Defeating Alzheimer's disease and other dementias: a priority for European science and society

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Executive summary

Alzheimer's disease (AD) is the leading cause of dementia, and because the primary risk factor for AD is old age, the prevalence of the disease is increasing dramatically with ageing populations worldwide. Even in high-income countries, the cost of medical care and associated societal burdens of dementia threaten to become overwhelming as more people live into old age. In view of the lack of progress in developing a cure for AD and the rapidly increasing costs of dementia, policy makers and governments have a powerful incentive to provide more resources to develop AD therapeutics. The *Lancet Neurology* Commission was formed with the overarching aim to provide information and expert recommendations to policy makers and political leaders about the growing problem of AD and related dementias of ageing.

The past two decades have seen remarkable improvements in the quality of care for patients with AD, with a research-driven shift to more personalised and integrated team-oriented care. Epidemiological and genetic studies have identified many factors that increase the risk of AD. Prevention studies have highlighted the possibility of targeting risk and protective factors to delay onset, with the promise of reducing the overall prevalence of dementia. However, no treatment is yet available to halt or reverse the underlying pathology of established AD. Indeed, an effective therapy for AD is perhaps the greatest unmet need facing modern medicine. Basic biomedical research has provided insights into the causes and pathogenesis of AD and other neurodegenerative diseases, but improved understanding of disease mechanisms will be needed to develop safe and effective disease-modifying treatments. Nonetheless, several drugs are currently in late phases of clinical development.

The Commission considered a range of challenges that need to be addressed to reduce the burden of dementia, and these challenges are discussed in detail in the main sections of our report: health economics (section 1), epidemiology (section 2), prevention (section 3), genetics (section 4), biology (section 5), diagnosis (section 6), treatment (sections 7, 8), care (section 9), and ethics (section 10). In panel 1 we summarise the key findings of the Commission, with recommendations about how patient care and related research—from basic to clinical—in AD and other dementias should be organised in the future. A concerted effort to tackle dementia is needed, with a substantial overall increase in government and private investment in the care of patients and the search for AD therapeutics.

Europe is well placed to take the world lead, in partnership with international organisations, to develop new approaches to prevent or cure AD and other dementias and to provide models of compassionate care for patients. As the cost of care increases, funds must not be shunted from basic research, clinical research, and drug-discovery programmes. In fact, a substantial increase in long-term funding for multidisciplinary research programmes is absolutely essential to reduce the burden of individual suffering and the enormous societal cost of AD. Only targeted increases in research investment will provide any hope of finding a cure for AD or developing strategies to delay the onset or slow the progression of the disease.

Introduction

Dementia encompasses a range of neurological disorders characterised by memory loss and cognitive impairment. Alzheimer's disease (AD) is the most common form of dementia, accounting for 50–70% of cases. The most common early symptom of dementia is difficulty in remembering recent events. As the disorder develops, a wide range of other symptoms can emerge, such as disorientation, mood swings, confusion, more serious memory loss, behavioural changes, difficulties in speaking and swallowing, and problems with walking. Progressive accumulation of disability, with deterioration in multiple cognitive domains, interferes with daily functioning, including social and professional functioning.[1] Thus, dementia substantially affects the daily lives of patients, their families, and wider society.

Increasing age is the most important risk factor for AD and other dementias, and as life expectancy increases and demographic ageing occurs in populations around the world, the number of people with dementia is expected to increase. In 2015, almost 47 million people worldwide were estimated to be affected by dementia, and the numbers are expected to reach 75 million by 2030, and 131 million by 2050, with the greatest increase expected in low-income and middle-income countries.[2] In 2012 and 2015, the World Health Organization (WHO) presented reports in which it acknowledged this trend—sometimes described in terms of a fast-growing epidemic—and concluded that AD and other dementias should be regarded as a global public health priority.[3,4]

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***Panel 1:* Key recommendations**

Progress in dementia care, treatment, and prevention

1 All individuals with Alzheimer's disease (AD) should have access to reliable and timely diagnosis and treatment, irrespective of social inequalities. Accurate and timely diagnosis is a prerequisite for cost-effective care with available interventions. The cost-effectiveness of new therapies will be uncertain when they are introduced and should not be a limiting factor for treatment of this group.
2 Guidelines for the provision of dementia care are needed in all countries as part of national policy strategies or national plans. Such frameworks should promote coordination between health-care, social-care, and other relevant sectors (eg, welfare benefits and housing), and include affordable long-term funding plans for dementia care that span these sectors.
3 An infrastructure is needed to enable the use of non-pharmacological interventions (eg, psychosocial, behavioural, and environmental interventions, including multidomain approaches) for which clear evidence of benefit already exists. With guidance and advice from public health authorities, evidence-based interventions should be put into practice with appropriate training, support, and maintenance of fidelity.
4 Prevention studies need to start in midlife and have a long duration to identify windows of opportunity for effective interventions. Many modifiable risk factors—including high blood pressure, obesity, physical inactivity, and unhealthy diet—are shared among dementias, including AD, and other major late-life chronic disorders, such as heart disease and stroke. Public health efforts to promote healthier lifestyles in midlife have the potential to improve the general health status of the population in old age.
5 Available biological markers for AD—including cerebrospinal fluid and brain imaging biomarkers—need to be validated and standardised for use in research and clinical practice, and the search for novel biomarkers with high predictive value at pre-dementia stages needs to be supported and improved. Simple biomarkers (eg, in blood) are needed for use in general practice.
6 The discovery of a cure or an effective therapy for AD remains imperative. Ambitious multidisciplinary programmes in basic research are needed to learn more about the causes and pathological mechanisms of AD and to identify new, valid treatment targets.
7 Ethical considerations are of increasing importance as diagnosis and treatment shift to earlier disease stages, with a risk of false-positive cases. Important ethical questions need to be addressed in disclosing the genetic status of patients (eg, in families with causal mutations or individuals with a high risk of AD). At more advanced stages of disease, ethical considerations relate to improved and more timely decision making for end-of-life care.
8 Public awareness of AD and other dementias needs to be improved through outreach activities such as public lectures and open-house sessions in clinical care settings, and information provided via mass media, social media, and patient organisations.

Development of an improved infrastructure for research

9 Harmonised international databases are needed for population-based longitudinal studies of ageing and dementia to further understand the burden (eg, prevalence, incidence, mortality), natural history (eg, identification of genetic and clinical markers for early detection), and pathogenesis of AD and other dementias (eg, potential contributions of cardiovascular risk factors, nutrition, psychosocial stress, and frailty).
10 For optimum use of genetics in pre-symptomatic and early (preclinical or prodromal) diagnoses, current and future treatment approaches, and dementia prevention, DNA and clinical data from epidemiological studies, clinical settings, and clinical trials need to be collected and stored systematically; a legal framework is needed to regulate the use of data for research and to protect affected individuals and their families.
11 Scientific collaboration among international research groups demands the development of appropriate infrastructures to enable more effective use of existing data and rapid recruitment of participants in multinational interventional trials. Increased collaboration among governments, and between public and private institutions, will help to accelerate and increase the power of clinical research.
12 Redundant research in AD drug development could be avoided by increased openness. Detailed results, outcomes, and databases of clinical trials should be made broadly available immediately after studies have been completed in a manner that is accessible to researchers and the general public.
13 Clinical drug development and clinical trials should be coordinated internationally. Budgets for drug discovery, development, and clinical trials should be increased to allow international cohorts, ethical and regulatory frameworks, and standardised methods to be established, which will facilitate clinical trials and accelerate progress.
14 Public, private, and corporate funding decisions should be based on evidence and scientific merit, rather than being driven by advocacy, opinion, persuasion, or corporate considerations.

Similar policy declarations have been made by the European Union[5] (EU) and by some individual countries.

The global economic costs of dementia were estimated to be more than US$600 billion in 2010,[6] and $818 billion in 2015.[2] The direct costs of medical and social care, $487 billion,[2] represent 0·65% of the aggregated global gross domestic products (GDP)—an enormous economic impact for a single group of disorders, especially given

that 87% of the costs occur in high-income countries. Care for people with dementia is provided by several sectors in society, with the social-care (long-term care and home services) and informal-care (provided by non-professional caregivers) sectors accounting for the greatest proportion of costs—even greater than the cost of direct medical care.[6] In cost-of-illness studies, total societal cost estimates for dementia in Europe in 2010 were between $238·6 billion[6] and €105·6 billion.[7]

The economic costs of caring for a growing number of people with AD and other dementias are formidable, but the combined economic and societal burden of dementia is more daunting still, corresponding to the aggregate burden of people with dementia and their next of kin. No cure or substantial symptom-relieving treatment is available for AD or other dementias, and the progressive nature of dementia can profoundly affect the lives of patients and their families over many years. The impact of this terminal disorder is already enormous, and in view of the predicted rise in prevalence (proportion of the population with the disorder) over the next few decades, AD and other dementias represent a huge challenge for any society.

To tackle the global burden of dementia and its economic and societal ramifications, substantially increased investment in research is needed to accelerate the discovery and development of effective treatments, coupled with a broad, evidence-based public health approach to disease prevention. Progress in understanding the causes and disease mechanisms of AD and other dementias is needed to underpin new diagnostic and therapeutic strategies. Importantly, there is an opportunity and a need to shift the treatment-development paradigm: to establish stronger proof of concept before launching expensive phase 3 trials, to develop multimodal combination treatment approaches, and to allow precompetitive data sharing to accelerate learning and improve the likelihood of success.

At present, awareness about the many challenges of dementia that need to be (and can be) addressed varies substantially among patients and their family members, health-care professionals, politicians, and other stakeholders. It is essential that new knowledge from research is quickly translated into clinical practice and disseminated broadly. In all education programmes, health-care professionals should be made aware of the best available evidence-based care. Our public-sector representatives and policy makers are ultimately responsible for ensuring that clinical and basic research advances are effectively implemented into public health policy. Such an aim demands that our research agenda is broad and engages a wide range of sectors. Policy makers in Europe must support universal access to better diagnosis, care planning, and evidence-based treatment. Simultaneously, European countries must implement disease-prevention programmes and provide incentives for drug development and clinical trials. The overall aim of this Commission—written by leading health-care professionals representing the areas of health economy, epidemiology, genetics, biology, diagnosis, treatment, care, and ethics—is to inform, guide, and stimulate public debate about the growing burden of dementia in Europe, with a focus on AD as the leading cause of dementia.

Section 1. Health economics of Alzheimer's disease

AD has a substantial economic impact for each person and family affected. A 2011 study[8] of a multinational (Spain, Sweden, the UK, and the USA) sample of 1222 patients estimated that societal costs amount to about €14 500 per year in patients at home with a high level of autonomy in activities of daily living (ADL), but rises up to €72 500 per year in patients who need residential care. In 2014, the direct cost of AD for payers in the USA alone was estimated to be $214 billion.[9] For comparison, the global direct cost (resources used for prevention and treatment) and indirect cost (resources lost owing to morbidity or mortality, such as lost work productivity) of cancer was estimated at $290 billion in 2010, the estimate for diabetes was $472 billion, and that for all cardiovascular disease (including cerebrovascular disease) was $863 billion.[10]

For diabetes, the direct costs amounted to 80% of the global economic burden of the disease (almost 90% in high-income countries) in 2010. Thus, indirect costs constituted a small proportion of the overall economic burden.[10] These substantial direct costs reflect the availability of effective medical therapy to manage glucose control, prevent complications when possible, and treat complications when they occur. By contrast, only 16% of costs for AD were direct medical costs, 41·7% were informal-care costs, and 42·3% were social-care costs (section 9).[10] Thus, the costs of AD are driven mainly by compensating for lost function rather than treatment or prevention. The entire global market for pharmaceuticals and diagnostics for AD was estimated to be $10 billion in 2015, or roughly 1% of the total costs of the disease.[11] This highlights not only the absence of effective therapy for AD (section 7), but also the opportunity for new treatment options to provide benefit by improving health outcomes and shifting from indirect to direct costs.

