. (2022).
248. Aldridge, Z., Oliver, E., Gardener, H. & Dening, K. H. Admiral nursing—A model of specialist dementia care in acute hospitals. SAGE Open Nursing 6, 2377960820952677 (2020) https://doi.org/10.1177/2377960820952677.
249. Kingston, A., Comas-Herrera, A. & Jagger, C. Forecasting the care needs of the older population in England over the next 20 years: estimates from the Population Ageing and Care Simulation (PACSim) modelling study. The Lancet Public Health 3, e447–e455 (2018) https://doi.org/10.1016/S2468-2667(18)30118-X.
250. Liu, K. Y. et al. Dementia wellbeing and COVID-19: Review and expert consensus on current research and knowledge gaps. International Journal of Geriatric Psychiatry 36, 1597–1639 (2021) https://doi.org/10.1002/gps.5567.
251. Jönsson, L., Tate, A., Frisell, O. & Wimo, A. The costs of dementia in Europe: An updated review and meta-analysis. Pharmacoeconomics 41, 59–75 (2023) https://doi.org/10.1007/s40273-022-01212-z.
252. Gómez Maldonado, L., de Mora-Figueroa, R., López-Angarita, A., Maravilla-Herrera, P. & Merino, M. Cost of patients with Alzheimer's disease in Spain according to disease severity. PharmacoEconomics - Open (2023) https://doi.org/10.1007/s41669-023-00451-w.
253. Jutkowitz, E., Kane, R. L., Gaugler, J. E., MacLehose, R. F., Dowd, B. & Kuntz, K. M. Societal and family lifetime cost of dementia: Implications for policy. Journal of the American Geriatrics Society 65, 2169–2175 (2017) https://doi.org/10.1111/jgs.15043.
254. Jönsson, L. The personal economic burden of dementia in Europe. The Lancet Regional Health - Europe 20, 100472 (2022) https://doi.org/10.1016/j.lanepe.2022.100472.
255. Guillén, M. & Comas-Herrera, A. How much risk is mitigated by LTC protection schemes? A methodological note and a case study of the public system in Spain. The Geneva Papers on Risk and Insurance. Issues and Practice 37, 712–724 (2012).
256. Oliva, J., Peña Longobardo, L. M. & Vilaplana-Prieto, C. Personas que reciben cuidado informal en casa según la Encuesta de Discapacidades del INE 2020 y 2008.
257. Vilaplana-Prieto, C. & Oliva-Moreno, J. Time value of informal care of people with Alzheimer's disease in Spain: a population-based analysis. En evaluación en revista científica (2023).
258. García-Mochón, L., Peña-Longobardo, L. M., del Río-Lozano, M., Oliva-Moreno, J., Larrañaga-Padilla, I. & García-Calvente, M. del M. Determinants of burden and satisfaction in informal caregivers: two wides of the same coin? The CUIDAR-SE study. International Journal of Environmental Research and Public Health 16, 4378 (2019) https://doi.org/10.3390/ijerph16224378.

259. Peña-Longobardo, L. M. & Oliva-Moreno, J. Caregiver burden in Alzheimer's disease patients in Spain. Journal of Alzheimer's Disease 43, 1293–1302 (2015) https://doi.org/10.3233/JAD-141374. https://www.ine.es/dyngs/INEbase/es/operacion.
260. Peña-Longobardo, L. M., Río-Lozano, M. D., Oliva-Moreno, J., Larrañaga-Padilla, I. & García-Calvente, M. del M. Health, work, and social problems in Spanish informal caregivers: Does gender matter? (The CUIDAR-SE study). International Journal of Environmental Research and Public Health 18, 7332 (2021) https://doi.org/10.3390/ijerph18147332.
261. Parisé, H. et al. Direct and indirect cost burden associated with multiple sclerosis relapses: Excess costs of persons with MS and their spouse caregivers. Journal of the Neurological Sciences 330, 71–77 (2013) https://doi.org/10.1016/j.jns.2013.04.007.
262. Klietz, M. Caregiver burden in movement disorders and neurodegenerative diseases: Editorial. Brain Sciences 12, 1184 (2022) https://doi.org/10.3390/brainsci12091184.
263. Hung, L. et al. Creating dementia-friendly communities for social inclusion: A scoping review. Gerontology and Geriatric Medicine 7, 23337214211013596 (2021) https://doi.org/10.1177/23337214211013596.
264. Evans, S. C., Atkinson, T., Rogerson, M. & Bray, J. Nature-based activities for people living with dementia: a nice day out or a matter of human rights? Working with Older People 26, 64–75 (2021) https://doi.org/10.1108/WWOP-08-2021-0040.
265. Bould, E. Dementia-friendly garden centre. A practical guide to becoming dementia-friendly. Alzheimer's Society. (2017).
266. Ministerio de Derechos Sociales y Agenda 2030. Estrategia estatal de desinstitucionalización. https://estrategiadesinstitucionalizacion.gob.es/ [21/03/2023].
267. Evans, S., Waller, S., Bray, J. & Atkinson, T. Making homes more dementia-friendly through the use of aids and adaptations. Healthcare 7, 43 (2019) https://doi.org/10.3390/healthcare7010043.
268. Evans, S. C. et al. Can extra care housing support the changing needs of older people living with dementia? Dementia (London, England) 19, 1492–1508 (2020) https://doi.org/10.1177/1471301218801743.
269. Díaz-Veiga, P. Unidades de convivencia para personas mayores en el marco del proceso de desinstitucionalización. (2022).
270. Sancho Castiello, M. Viviendas y alojamientos para personas mayores. La experiencia internacional. Revista Internacional de los Estudios Vascos (2020).
271. adEla, R. La Comunidad de Madrid pondrá en marcha el primer centro público residencial para enfermos de ELA. adELA https://adelaweb.org/la-comunidad-de-madrid-pondra-en-marcha-el-primer-centro-publico-residencial-para-enfermos-de-ela/ [08/09/2023].
272. admin. Decisiones ante la Traqueotomía en la ELA: Sí o No. ELA ANDALUCÍA https://www.elaandalucia.es/decisiones-ante-la-traqueotomia-la-ela-no/ [15/09/2023].
273. adEla, R. El Zendal albergará un Centro de Atención Diurna para pacientes con ELA. adELA https://adelaweb.org/el-zendal-albergara-un-centro-de-atencion-diurna-para-pacientes-con-ela/ [22/09/2023].