Costs of diagnosing AD

Insufficient diagnostic services remain a major barrier to the provision of appropriate care for patients with dementia. Although disease-modifying treatments are not available at present, timely and correct diagnosis is a prerequisite for access to support services (eg, help with living arrangements) and symptomatic treatment (sections 6–9).

It is estimated that only 20–50% of patients living with dementia have a documented diagnosis in primary care, and this proportion is substantially lower in low-income and middle-income countries.[12] On the basis of data from the Swedish Dementia Registry (SveDem), the average

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For more on the **SveDem registry** see http://www.ucr.uu.se/svedem/

cost of diagnosing a case of AD in primary care was estimated to be €753, whereas the corresponding cost in specialist care was €1298 in 2010.[13] Table 1 presents an example from Sweden of the costs involved in diagnosing a case of AD, and a calculation of the cumulative costs as each new diagnostic procedure is added, starting in primary care and transitioning to specialist care.[13] Even though the maximum diagnostic cost (assuming all available diagnostic procedures are done) is more than €5000, which is high compared with the costs of diagnosing other common chronic disorders for which diagnostic biomarkers are available (eg, diabetes), this cost would be only a small fraction of the lifetime costs of care incurred by a patient with AD.

	Unit cost (€)	Cumulative cost (€)
Primary care		
Visit to family physician	122	122
Routine blood tests	33	156
CT	200	356
Visit to occupational therapist	144	500
Specialist care		
Visit to specialist physician	367	867
Neuropsychological testing	422	1289
EEG	100	1389
CSF tests	622	2011
MRI	289	2300
SPECT	378	2678
PET	1711	4389
Analyses of amyloid markers	1166	5555

According to level of primary and specialist care, and cumulative cost as each new diagnostic procedure is added.[13] Costs in Swedish kronor have been converted to euros on the basis of the exchange rate €1=9kr. Figures are rounded to the nearest euro. CT=computed tomography. EEG=electroencephalography. CSF=cerebrospinal fluid. MRI=magnetic resonance imaging. SPECT=single-photon emission computed tomography. PET=positron emission tomography.

Table 1: **Costs of diagnosing a case of Alzheimer's disease**

Panel 2: **QALYs and DALYs explained**

One quality-adjusted life-year (QALY) corresponds to a year spent in perfect health. Years spent in less than perfect health states (eg, with Alzheimer's disease) are assigned a weight (health utility), calculated on the basis of preferences for the health state. A weight of 1 signifies perfect health, whereas a weight of 0 means that the health state is equivalent to death. Weights below 0 are also theoretically possible (ie, a health state worse than death).

The disability-adjusted life year (DALY) is a construct that, like the QALY, summarises morbidity and mortality in terms of a single index. The number of DALYs is calculated as:

DALYs = YLL + YLD

YLL is years of life lost—an estimate of the average years a person would have lived if he or she had not died prematurely. The formula for YLL (without including social preferences) is:

YLL = N × L

N is number of deaths in a particular population and L is the standard life expectancy at age of death (in years) for that population.

YLD is years of life with disability. To estimate the YLD for a particular disease over a specific period, the number of incident cases in that period is multiplied by the mean disease duration (until remission or death) and a disability weight reflecting the severity of the disease on a scale from 0 (perfect health) to 1 (dead). The basic formula for YLD (again, without applying social preferences) is:

YLD = I × DW × L

I is the number of incident cases, DW is disability weight, and L is the average duration of disease.

The economic costs for individuals with dementia who remain undiagnosed are largely borne by caregivers and by patients themselves. With the possible future availability of effective treatments, early identification of AD pathological changes becomes even more important. The cost-effectiveness of treatment will ultimately depend on the strategy for identification of patients eligible for that treatment.

Indirect and intangible costs of AD

Methodological challenges exist in measuring the costs of informal care for patients with AD, both in the estimation of the amount of time spent caring for a patient and in how this time should be valued. Studies have suggested that caregivers would be prepared to pay between £59 and £144 per hour, depending on the country of study, for reductions in the time spent on caregiving tasks.[14] In addition to the direct and indirect economic costs of AD, the associated burden of illness includes the intangible costs of reduced quality of life and mortality. In health-economic evaluations, these costs are often quantified in terms of quality-adjusted life years (QALYs; panel 2).

Health utility weights for disease states in AD (panel 2) calculated with the Health Utilities Index (in which 1 equals perfect health and 0 is equivalent to death) range from 0·69 in mild disease to 0·14 in severe disease.[15] Using a different instrument, EuroQoL's EQ-5D, weights have been estimated as ranging from 0·69 in mild dementia to 0·33 in severe dementia.[16] For comparison, the population mean health utility weight in the age group 65–74 years is 0·78 and the utility weight for legal blindness has been estimated as 0·26.[17] DEMQoL is an instrument that, unlike the Health Utilities Index and the EQ-5D, was specifically developed to measure quality of life in dementia, and a tariff linking responses on the DEMQoL to health utilities has been developed.[18] Most studies have relied on proxy assessments of the health status of patients with AD. The agreement between patient and proxy ratings with the EQ-5D and DEMQoL has varied across studies; however, agreement is generally poorer in severe disease states. The quality of life of caregivers themselves can also be affected. Studies have shown an increased prevalence of depression in caregivers of patients with AD.[19] However, no direct link between caregiver health utilities and the severity of dementia in the patient whom they care for was noted using the

EQ-5D.[16] More specific and sensitive instruments are needed to measure the potential disutility associated with caregiving.

WHO has estimated the disability weights (where 0 equals no disability and 1 equals complete disability) in AD and other dementias as 0·082 for mild dementia, 0·346 for moderate dementia, and 0·438 for severe dementia.[20] In 2012, AD and other dementias were estimated to be the cause of 18 million disability-adjusted life years (DALYs) globally—years lost because of ill health, disability, or early death (panel 2). This is just 0·7% of all DALYs; however, in European women aged 70 years or older, AD causes 6% of DALYs.[21]

Valuing each DALY at three times the gross domestic GDP per person, the intangible cost of illness of AD and other dementias is around $550 billion (table 2).[22] Thus, the intangible cost of dementia might be almost as high as the total direct and indirect costs of care for AD.

	Total DALYs (millions)	DALYs due to AD and other dementias (millions)	Proportion of DALYs due to dementia (%)	GDP per person (US$)	Intangible cost (US$ billion)
World	1523	11·16	0·7%	..	550
High income	122	4·39	3·6%	38 182	503
Upper-middle income	121	1·04	0·9%	7289	23
Lower-middle income	452	3·73	0·8%	1924	22
Low income	828	2·00	0·2%	596	4

Data obtained from the World Bank. Intangible costs are valued at three times the GDP per person per DALY. DALY=disability-adjusted life year. AD=Alzheimer's disease. GDP=gross domestic product.

Table 2: **DALYs due to, and intangible cost of, Alzheimer's disease and other dementias in world regions according to World Bank income level**

Current challenges and future goals

New treatment modalities and strategies for prevention and care will be key to reversing the increasing prevalence (and associated morbidity) of AD (section 2). As new options for diagnosis and treatment become available (sections 6, 7), they will undergo two stages of assessment, the first by regulatory agencies to determine risk and benefit, and the second by health technology assessment (HTA) agencies and payer organisations to determine value relative to the current standard of care and to inform coverage and reimbursement decisions. Tools are needed that allow determination of the value of these new technologies with a sufficient degree of certainty to make correct coverage decisions. If a new treatment receives regulatory approval but faces negative reimbursement decisions owing to inadequate demonstration of value, uptake of the new treatment will be low and patients and caregivers will miss out on potential treatment benefits.

An important issue in establishing the value of new treatments for AD is that the benefits will largely fall outside the health-care sector, because most of the potentially preventable costs of dementia relate to long-term care and burden on informal caregivers. Increasing availability of treatment options with the potential to change the long-term course of AD will probably necessitate substantial upfront investments in diagnosis and medical expenditure, at least in the short term, and the full benefits could take years or decades to be realised. The benefits of reducing the need for informal caregiving will not appear on any budget and cannot easily offset treatment costs. Furthermore, for funding decisions a short time horizon is sometimes used or discounting applied, such that the value of future costs and effects is decreased (relative to current costs and effects) to reflect negative time preferences. Although it is common for budgeting constraints to prevent the flow of funds between so-called silos—eg, savings made through reduced need for long-term care being used to finance increasing costs of drug therapy—it is crucial that the long-term value of investment in medical care is recognised.

The main value of therapies that affect the long-term course of disease will lie in shortening the time spent in the severe stages of dementia. However, because this outcome is not being studied in trials of new drugs, value will need to be estimated through forecasting models before treatments are even introduced in clinical practice. The accuracy of such models depends on the availability of long-term, high-quality data for disease progression rates, costs, and health outcomes. Several epidemiological studies have followed up patients with AD longitudinally from diagnosis until the end stages (eg, the Swedish National Study on Aging and Care [SNAC][23] and the European Alzheimer's Disease Consortium–Impact of Cholinergic Treatment Use [EADC-ICTUS][24] studies). Far fewer data are available from the very early phases of AD, before the onset of dementia. New therapies are being assessed in preclinical states of dementia, and thus new data sources are needed to model accurately the long-term benefits of these treatments.

For more on the **European Alzheimer's Disease Consortium** see http://www.eadc.info/

Results from economic models are highly contingent on assumptions about long-term treatment benefits that will not be immediately available from clinical trials. For instance, the potential impact of treatment on overall mortality has important implications for costs of care.[25] If treatment improves survival but prolongs the time spent with severe dementia, it might bring only marginal health benefits for patients but increase care costs substantially. However, if late-stage morbidity is compressed and patients spend proportionally more time in less severe states, cost savings could be substantial. Thus, the goal of therapy is not merely to slow disease progression, but to minimise the time spent with severe dementia and maximise the time with conserved cognitive resources, autonomy in ADL, and quality of life.

Patients who receive new therapies will need to be followed up in clinical practice, and data will need to be gathered for resource use and health outcomes to gain further understanding of the value provided as new treatment options are implemented. Few countries have the infrastructure available at present to follow up patients prospectively, as can be done through SveDem.[13]

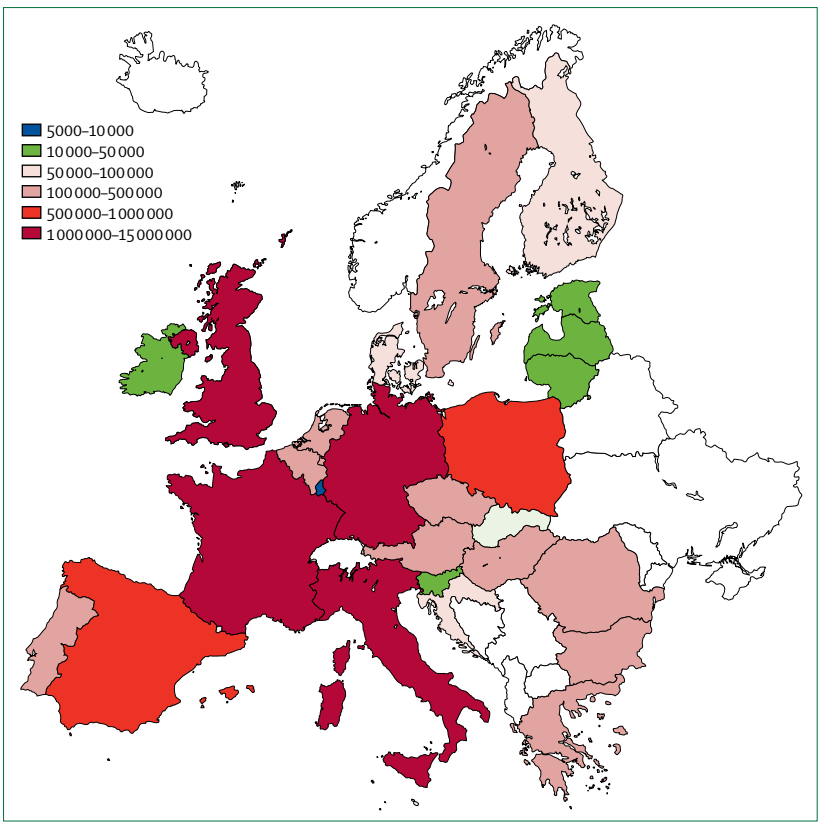

Figure 1: **Number of people with dementia in 28 European countries in 2013**
Estimates of the total number of people with dementia in each of 28 European countries were obtained from Alzheimer Europe.[26]

Furthermore, data collected might not immediately be relevant for other countries because of international differences in care organisation and delivery. Observational studies, such as EADC-ICTUS, in which data are gathered across several countries will be an important addition.

Summary and recommendations

The societal costs of AD will increase substantially as global prevalence increases. Despite some evidence of a decrease in incidence (the number of individuals who develop a disorder during a particular period) in Europe and the USA, a substantial increase in prevalence seems unavoidable as people live longer. At present, only about 16% of costs associated with AD are direct (related to resources used for prevention and treatment); most costs are indirect, including care and societal costs. New approaches to diagnose and treat AD should be assessed in the context of new paradigms for cost–benefit analysis to optimise the use of resources and improve quality of life for patients with AD.

(1) Economic assessments of new methods to diagnose and treat AD should include all costs of the disorder and adopt a broad measure of outcome that captures full societal benefits of treatment.

(2) The aim should be to offer accurate, reliable, and timely diagnosis to patients to provide cost-effective care with available therapies and to realise the potential value of new disease-modifying therapies.

(3) The cost-effectiveness of new therapies will be uncertain when they are introduced, because experience of long-term benefits will be limited, whereas upfront treatment costs can be substantial. Follow-up with data collection in clinical practice on resource use and patient-relevant outcomes should be done routinely to facilitate the assessment of treatment benefits and cost-effectiveness in clinical practice.

Section 2. Epidemiology of Alzheimer's disease and dementia

The burden of AD and other dementias, which is projected to surge in the coming decades, poses a serious threat to the sustainable development of economies and the social welfare systems of Europe. Epidemiological studies generate knowledge about the occurrence (eg, prevalence and incidence), distribution (eg, demographic, geographical, and temporal variations), determinants (eg, genetic and non-genetic risk or protective factors), health economics (eg, costs of health care and cost-effectiveness of treatment and intervention), and intervention strategies (eg, therapeutic and preventive interventions) of AD and other dementias. Such studies are therefore key to understanding and tackling the challenges of this devastating disorder. In EU countries, knowledge about the number of people with dementia is available, but fewer data have been reported on the prevalence of dementia in eastern European countries (figure 1).[26] To cope with the challenges of AD and other dementias, policy makers need this information, which will help to guide the design and development of care and social welfare systems, and allow appropriate use of scarce resources for the care of people with dementia. Specialist terms that are key to our discussion are defined in panel 3.[27,28]

Although AD diagnosed by current clinical criteria (section 6) accounts for 50–70% of all dementia cases, autopsy-verified studies have suggested that mixed dementia, with vascular and neurodegenerative AD pathology, accounts for most dementia cases. Additionally, AD with onset before age 65 years (early-onset AD) accounts for up to 5% of all cases. Most of the early-onset AD cases are familial AD—a rare form of AD caused by mutations in the amyloid precursor protein (*APP*), presenilin 1 (*PSEN1*), or *PSEN2* genes (section 4).[29] Patients with non-familial (sporadic) early-onset AD have no reliable family history and usually have an older age of onset than do patients with familial early-onset AD.[30] Late-onset sporadic AD (from 65 years of age) is the most common form of AD, accounting for about 95% of all cases. The enormous costs of medical and social care for patients with early-onset and late-onset AD depend on

Panel 3: Definitions

Allele: any of the alternative genetic variants of a specific gene or locus.

Attributable fraction of risk: the fraction of cases that would be avoided if a risk factor could be totally suppressed.

Autosomal dominant: a mode of inheritance in which a single copy of a mutant allele located on one of the 22 pairs of autosomes (non-sex chromosomes) is sufficient to cause a disease. In diseases with mendelian autosomal dominant transmission, which does not depend on the sex of the carrier parent, each child of an affected parent has a one in two (50%) risk of inheriting the disease.

Brain reserve: the brain's ability to tolerate age-related or disease-related pathology before the threshold is reached for clinical symptoms to appear. Brain reserve is directly related to brain size, number of neuronal cells, or density of synapses, such that a large brain or large number of cells is able to tolerate more pathology.[27]

Cerebral small vessel disease: a cerebrovascular disease characterised by a range of neuroimaging, pathological, and associated clinical features. Signs of cerebral small vessel disease on conventional magnetic resonance imaging (MRI) scans include small subcortical infarcts, white matter hyperintensities, lacunes, prominent perivascular spaces, and cerebral microbleeds.[28]

Codominance: an additive relation between variants of one gene (alleles), in which an increased effect on phenotype is noted with increasing number of alleles (ie, two copies of the allele result in a more severe phenotype than one copy of the allele).

Cognitive reserve: the brain's ability to perform cognitive tasks adequately despite neuropathological damage to the brain. Cognitive reserve represents an enhanced ability to use brain networks more efficiently or to recruit alternative networks. It is associated with high education, mentally stimulating activity, physical and mental leisure activities, and rich social networks.[27]

Cognitive stimulation: an intervention for people with dementia that offers various interactions and activities that are designed to keep the brain active. The notion that cognitive stimulation is beneficial for people with dementia is based on the use-it-or-lose-it philosophy.

Confounder: a factor related to both an exposure of interest and an outcome (eg, a disease). The factor (confounder) might explain all or part of an association between an exposure and an outcome; a spurious relation between exposure and outcome might be inferred if the confounder is not taken into account.

Delphi consensus: a structured method to achieve expert consensus. Experts answer several iterations of questions, with a facilitator providing an anonymous summary of the experts' forecasts from the previous round and the reasons they provided for their judgments. Through discussion and reconsideration of their answers to the stated questions, a consensus is achieved.

Epigenetic modifications: variations in genetic make-up that do not include the DNA sequence (code) itself, such as DNA methylation (methyl groups added to the nucleotide cytosine) and modification (eg, acetylation) of proteins that bind to the DNA. Such variations, which can be heritable, make the DNA more or less accessible for activation (transcription).

Implicit memory: an aspect of memory in which previous experiences help with the performance of a task even though there is no conscious awareness of these experiences.

Life-course approach: in epidemiology, a life-course approach is used to study the biological, physical, and social hazards during gestation, childhood, adolescence, young adulthood, and midlife that might affect risks for chronic diseases and health outcomes in later life. The approach aims to identify the underlying biological, behavioural, and psychosocial processes that operate across the lifespan.

Locus: in genetics, a locus is a specific location or position of a gene or DNA sequence on a chromosome, analogous to the specific coordinates of a geographical location on a map.

Mediterranean diet: a modern nutritional recommendation based on traditional dietary patterns of the Mediterranean region. Key components of the diet include olive oil, vegetables, and fish, with moderate consumption of dairy products (mostly as cheese and yoghurt) and low consumption of meat products.

Minor allele frequency (MAF): the frequency of the less common allele (genetic variant) in the population. The term usually refers to the less common of two different alleles of a single-nucleotide polymorphism.

Population attributable risk (PAR): the proportion of cases that would not occur in a population if a factor were completely eliminated from the population. The PAR or population attributable fraction (%) in a population depends on the prevalence of the risk factor (P_e) and the strength of its association (relative risk) with the disease (RR_e). The formula is:

$$PAR = \frac{P_e (RR_e - 1)}{[1 + P_e (RR_e - 1)]}$$

Precision medicine: an approach to health care, also known as personalised medicine, in which choices for treatment and prevention are tailored to the individual. When a trait or disease is influenced by genetic make-up, health-care decisions can potentially be made on the basis of the specific genetic background of the individual (ie, genomics). The notion can be extended to transcriptomics, proteomics, metabolomics, and so on.

(Panel continues on next page)

(Panel 3 continued from previous page)

Reality orientation: a programme designed to improve cognitive function in people with dementia. The aim is to use verbal interaction, aids such as calendars and clocks, and sensory stimuli such as distinctive sights, sounds, and smells to improve orientation and sensory awareness.

Reminiscence therapy: a therapeutic approach in which tools such as life histories, shared memories, and familiar objects from past periods are used to improve wellbeing, usually in a group setting.

Single-nucleotide polymorphism (SNP): a genetic variation in a single-nucleotide base pair. The DNA sequence (code) of the human genome is made up of billions of nucleotide base pairs. Generally there are two alleles for each SNP.

Somatic mutation: acquired genetic variation that occurs during cell division (mitosis) in the cells of the body and is not transmitted to the next generation because for trans-generational transmission the mutation has to be present in the gonadal cells.

disease severity (section 1);[31] however, prevalence data of dementia according to severity or stage are scarce.[32,33]

Living with dementia

Several population-based studies have suggested that people aged 65 years or older survive a median of 3–9 years after a diagnosis of dementia, with some living for as long as 20 years.[34–42] Clinical deterioration of people with dementia, and particularly of people with AD, is progressive, although the rate of decline in mental and physical function can vary. According to WHO, people can generally expect to be in the mild or early stage of dementia (eg, forgetful, some language difficulties, and mood changes) for the first year or two, the moderate or middle stage (eg, very forgetful, increasing difficulty with speech, and help needed with self-care activities) from the second to the fourth or fifth years, and the severe or late stage (eg, serious memory disturbances and nearly total dependence and inactivity) from the fifth year onwards.[3] Data from the Kungsholmen Project of community dwellers aged 75 years or older in central Stockholm showed that people with incident dementia (ie, cases newly diagnosed during the study) spend a few months in the very mild stage of dementia, around 2 years in the mild phase, 1–2 years in the moderate stage, and a year in the severe stage.[43]

For more on the **Kungsholmen Project** see http://www.kungsholmenproject.se/

Women with dementia live longer than men, because they tend to survive longer in the severe stage.[43,44] More than 50% of dementia cases are estimated to reach the severe stage within 3 years. A population-based study[45] of prevalent dementia cases (ie, those diagnosed at the start of the study) showed an increase in the proportion of severe dementia from 19% at baseline to 48% after 3 years, and 78% after 7 years. By contrast, in a population-based prospective study[46] of dementia progression (Cache County), 40–50% of patients with incident AD deteriorated slowly in cognitive and functional ability (eg, a decline of 1 point per year on the Mini-Mental State Examination [MMSE] score and the Clinical Dementia Rating Sum of Boxes). Although several studies have been done,[45,47–50] the effect of cognitive decline on specific tasks of self-care ADL (eg, eating, dressing, toileting) or instrumental ADL (IADL; eg, shopping, cooking, basic housework) has still not been completely clarified, largely as a result of the short periods of follow-up for most studies.[51–53] Furthermore, knowledge about the effect of potential compensatory factors (eg, social engagement, cognitive training, and mentally stimulating activity) is still poor.

For more on the **Cognitive Function and Ageing Studies** see http://www.cfas.ac.uk/

In many countries, health-care policy aims to avoid or postpone admission of patients with dementia to nursing homes and institutions. Informal care (eg, home care provided by family and friends) tends to be less costly than formal care (eg, care provided in nursing homes or institutions) for the social security system,[54] although this is not necessarily true when the costs are assessed from a societal perspective.[55] In addition to health-care and social-care policies, the proportion of people with dementia living at home depends on several factors, including the characteristics of patients (eg, severity of cognitive and functional disability) and caregivers (eg, perceived burden and coping strategies), and cultural factors.

Worldwide, most people with AD and other dementias are cared for at home, usually by a spouse or a daughter. In low-income and middle-income countries, the estimated proportion of people with dementia living at home is around 94%, compared with around 66% in high-income countries.[56] The proportion of people with dementia cared for at home is higher in rural than in urban areas.[57] A longitudinal study in Australia showed that several baseline clinical features of dementia predicted a shorter time before admission to an institution, such as lower cognitive and functional ability, more neuropsychiatric symptoms, and use of antipsychotic drugs.[58] Moreover, greater deterioration in these factors within the first 3 months after baseline was also predictive of shorter time to admission to an institution, which suggests that rate of disease progression is an important factor.

Dying with dementia

Several follow-up studies have consistently shown that the extent to which dementia shortens life expectancy depends on age at onset, sex, and dementia subtype.[44] Data from the UK Medical Research Council Cognitive Function and Ageing Study (MRC CFAS) showed that the prevalence of dementia and severe cognitive

impairment in the period before death rises steeply with age; by age 90 years, around 60% of people died with dementia or severe cognitive impairment.[59,60] Finally, not only dementia shortens life expectancy: a subtle decrement in global cognitive function, even in the absence of clinically recognised impairment, is also strongly associated with shorter survival.[61]

The potential years of life lost (YLL)—ie, the average number of additional years a person would have lived if he or she had not died prematurely—because of dementia in people aged 75 years or older has been estimated at 3–5 years.[43,44] A Swedish study of people aged 75 years or older suggested that the impact of dementia on lifespan (YLL 3·41) is similar to that of cardiovascular disease (YLL 3·58) but lower than that of cancer (YLL 4·40).[43] Mortality risk in patients with dementia or cardiovascular disease is twice as high as that of people without these disorders, whereas patients with a diagnosis of cancer have a mortality risk three times higher than that of people without cancer.[43] Furthermore, the estimated years lived with or lost because of one of these disorders is most dependent on age at diagnosis, being higher among the younger old (those aged 75–84 years) than in the oldest old group (85 years or older; figure 2).[43] This finding is supported by a 2014 study in the USA showing that the mortality risk for AD was higher for younger old participants than for the oldest old participants (relative risk 4·30 *vs* 2·77; p<0·05).[62]

AD and other dementias are substantially under-reported on death certificates and medical records, although the situation has improved in the past 20–30 years as a result of increasing awareness of the disease among health professionals and the public. The contribution of dementia to mortality is difficult to assess solely on the basis of death certificates, because dementia is rarely thought of as an immediate or an underlying cause of death in this context.[63] Indeed, older people often have different chronic and acute illnesses that might be related to the dementia process[64] and a direct or indirect cause of death. A population-based study estimated that the population attributable risk (%) of death owing to AD was about 36% for people aged 75 years or older, and that in the USA, AD might contribute to almost as many deaths as does heart disease or cancer.[62] Similarly, in a US nationwide study of individuals aged 65 years or older, deaths with AD were estimated to comprise 32% of all deaths in 2010, with the proportion projected to reach 43% by 2050.[65] In 2013, the US Alzheimer's Association reported that AD was the sixth leading cause of death across all ages, and the fifth leading cause of death for people aged 65 years or older in the USA.[66] In the UK, the rank (among all other diseases) of the age-standardised YLL for AD increased from 24th in 1990, to 10th in 2010.[67] When death with dementia is examined, the proportion of deaths attributable to dementia reached around one-third in people aged 85 years or older.[68]

Temporal and geographical variations

The age-standardised prevalence of dementia for people aged 60 years or older is 5–7% in most regions of the world. In the past decade, the work of the 10/66 Dementia Research Group has contributed to understanding of the epidemiology of dementia in low-income and middle-income countries, such as Brazil, India, and China.[69–71] Systematic reviews and meta-analyses provide more precise global and regional estimates of dementia prevalence.[3,5,72,73] They also show similar patterns of age-specific prevalence of AD and dementia across worldwide regions, although substantial variations are evident among the oldest old (90 years or older; figure 3).[72–75] Higher prevalence and incidence of dementia and AD in women than in men, especially among the oldest old,

For more on the **10/66 Dementia Research Group** see http://www.alz.co.uk/1066/

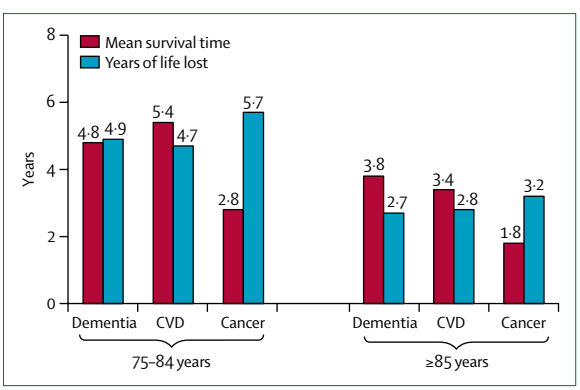

Figure 2: **Mean survival time and years of life lost to dementia, cardiovascular disease, and cancer**
Data are stratified by two age groups.[43] In people aged 75 years or older, the effect of dementia on lifespan is similar to that of CVD, but lower than that of cancer. Years of life lost is an estimate of the average additional years a person would have lived if he or she had not died prematurely. It is an alternative to death or mortality rates, but gives more weight to deaths that occur among young people. Years of life lost can be estimated from the number of deaths multiplied by a standard life expectancy at the age at which death occurs. CVD=cardiovascular disease.

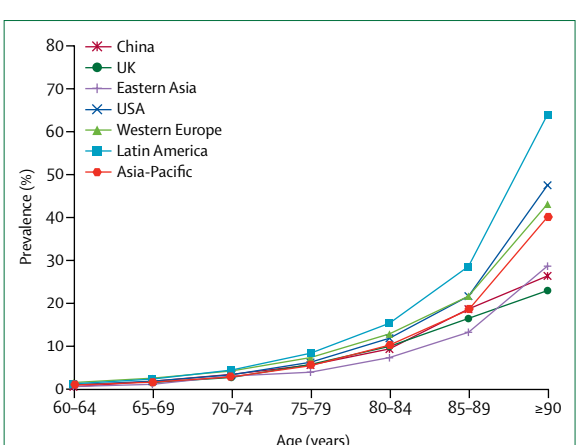

Figure 3: **Age-specific prevalence of dementia by world region and in major countries**
Patterns of age-specific prevalence of dementia are similar across worldwide regions, but vary substantially among the oldest old (age ≥90 years).[72–75]

For more on the **Alzheimer's Association** see https://www.alz.org/

have been reported in several studies in Europe and Asia, although data about sex differences have been less consistent in North American studies.[76]

Study of the secular trends and geographical variations of dementia occurrence and their determinants is crucial for policy development in a world that faces a rapid increase in the absolute number and proportion of older adults in the population. Thus, there has been increasing interest in investigating the time trends of dementia occurrence (eg, incidence and prevalence; table 3)[68,77–92] and possible geographical differences in dementia distribution in the past few years.[74] Although findings from various regions across the world have not been consistent, the results of several population-based community surveys point to a stable or declining age-specific prevalence or incidence of dementia among elderly people in Europe and North America.[93–95] Identification of temporal and geographical variations in the prevalence and incidence of dementia will help to establish modifiable risk and protective factors for dementia disorders, and could help to shape public health policy in Europe and elsewhere.

North America

A decline in the prevalence of dementia and cognitive impairment has been reported in a few studies from the USA,[77,96,97] and another study suggested a stable age-adjusted prevalence of dementia and AD in African American people aged 70 years or older from 1992 to 2001.[78] Additionally, several population-based studies from the USA have shown a decline (2–3% per annum) in the incidence of dementia and AD from the 1990s through the 2000s.[79,80] More recently, two studies from the USA provide direct evidence supporting the declining trend of age-specific incidence of dementia starting even from the 1970s.[81,82]

Europe

Two population-based surveys[68,85] in Sweden showed a stable age-specific prevalence of dementia over the past 20–30 years. Repeated cross-sectional surveys[83] in 1988 and 1994 in Spain suggested an age-standardised stable prevalence of dementia in women but a decreased prevalence in men. Finally, the large-scale MRC CFAS study[86] provided evidence that a cohort effect might exist in the age-specific prevalence of dementia among community residents, such that later-born populations had a lower likelihood of prevalent dementia than those born earlier in the past century, whereas the prevalence of dementia among older people living in care settings increased. However, the study showed no evidence of variations in the incidence or prevalence of dementia across five regions in England and Wales. A systematic review[74] revealed evidence of geographical variations in the incidence or prevalence of dementia and, specifically, a higher risk of AD in rural as opposed to urban areas. Studies from the Netherlands, Sweden, and England have also provided evidence suggesting a declining incidence of dementia among community-dwelling older people.[68,84,86] Given the diversity in social service systems and economic development across Europe, epidemiological studies of dementia and AD in eastern and middle European countries are needed.[98,99]

Asia-Pacific region

In mainland China, the prevalence of dementia and AD increased steadily across all age groups of people aged 55 years or older from the 1990s to 2010,[89] although the reported trends might be attributable partly to methodological variations during the periods of study (eg, diagnostic criteria, age range, and sampling methods).[90] The number of people with dementia was estimated to have increased by 63·5% from 2000 to 2010 in China—compared with an average increase of 46·5% worldwide during almost the same period[72,73]—largely owing to the fast pace of population ageing in China. Rural and urban differences in the prevalence of dementia and AD are supported by a large-scale study from China,[100] which suggested that early experience of, or exposure to, rural living (with low education and socioeconomic status) might contribute to the association between rural life and an increased risk of late-life dementia and AD. In Hong Kong, a systematic review[88] showed that the prevalence of clinically diagnosed dementia among community-dwelling people aged 70 years or older increased from 4·5% in 1995, to 9·3% in 2005–06. In Japan, the population-based Hisayama study[91] suggested that the age-specific prevalence of all-cause dementia and specific AD significantly increased from the early 1990s to 2005 in a general population of elderly people. After all methodological variations were carefully assessed, an increasing prevalence of dementia in Japan was confirmed by a systematic review.[92] These findings suggest that previous estimates of dementia burden and long-term trends in dementia occurrence across the world, especially in the Asia-Pacific region, were probably underestimates.[101]

Determinants of temporal and geographical variations

Many factors can affect estimates of the occurrence of dementia, so it is no surprise that temporal trends vary within and between countries. For instance, the upward trend in the prevalence of dementia from the 1990s to 2010 in China is consistent with the time trends for increasing prevalence of stroke and ischaemic heart disease, and related lifestyle and metabolic risk factors (eg, smoking, physical inactivity, obesity and overweight, hypertension, diabetes), over similar periods,[102] together with a fast pace of population ageing in China. Similarly, a substantial reduction in the prevalence of dementia in England from 1991 to 2011, and the suggested reduction of dementia risk in the Netherlands and Sweden, imply that changes in health behaviours (eg, smoking cessation, physical activity), improved management of cardiovascular risk factors (eg, hypertension, high cholesterol), and reduced

	Study design	Study population and period	Outcome (diagnostic criteria)	Findings
North America				
Langa et al, 2008 (USA)[77]	Repeated surveys in the Health and Retirement Study	Age ≥70 years for both waves: wave 1 (1993; n=7406), wave 2 (2002; n=7104)	Prevalence of cognitive impairment (≤10 on 35-point cognitive scale)	Prevalence decreased from 12·2% to 8·7%
Hall et al, 2009 (Indiana, USA)[78]	Repeated cross-sectional surveys	African Americans ≥70 years: wave 1 (1992; n=1500), wave 2 (2001; n=1892)	Prevalence of dementia and AD (ICD-10)	Prevalence stable for dementia (6·75% to 7·45%) and AD (5·47% to 6·77%)
Hebert et al, 2010 (Chicago, USA)[79]	Repeated cross-sectional surveys every 3 years	Age ≥65 years for all cycles (1997–2008; n>10 000): cycle 1 (n=6158)	Incidence of AD (NINCDS–ADRDA)	Risk of AD stable over time (OR for trend variable 0·97, 95% CI 0·90–1·04)
Rocca et al, 2011 (USA)[80]	Review	1993–2002	Prevalence or incidence of dementia and AD (DSM-III-R, DSM-IV, NINCDS–ADRDA, ICD-10, others)	Prevalence and incidence stable
Gao et al, 2015 (Indiana, USA)[81]	Repeated surveys in the Indianapolis-Ibadan Dementia Project	African Americans ≥70 years: 1992 cohort (n=1440), 2001 cohort (n=1835)	Incidence of dementia (DSM-III-R) and AD (NINCDS–ADRDA)	Age-standardised annual incidence rate declined from 1992 to 2001 for dementia (3·6% [95% CI 3·2–4·1%] *vs* 1·4% [1·2–1·7%]) and AD (2·5% [2·1–2·9%] *vs* 1·3% [1·0–1·5%])
Satizabal et al, 2016 (Boston, USA)[82]	Repeated surveys in the Framingham Heart Study	Age ≥60 years: epoch 1 (1977–83; n=2457), epoch 2 (1986–91; n=2135), epoch 3 (1992–98; n=2333), epoch 4 (2004–08; n=2090)	Incidence of dementia (DSM-IV), AD (NINCDS–ADRDA), and vascular dementia (NINDS–AIREN)	Decline in incidence rate per decade of 20% (95% CI 10–28%) for dementia, 12% (0–23%; p=0·052) for AD, and 29% (10–44%) for vascular dementia
Europe				
Lobo et al, 2007 (Spain)[83]	Repeated cross-sectional surveys	Age ≥65 years for both waves: wave 1 (1988–89; n=1080), wave 2 (1994–96; n=3715)	Prevalence of dementia (DSM-IV)	Prevalence stable overall (5·2% to 3·9%) and decreased in men (5·8% to 2·3%)
Schrijvers et al, 2012 (Rotterdam, Netherlands)[84]	Repeated cross-sectional surveys	Age ≥60 years for both waves: wave 1 (1990; n=5727), wave 2 (2000; n=8384)	Incidence of dementia (DSM-III-R)	Incidence decreased, but not significantly (age-adjusted IRR 0·75, 95% CI 0·56–1·02; p=0·06)
Qiu et al, 2013 (Stockholm, Sweden)[68]	Repeated cross-sectional surveys	Age ≥75 years for both waves: wave 1 (1987–89; n=1700), wave 2 (2001–04; n=1575)	Prevalence and survival of dementia (DSM-III-R)	Prevalence stable (17·5% to 17·9%); evidence suggests decline in incidence
Wiberg et al, 2013 (Gothenburg, Sweden)[85]	Repeated cross-sectional surveys	Wave 1 (1976–77; age=70 years, n=404; age=75 years, n=303), wave 2 (2000–01; age=70 years, n=579; age=75 years, n=753)	Prevalence of dementia (historical criteria in wave 1; DSM-III-R in wave 2)	Prevalence stable (70 years, 2·0% to 2·4%; 75 years, 5·0% to 6·0%)
Matthews et al, 2013 (England)[86]	Repeated cross-sectional surveys	Age ≥65 years for both waves: wave 1 (1989–94; n=7635), wave 2 (2008–11; n=7796)	Prevalence of dementia (Geriatric Mental State scale)	Prevalence decreased (8·3% to 6·5%)
Asia				
Li et al, 2007 (Beijing, China)[87]	Repeated cross-sectional surveys	Age ≥60 years for both waves: wave 1 (1986–89; n=1090), wave 2 (1997–99; n=1593)	Prevalence and incidence of dementia (ICD-10, DSM-IV)	Prevalence increased (1·7% to 2·5%); incidence increased (0·6% to 0·9%)
Yu et al, 2012 (Hong Kong, China)[88]	Review	Age ≥70 years (1995–2006)	Prevalence of dementia (ICD-9, ICD-10)	Prevalence increased from 4·5% to 9·3%
Chan et al, 2013 (China)[89]	Systematic review of 75 cross-sectional surveys	Age ≥55 years (1990–2010; n=340 247)	Prevalence of dementia and AD (DSM-III, DSM-III-R, DSM-IV, NINCDS–ADRDA, ICD-9, ICD-10)	Prevalence increased in all age groups
Wu et al, 2014 (China, including Hong Kong and Taiwan)[90]	Systematic review of 70 prevalence studies	Age ≥60 years (1990–2012)	Prevalence of dementia by survey years, age groups, and birth cohorts (DSM-III, DSM-III-R, DSM-IV, ICD-10, others)	Controlling for methodological factors, prevalence increased slightly from 1995 to 2012; a birth cohort effect was reported (ie, a more recent cohort of the same age had higher dementia prevalence)
Sekita et al, 2010 (Hisayama, Japan)[91]	Repeated cross-sectional surveys	Age ≥65 years for all waves: wave 1 (1985; n=887), wave 2 (1992; n=1189), wave 3 (1998; n=1437), wave 4 (2005; n=1566)	Prevalence of all-cause dementia and AD (DSM-III, DSM-III-R)	Prevalence increased from 1985 to 2005 for all-cause dementia (6·0% to 8·3%) and for AD (1·1% to 3·8%)
Dodge et al, 2012 (Japan)[92]	Systematic review of eight cross-sectional surveys	Age ≥65 years (1985–2008; n=13 396)	Prevalence of dementia (DSM-III, DSM-III-R, DSM-IV)	Prevalence increased (6·7% to 11·3%)

Population-based surveys and systematic reviews of population surveys about the temporal trends of dementia occurrence. AD=Alzheimer's disease. ICD=*International Classification of Diseases* criteria. NINCDS–ADRDA=National Institute of Neurological Disorders and Stroke–Alzheimer's Disease and Related Disorders Association criteria. OR=odds ratio. DSM=*Diagnostic and Statistical Manual of Mental Disorders* criteria. NINDS–AIREN=National Institute of Neurological Disorders and Stroke–Association Internationale pour la Recherche et l'Enseignement en Neurosciences criteria. IRR=incidence rate ratio.

Table 3: **Temporal trends of dementia occurrence according to continent**

risk of stroke and heart disease have had a substantial role in reducing the risk of dementia and AD, possibly by reducing the number of brain lesions and thereby preventing or delaying the onset of dementia in the general population.[86,103] In support of this notion, the Rotterdam Study has provided evidence that the suggested decline in

For more on the **Rotterdam Study** see http://www.epib.nl/research/ergo.htm

dementia incidence with time might be a result of less brain atrophy and less cerebral small vessel disease.[84]

New evidence about temporal changes in dementia occurrence will affect estimates of worldwide and regional future burden of disease, because earlier estimates and projections were based on the assumption that age-specific prevalence of dementia remained constant. Even for regions such as Europe, with some evidence of declining prevalence or incidence, the future burden of dementia is likely to increase as a result of population ageing.

Dementia is not an unavoidable consequence of ageing

Genetic susceptibility, environmental factors (eg, psychosocial, lifestyle, and biological factors), and their interaction over the lifespan contribute to the pathological processes and clinical expression of dementia. However, not all nonagenarians, or even centenarians, develop AD or other dementias,[104,105] which shows that some people are able to reach very advanced ages without severe mental deterioration. Neuropathologically, the population-based 90+ Autopsy Study, an ancillary of the 90+ Study of people aged 90 years or older in the USA, showed that nearly 50% of people with dementia did not have sufficient neuropathology in their brain to explain their cognitive symptoms.[106] By contrast, intermediate or high levels of AD pathology were present in about a third of very old people without dementia or cognitive impairment.[107] Furthermore, the association between the pathological hallmarks of AD—neuritic plaques (deposits of amyloid β peptide [Aβ]) and neurofibrillary tangles (aggregates of hyperphosphorylated tau protein)—and the clinical syndrome of dementia was less strong in the oldest old than in younger old people.[108,109]

For more on the **90+ Study** see http://90study.org/

These findings indicate that certain compensatory factors—eg, high education, social engagement, maintenance of cardiovascular health—provide brain reserve (related to brain size, number of neuronal cells, or density of connections) and cognitive reserve (related to the brain's ability to use brain networks more efficiently or to recruit alternative networks in the presence of pathology),[27] which might enable individuals to tolerate a substantial amount of AD pathology without experiencing an obvious dementia syndrome, even in carriers of susceptibility genes for AD, such as the apolipoprotein E (*APOE*) ε4 allele.[110] Several risk and protective factors are the focus of epidemiological studies and are discussed in more detail in the following subsections.

Risk and protective factors

Dementia, including AD, is a multifactorial disorder that is determined by the interplay of genetic susceptibility and environmental factors across the lifespan (panel 4). Older age is the strongest risk factor for AD and other dementias, and patients who develop dementia before age 65 years as a result of gene mutations (section 4) account for only a very small proportion of all cases (1–5%). Most cases of dementia and AD are at least partly attributable to cardiovascular risk factors (eg, hypertension, diabetes, and obesity) and psychosocial factors (eg, education, social engagements, and leisure activities), which are the main modifiable factors that can be targeted for intervention (section 3). The qualitative and quantitative effects of most of these factors on AD and dementia have been assessed in several systematic reviews and meta-analyses.[111,112]

Lifestyle-related cardiovascular risk factors

Smoking is associated with a 50–80% increased risk of dementia, and even second-hand smoking could increase dementia risk.[113,114] Diabetes in middle age or later in life increases the risk not only of vascular dementia, but also of AD (by about 50%).[115,116] By contrast, light-to-moderate alcohol consumption has been associated with a 30–40% reduced risk of dementia.[117,118] Likewise, regular physical activity, even low-intensity activity such as walking, seems to reduce dementia risk by about 40%.[119] Of note, systematic reviews from the life-course perspective (ie, from the point of view of exposure across the lifespan) have revealed age-dependent associations of dementia and AD with major cardiometabolic risk factors—including hypertension, high cholesterol, and obesity or overweight—such that having these factors in young adulthood or middle age (eg, age <65 years), but not necessarily in late life (eg, age ≥75 years), is associated with an increased risk of dementia and AD.[112,120] Indeed, long-term follow-up studies[121–124] reveal that blood pressure, total cholesterol, and body-mass index begin to decline years to decades before dementia onset, possibly as a result of ongoing AD pathology. Thus, low levels of these metabolic factors in later life might actually be part of prodromal (or preclinical) dementia.

More importantly, population-based studies have also shown that having multiple cardiovascular risk factors (eg, smoking, hypertension, diabetes, hypercholesterolaemia) concurrently in middle age or several years before dementia onset incrementally increases the risk of dementia and AD.[120] Thus, to delay the onset of dementia, the optimum time window for interventions that target lifestyle-related cardiovascular risk factors might be young adulthood or middle age, and interventions that target multiple domains are likely to be more effective. Indices for use in middle age or later life to predict dementia risk have been developed and validated, and have an accuracy of between 70% and 80%; unhealthy lifestyle and cardiometabolic risk factors constitute a major part of these indices.[125–129]

Psychosocial factors

High educational achievement in early life has consistently been associated with reduced risk of late-life dementia and AD.[130] Cognitive activity or mentally stimulating activity (eg, reading, doing crossword puzzles, playing games), which might be related to early life education, has also

Panel 4: **Putative risk and protective factors for late-onset dementia and Alzheimer's disease**

Risk factors

Older age

Genetic factors
- Familial aggregation (two or more family members with the disease)
- *APOE* ε4 allele
- Other susceptibility genes (eg, *CR1*, *PICALM*, *CLU*, *TREM2*, *TOMM40*)

Vascular risk and metabolic factors
- Atherosclerosis
- Cerebral macrovascular and microvascular lesions
- Cardiovascular diseases
- Diabetes mellitus and pre-diabetes
- Midlife hypertension
- Midlife overweight and obesity
- Midlife high serum cholesterol

Lifestyle factors
- Sedentary lifestyle
- Smoking
- Heavy alcohol consumption

Diet and nutritional factors
- Saturated fats
- Hyperhomocysteinaemia
- Deficiencies in vitamin B6, B12, and folate

Other factors
- Depression
- Traumatic brain injury
- Occupational exposure (eg, heavy metals, extremely-low-frequency electromagnetic fields)
- Infectious agents (eg, herpes simplex virus type I, *Chlamydophila pneumoniae*, spirochetes)

Protective factors

Genetic factors
- Some genes proposed (eg, *APP*, *APOE* ε2 allele)

Psychosocial factors
- High education and socioeconomic status
- High work complexity
- Rich social network and social engagement
- Mentally stimulating activity

Lifestyle factors
- Physical activity
- Light-to-moderate alcohol intake

Diet and nutritional factors
- Mediterranean diet
- Polyunsaturated fatty acid and fish-related fats
- Vitamin B6, vitamin B12, and folate
- Antioxidant vitamins (A, C, E)
- Vitamin D

Drugs
- Antihypertensive drugs
- Statins
- Hormone replacement therapy
- Non-steroidal anti-inflammatory drugs

Many risk and protective factors for dementia and Alzheimer's disease have been proposed and investigated; however, the evidence to support the factors listed here is variable, and the relevance of several proposed factors is open to debate. The most pronounced risk factors are advancing age and carrying one or two *APOE* ε4 alleles.

APOE=apolipoprotein E. *CR1*=complement component receptor 1. *PICALM*=phosphatidylinositol-binding clathrin assembly protein. *CLU*=clusterin. *TREM2*=triggering receptor expressed on myeloid cells 2. *TOMM40*=translocase of outer mitochondrial membrane 40 homologue. *APP*=amyloid precursor protein.

been associated with reduced dementia risk, as have social engagement and maintenance of a rich social network. Finally, although the temporal relation between depression and dementia in older people remains debatable, evidence from long-term follow-up studies suggests that depression might be a risk factor for dementia and AD.[131,132]

Potential pathological mechanisms

In the past decade, population-based neuroimaging and neuropathological studies have contributed substantially to understanding of the pathophysiological mechanisms linking cardiovascular risk factors and psychosocial factors to AD and dementia. Evidence from multidisciplinary research points to vascular mechanisms and the importance of brain and cognitive reserve. Thus, two pathways could be targeted to prevent or delay the onset of dementia.

Vascular mechanisms

It is well known that cardiovascular risk factors (eg, hypertension and diabetes) cause cerebrovascular lesions. Research has also provided evidence that these factors contribute to global and regional brain atrophic lesions (loss of brain tissue) and to neurodegenerative pathologies such as AD.[133–135] Biologically, cerebral atherosclerosis and neurodegeneration might have shared mechanisms, such as oxidative stress (damage resulting from high levels of reactive oxygen species), inflammation, and deposition of toxic Aβ. Intracranial atherosclerosis could also induce cerebral hypoperfusion and trigger accelerated deposition of Aβ, which in turn contributes to cognitive deterioration and dementia.[136] Furthermore, cerebral macrovascular (eg, atherosclerosis and infarction), microvascular (eg, lacunar infarcts, white matter lesions, microbleeds), and neurodegenerative pathologies might converge during ageing to cause additive brain damage and thus promote clinical manifestation of a dementia syndrome.[137–140] This possibility is supported by neuroimaging and neuropathological studies,[141–143] which show that most cases of clinically diagnosed dementia and AD in older people living in the community are associated with mixed vascular and neurodegenerative pathologies in the brain.

Reserve hypothesis

Neuropathological studies have shown that psychosocial factors can modify the association of neurodegenerative pathologies with cognitive function, such that cognitive ability can remain high in individuals with a heavy burden of global neuropathology if they also engage in cognitively stimulating activities or have high levels of education or rich social networks.[144–146] How these factors compensate for the deleterious effects of cerebrovascular and AD pathologies on cognitive performance in ageing remains open to debate. The related concepts of brain reserve and cognitive reserve are the focus of intensive research.[27]

Public health implications

According to a US National Institutes of Health (NIH) state-of-the-science review[147] published in 2010, firm conclusions cannot be drawn about the association of any modifiable risk factor with cognitive decline or AD. Indeed, many studies have been hampered by methodological issues, such as self-reported measurements of exposure to risk factors, inconsistent control of relevant confounders (eg, depression), and variations in diagnostic procedure and criteria for dementia and AD.[148,149] However, a different picture would have emerged if the evidence had been assessed from a life-course perspective.[112] For instance, a systematic review[111] of epidemiological studies that focused on seven modifiable risk factors (low education, smoking, diabetes, midlife hypertension, midlife obesity, depression, and physical inactivity) suggested that a 10% reduction in exposure to these risk factors in midlife could potentially prevent up to 1·1 million cases of AD per year worldwide. Therefore, the proper time windows over the lifespan (eg, midlife or younger old age) for intervention to prevent or delay the onset of dementia should be kept in mind when designing intervention programmes (section 3).[150]

It has been suggested that some interventions (eg, pharmacological control of hypertension), if implemented in middle-aged or younger old adults, might effectively reduce the incidence of dementia.[151] Thus, although age remains the main driving force for dementia development,[152] interventions that target multiple modifiable risk factors, if implemented earlier in life, might be more promising than later interventions in reducing the risk or postponing the onset of dementia,[76] and several intervention studies to assess effects on disease onset are underway in Europe (section 3).[153] It has been estimated that delaying the onset of dementia by 5 years would halve the prevalence of dementia and substantially decrease the number of dementia cases in the community. Delaying the onset of dementia by even 2 years would have substantial public health, economic, and societal benefits.[154]

Traumatic brain injury and dementia

Although a systematic review showed no convincing evidence in support of an increased risk of AD or dementia after mild traumatic brain injury (TBI),[155] results of several epidemiological studies[156–159] suggest that a history of head trauma or mild TBI is associated with an increased risk of AD and other dementias and results in an earlier age at onset in affected individuals compared with those without head trauma. Autopsy studies have shown substantial Aβ deposition in up to 30% of people who die acutely after a brain injury.[160,161] Moreover, brain interstitial fluid concentrations of the aggregation-prone 42-aminoacid form of Aβ (Aβ42) and the axonal injury marker tau are reported to be higher immediately after severe TBI.[162–164]

A history of head trauma is associated with greater Aβ deposition in patients with mild cognitive impairment,[165] and data suggest that an important cause of dementia in individuals with a lifestyle associated with increased risk of repetitive mild TBI or concussion (the terms are used interchangeably) is chronic traumatic encephalopathy, a neuropathologically defined condition previously described in professional boxers.[166] It is now clear that athletes engaged in contact sports such as boxing, American football, and ice hockey constitute a new group at risk of dementia. The underlying mechanisms seem to involve diffuse axonal injury and Aβ and tau deposition resulting from repetitive acceleration–deceleration and rotational forces on the brain tissue.[166] Evidence of smaller hippocampus (a brain region associated with emotions, learning, and memory) volumes in American football players, of chronic traumatic encephalopathy pathology in American footballers, ice hockey players, and military personnel, and of biomarker changes associated with brain injury after sub-concussive head blows in amateur boxing emphasise the need to explore further the relation between TBI and dementia.[167–169]

Summary and recommendations

Epidemiology has provided powerful methods to study the burden and geographical variations in the occurrence of AD and other dementias in society, to understand the natural history of dementia and identify risk and protective factors, to identify populations at increased risk of dementia, to monitor time trends in dementia occurrence, to investigate the effects of new therapies for dementia, and to assess the different protective strategies for intervention against dementia. However, we are still far from developing a cure or an effective pharmacotherapy for AD, providing cost-effective medical and social care for the many patients affected by dementia, and implementing successful intervention strategies against dementia.

Additional epidemiological surveillance is required to provide a complete picture of the epidemiology of dementia in Europe and worldwide. AD, which accounts for up to 70% of all dementia cases in most studies, is an age-related disease that develops over many years, but it is not an inevitable consequence of ageing—up to 50% of people who reach the age of 90 years do not have dementia—and more work is needed to understand why. From an epidemiological perspective, implementation of the

following recommendations will be key to meeting the future challenges of dementia and AD.

(1) A harmonised international database for population-based longitudinal studies of ageing and dementia should be established. The aim should be to provide powerful resources to further understand the burden (economic and societal costs), temporal trends (prevalence, incidence, and mortality), natural history (eg, with identification of genetic and clinical markers for early detection), and aetiopathogenesis (eg, exploration of the potential contributions of psychosocial stress, mild TBI, nutrition, and frailty) of AD and other dementias.[99,170]

(2) Knowledge about the effects of dementia at the individual and societal levels is needed—such as prevalence stratified by severity, factors linked to progression in cognitive and functional disability, and factors linked to admission to institutions.

(3) Multidisciplinary research projects that integrate epidemiological approaches with genetic, neuro-biological, neuroimaging, and clinicopathological techniques are needed to improve understanding of the pathophysiological processes of ageing and dementia. Such knowledge will facilitate the development of new therapeutic approaches for dementia in the clinical setting and intervention strategies against dementia in the community.

(4) Life-course approaches should be applied to epidemiological studies of AD and other dementias. These approaches are particularly relevant with regard to understanding the causes and natural history of dementia, and in developing intervention strategies for multifactorial chronic diseases such as AD.

(5) Long-term studies with harmonised methods should be done to understand better the temporal trends and geographical variations of dementia occurrence within single countries and across Europe. In particular, more research is needed to clarify whether and to what extent the secular trends in cardiovascular risk and dementia occurrence in Europe are causatively correlated.

(6) A collaborative project in Europe should be initiated to understand the occurrence, non-genetic determinants, natural history, and individual and societal burden of early-onset dementia.[171,172]

Section 3. Prevention of cognitive impairment and dementia

WHO[3] and health and science ministers of the G8 dementia summit[173] have recognised dementia as a public health priority, and prevention has been identified as one of the key elements in addressing the dementia epidemic, as for other major non-communicable diseases (eg, cardiovascular disease). It is estimated that a third of AD cases worldwide might be attributable to seven modifiable risk factors—low education, midlife hypertension, midlife obesity, diabetes, physical inactivity, smoking, and depression—and a reduction in the prevalence of these risk factors by 10–20% per decade could reduce the worldwide prevalence of AD in 2050 by 8–15% (between 8·8–16·2 million cases).[174] Furthermore, delaying the onset of dementia by just 5 years might reduce the number of cases in total by up to 50% over 50 years.[175,176]

Observational studies in the general population, starting in early adulthood, are needed to monitor the distribution of risk and protective factors in different age groups and in different generations over long periods. Few such studies have been done, and data from the 1960s and 1970s might not be entirely applicable because of changes in lifestyle, society, pharmacological treatments, and the type of risk factors.[177] In the past few decades, for example, there has been a widespread and substantial increase in the prevalence of obesity and diabetes mellitus.[178,179] Knowledge about risk-factor distribution in different populations can help to obtain reliable estimates of the effects of preventive interventions on future dementia prevalence, thus aiding health education and community planning.

Epidemiological studies can identify potential modifiable risk and protective factors that could be targeted in dementia prevention programmes (section 2). However, a big challenge is to design such programmes on the basis of firm evidence from well designed and ethically sound clinical studies. Large-scale randomised controlled trials (RCTs) are needed to establish whether prevention strategies that target potential risk and protective factors—from lifestyle factors to drugs for prevention, including multifactorial interventions—can decrease substantially the incidence of dementia.

Evidence from observational studies and clinical trials

During the past 10–15 years, various modifiable risk and protective factors have been linked in long-term observational studies to an increased risk of dementia and AD (panel 4). Vascular risk factors at midlife (eg, high blood pressure, cholesterol, obesity, diabetes) have been linked to an increased risk of dementia and AD later in life.[76] Psychosocial factors, such as depression, loneliness, and stress, have also been identified as possible risk factors.[76,177] Conversely, factors such as physical, cognitive, and social activities and healthy diet might reduce the risk of dementia.[76,177] Complex gene–environment interactions underlie the development of dementia, and some environmental factors might have more pronounced effects in genetically susceptible individuals, such as carriers of the *APOE* ε4 allele, the most important genetic risk factor for sporadic AD (section 4).[76,177]

Although observational studies have provided information about potential modifiable risk and protective factors, large RCTs are needed to confirm that interventions targeting these factors can efficiently postpone or prevent cognitive impairment and dementia, and to test which of a wide range of interventions are most effective in preventing or delaying onset in different

at-risk groups. Positive results from observational studies have not automatically led to successful prevention strategies in RCTs. For example, encouraging data from observational studies of the preventive properties of hormone replacement therapy (HRT) and non-steroidal anti-inflammatory drugs (NSAIDs) were not confirmed in RCTs.[180–182] An important reason for this disparity is the problematic translation of observational data into intervention design. Trials based on the assumption that AD is a monodimensional condition (ie, due mainly to a single risk factor or cause) have consistently failed to identify efficacious prevention interventions. Additionally, use of compounds with different mechanisms of action (eg, HRT, NSAIDs, statins, vitamins, ginkgo biloba extract) has often been tested in prevention RCTs that were add-ons to trials with other primary outcomes (eg, cardiovascular or cerebrovascular events).[177] Such trial designs might have limited the ability to detect an effect on cognition or dementia risk because of low statistical power or short duration. So far, no study has convincingly shown a single-drug approach to be effective in the prevention of dementia. Antihypertensive drugs are the only exception, with some evidence for a protective effect against dementia.[183] Single lifestyle-related intervention trials (eg, physical activity and cognitive training) have shown only modest or short-term positive results.[147]

Prevention RCTs have highlighted several key issues that should be taken into account when designing and testing prevention strategies.[184] Effective approaches depend on appropriate timing of the intervention. Starting during preclinical or prodromal AD—ie, before the onset of dementia—is likely to be more effective than starting when dementia is already established, and some interventions might have critical time windows (eg, beneficial effects only in midlife or during the preclinical phase). Preventive measures need to be adjusted to their intended target groups, and larger trials (ie, several thousand participants instead of hundreds) with longer-term interventions (ie, years instead of months) are needed to show preventive effects in healthy, younger individuals (around 60 years of age). The very definition of "effects" is important, and measuring changes in performance with cognitive tests that can capture subtle decline and the entire continuum of cognitive functioning might be a more sensitive outcome than conversion to dementia. In multifactorial disorders, single-agent interventions might not be enough to significantly affect cognition and function, and targeting several risk factors and disease mechanisms simultaneously might be needed for optimum preventive effects.

For more on the **FINGER project** see https://www.thl.fi/fi/web/thlfi-en/research-and-expertwork/projects-and-programmes/finger-research-project

Some risk or protective factors for dementia and AD have been investigated in clinical trials, but the amount and quality of available evidence for such factors is variable. Moreover, opinions are divided about what constitutes sufficient evidence to formulate specific prevention recommendations. RCTs are usually thought to provide the best evidence that an intervention has clinically meaningful effects. However, traditional RCTs are not always possible. Vascular risk factors cannot be left untreated in placebo groups for ethical reasons (there is already strong evidence that treating vascular risk factors protects against cardiovascular disease), and strict double-blinding is not always possible with lifestyle-related interventions. Vascular risk factors in midlife have been linked to an increased risk of dementia and AD 20–30 years later in long-term population-based observational studies.[76] However, it is not feasible to do such long-term RCTs to verify these effects. It would also be counterproductive to wait for successful RCTs before implementing every prevention strategy. The relation between smoking and lung cancer is a classic example of observational studies providing sufficient evidence for prevention. No RCTs have been needed for non-smoking guidelines and recommendations, because these studies would have been unethical.

As mentioned in section 2, epidemiological studies in several high-income countries (eg, the USA, the Netherlands, Sweden, the UK) suggest that the incidence or age-specific prevalence of dementia has declined in the past 20 years.[68,84,86] These findings imply that dementia risk is modifiable. Possible explanations for the fall in incidence include favourable changes in some vascular risk factors (eg, better and wider use of drugs and changes in behaviour), changes in education or employment, and fewer head injuries.

Research in progress

Several countries have already taken the step from observation to action and initiated large lifestyle-based multifactorial intervention trials. This approach includes interventions that target several risk factors simultaneously in individuals who are at increased risk of dementia. Table 4 summarises the main trials completed or in progress in Europe.[185–188] An at-risk group was selected for the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) study (ClinicalTrials.gov identifier NCT01041989) according to the Cardiovascular Risk Factors, Aging, and Incidence of Dementia (CAIDE) risk score, the first tool for estimating long-term risk of dementia on the basis of risk factors present at midlife (table 5). The CAIDE risk score, which has been validated in a large multi-ethnic population in the USA,[128] can help to identify individuals who might benefit from intensive lifestyle consultations and pharmacological interventions (ie, target interventions for those most at risk). The risk score can also be used as an educational and motivational tool—eg, to distribute easily understandable information about risk factors to those most at risk in the general population.

In the FINGER RCT, the 2 year multidomain intervention consisted of four components: nutritional guidance, physical exercise, cognitive training and social activity, and management of vascular risk factors. The

first results from this study suggest that it is possible to improve lifestyle factors in older adults at risk of dementia, and that such changes can significantly enhance cognitive performance and reduce the risk of cognitive decline.[189] Extended follow-up of FINGER study participants is ongoing to detect differences in dementia and AD incidence.

Another new approach is the use of technology. For example, in the Healthy Ageing Through Internet Counselling in the Elderly (HATICE) project (ISRCTN registry identifier ISRCTN48151589), an internet-based platform has been developed that aims to motivate and support lifestyle changes and improve management of cardiovascular factors. The platform is interactive, with nurse or coach support readily available, and the project will test whether making prevention more accessible for elderly people in the community can reduce cardiovascular risk factors and dementia. Finally, as part of the European Dementia Prevention Initiative (EDPI), a data-sharing platform has been established between the multidomain prevention RCTs in progress in Europe to allow in-depth joint analyses of data relating to different target groups and interventions, and collaborations between research groups in different countries. Differences in health-care systems across Europe can be taken into account in such analyses, which will be crucial in the planning of future multinational prevention studies and programmes.

Increased collaboration between governments and between research groups, including public and private institutions, is necessary to create the infrastructure needed for research into prevention of dementia and AD, and to facilitate the implementation of evidence-based prevention strategies. Some international large-scale initiatives have already been established to increase collaboration, including the EU Joint Programme for Neurodegenerative Disease Research (JPND), the Innovative Medicines Initiative, the G8 dementia summit,[173] and the Organisation for Economic Co-operation and Development's (OECD) mapping for big data in Alzheimer's research.[190] A common aim of these initiatives is to increase and coordinate investments and collaborations between participating countries by bringing together academic experts, private sectors (the pharmaceutical and other industries), and policy makers and by building on existing infrastructures. The main goal is to investigate key research questions about neurodegenerative diseases, including AD, and identify effective preventive and therapeutic measures that can be implemented in different settings (eg, in the general population and in clinical settings).

For more on the **JPND research initiative** see http://www.neurodegenerationresearch.eu/

For more on the **Innovative Medicines Initiative** see http://www.imi.europa.eu/

For more on the **HATICE project** see http://www.hatice.eu/

For more on the **EDPI collaboration** see http://www.edpi.org/

Prevention trials in populations at high risk of dementia

Increasing evidence that the disease process (ie, accumulation of pathology) can start many years before

	FINGER[185]	MAPT[186]	PreDIVA[187]	HATICE[188]
Sample size	1260 community dwellers from previous population-based observational cohorts	1680 community dwellers	3533 community dwellers	4600 community dwellers
Main inclusion criteria	Dementia CAIDE risk score >6 and cognitive performance at the mean level or slightly lower than expected for age	Frail elderly individuals (subjective memory complaint, slow walking speed, IADL limitations)	All elderly patients without dementia in general practices	Older adults without dementia with increased risk of cardiovascular disorders and dementia
Age at enrolment	60–77 years	≥70 years	70–78 years	≥65 years
Study design	Multicentre, randomised parallel-group controlled trial	Multicentre, randomised controlled trial	Multisite, cluster-randomised parallel-group controlled trial	Multinational, multicentre, randomised parallel-group controlled trial
Intervention	Multidomain: nutritional guidance, physical activity, cognitive training, social activity, management of vascular risk factors	Multidomain: vascular care, nutritional advice, exercise advice, cognitive training with or without 800 mg docosahexaenoic acid per day	Multidomain: nurse-led vascular care, including medical treatment of risk factors, nutritional advice, exercise advice	Multidomain e-health: interactive internet platform with nurse-led support to optimise management of vascular and lifestyle-related risk factors
Duration	2 years plus 5 years' follow-up	3 years plus 2 years' follow-up	6 years	1·5 years
Outcomes	Primary: change in cognitive function Secondary: dementia, depression, disability, cardiovascular events, quality of life, health-resource use, change in AD biomarkers	Primary: change in cognitive function Secondary: cognition, functional status, depression, health-resource use, change in AD biomarkers	Primary: dementia, disability Secondary: cognitive decline, depression, cardiovascular events	Primary: optimisation of cardiovascular and dementia risk management Secondary: change in cognitive function, dementia, cardiovascular conditions, mortality, hospital admission, depression, disability, cost-effectiveness
Status	Completed in 2014	Completed in 2014	Completed in 2015	Due to finish in 2017

FINGER=Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability. MAPT=Multidomain Alzheimer Prevention Study. PreDIVA=Prevention of Dementia by Intensive Vascular Care. HATICE=Healthy Ageing Through Internet Counselling in the Elderly. CAIDE=Cardiovascular Risk Factors, Aging, and Incidence of Dementia. IADL=instrumental activities of daily living. AD=Alzheimer's disease.

Table 4: **Randomised controlled trials of multidomain interventions for prevention of cognitive impairment, dementia, or Alzheimer's disease**

	Points
Age	
<47 years	0
47–53 years	3
>53 years	4
Education	
>9 years	0
7–9 years	2
<7 years	3
Sex	
Female	0
Male	1
Blood pressure	
≤140 mm Hg	0
>140 mm Hg	2
Body-mass index	
≤30 kg/m^2	0
>30 kg/m^2	2
Total cholesterol	
≤6·5 mmol/L	0
>6·5 mmol/L	2
Physical activity	
Yes	0
No	1

Probability of developing dementia in 20 years according to CAIDE midlife risk score categories. A total score of 0–5 corresponds to a dementia risk of 1·0%, a score of 6–7 to a risk of 1·9%, a score of 8–9 to a risk of 4·2%, a score of 10–11 to a risk of 7·4%, and a score of 12–15 to a risk of 16·4%. CAIDE=Cardiovascular Risk Factors, Aging, and Incidence of Dementia.

Table 5: **CAIDE risk score**

For more on the **A4 study** see http://a4study.org/

the onset of cognitive impairment and dementia in people with AD has driven a shift in focus from advanced disease to earlier stages, with trials for prevention (delaying or preventing disease onset) and treatment (targeting disease mechanisms to modify disease course) now targeting very similar groups of people in the preclinical stages of AD. Potential disease-modifying treatments (eg, anti-amyloid drugs), which were previously tested only in patients with AD dementia with a view to stopping or slowing the course of the disease, are now being tested in selected asymptomatic populations who are at high risk of AD because of an established biomarker burden or a specific genetic profile (section 7).[191] For example, the safety and efficacy of anti-amyloid drugs as preventives in participants with pre-symptomatic (or preclinical) AD are being tested in three RCTs, two of which focus on early-onset familial AD and one on sporadic AD.

For more on the **EPAD project** see http://www.ep-ad.org

For more on the **DIAN study** see http://www.dian-info.org/

For more on the **API study** see http://banneralz.org/research-plus-discovery/alzheimers-prevention-initiative.aspx

The Dominantly Inherited Alzheimer Network (DIAN; NCT01760005) and the Alzheimer's Prevention Initiative (API; NCT01998841) studies have enrolled individuals who carry mutations in one of *APP*, *PSEN1*, or *PSEN2*. These mutations cause dominantly inherited, early-onset AD, in which just one copy of the mutated gene in each cell is sufficient to cause the disease (autosomal dominant AD). Although such cases of early-onset familial disease account for only 1–5% of all cases, the fact that progression to symptomatic AD is almost inevitable in this group makes their inclusion in prevention and treatment trials an important endeavour.

Data from the DIAN study, an international study with 210 participants from North America, Australia, and Europe, have shown that phenotypic changes associated with the disease can be detected several years before the onset of cognitive symptoms in people with autosomal dominant AD—cerebrospinal fluid (CSF) concentrations of Aβ42 decline 25 years before expected symptom onset, and brain deposition of Aβ can be detected 15 years before symptoms emerge[192]—and the aim is to intervene before symptoms emerge in this high-risk group. The API trial focuses on the world's largest early-onset AD kindred, in Antioquia, Colombia. Of about 5000 individuals in this kindred, around 1500 carry a mutation in *PSEN1* (E280A), which causes disease with a mean age of onset of 45 years.[193] The Anti-Amyloid Treatment in Asymptomatic Alzheimer's (A4) study (NCT02008357) aims to prevent sporadic AD and assess the effect of an anti-amyloid compound in older adults with evidence of brain amyloid accumulation at neuroimaging assessment. The A4 study includes an ethics arm, which is examining the psychological effects of disclosing information to individuals about their risk of developing AD.[194]

Although Europe has been at the forefront of initiatives to promote lifestyle-based interventions for dementia prevention, North America has led the start of RCTs of anti-AD drugs in preclinical AD. However, studies of both pharmacological and non-pharmacological interventions for the prevention of cognitive decline and dementia are now being started in several world regions. In Europe, the launch of the European Prevention of Alzheimer's Dementia Consortium (EPAD), within the Innovative Medicines Initiative, is expected to create readiness cohorts and a novel framework for RCT testing of new disease-modifying drugs in the preclinical stages of AD. Indeed, enough evidence exists to justify some immediate actions in dementia prevention,[195] including public health policies that encourage middle-aged people to stop smoking, treat high blood pressure, and avoid obesity and diabetes.

Health economics of dementia prevention

Assessing the benefits of delaying or preventing the onset of dementia from an economic perspective is a complex endeavour. AD has a long, silent phase before the first symptoms emerge, and it can take time for milder symptoms to develop into full-blown dementia. Health-care services are needed less and costs are lower in the early stages of cognitive impairment than in the later stages of disease (section 1). Among the challenges of assessing the benefits of preventive strategies is

intervention methodology. For example, because dementia incidence is strongly related to age and dementia is rare in midlife, a very broad intervention in younger individuals (around 40–50 years) with no symptoms will be associated with a very low occurrence of dementia. Some prevention activities, such as targeting vascular and lifestyle factors, are implicit in daily life and in medical-care settings, making it difficult to estimate their costs separately. Public health prevention trials outside the medical-care system are easier to assess than trials embedded in the system, because the former tend to demand some kind of separate infrastructure, with associated programme costs.

Approaches such as economic simulations can be useful for the estimation of cost-effectiveness. For example, one study[196] assessed the cost-effectiveness of a potential dementia prevention programme using the CAIDE risk score and a Markov model adapted to Swedish conditions. The prevention programme consisted of a healthy-lifestyle promotion programme and pharmacological treatment of cardiovascular risk factors. Figures for costs (intervention costs and costs of care for people with and without dementia), utilities (health utilities expressed as QALYs), and mortality according to age group were obtained from published work or databases. The multidomain preventive intervention was less costly and was associated with better dementia-related outcomes than was usual care, supporting its cost-effectiveness. Thus, to assess the cost-effectiveness of prevention programmes, a multifactorial approach is desirable, with a filter to select at-risk participants and sufficient statistical power in terms of sample size and intervention duration.

Summary and recommendations

The pathology of AD is complex, but epidemiological studies have provided knowledge of protective factors and risk factors for the disease. The onset of AD and other dementias could probably be prevented or delayed, because many of the known risk factors are modifiable or amenable to management. Enough evidence exists to justify some immediate actions in dementia prevention,[195] including public health policies that encourage middle-aged people to stop smoking, treat high blood pressure, avoid obesity and diabetes, and increase their physical activity. However, knowledge about modifiable risk factors needs to be refined, and findings from observational studies need to be validated in large, well designed, and ethically sound intervention studies. Here we identify priorities for the implementation of effective dementia prevention programmes.

(1) Many modifiable risk factors—including high blood pressure, obesity, physical inactivity, and unhealthy diet—are shared among dementias, including AD, and other major late-life chronic disorders, such as heart disease and stroke. Public health efforts should aim to promote healthier lifestyles in midlife, because this approach has the potential to improve the general health status of the population in advanced age.

(2) Population surveillance of risk factors in different age groups and different countries is urgently needed to better estimate the effects of preventive interventions on future dementia and AD prevalence across Europe. This information should be used in the planning of public health policy.

(3) Observational studies need to start early in midlife and have a long duration to identify windows of opportunity for effective interventions. By building on existing infrastructures and cohorts developed for the study of other chronic diseases, resource use could be optimised.

(4) Effective prevention of dementia demands tailored intervention strategies for particular target groups (eg, appropriate interventions for different ages and contexts). The characteristics of target groups, in addition to differences in health-care systems between countries, need to be considered in developing preventive strategies that can be translated easily and implemented internationally.

(5) In view of the multifactorial causes of AD and dementia, multidomain interventions—with simultaneous management of various risk and protective factors through lifestyle changes and pharmacological treatment—should be considered for optimum preventive effects.

(6) Increased collaboration between governments and between public and private institutions will help to accelerate and increase the power of prevention research for AD and dementia. To allow scientific collaboration between research groups in Europe, an appropriate infrastructure is needed to enable more effective use of existing data and rapid recruitment of participants in multinational intervention trials.

Section 4. Genetic risk of Alzheimer's disease: individual susceptibility

Evidence from genetic studies explains how genetic variability, present in DNA from conception, contributes to the development of AD later in life. Genetic epidemiology attempts to understand how genetic make-up lends resistance or vulnerability to environmental exposures, such as lifestyle factors and medical illnesses. The effect of individual genetic susceptibility on the occurrence of AD is substantial, with the heritability of AD usually estimated to be greater than 60% (ie, >60% of variation in the phenotype is genetically determined).[197] Specialist terms that are key to our discussion in this section are defined in panel 3.

Several specific gene mutations cause, or contribute to, early-onset familial AD. About 5% of all patients have early-onset AD (age at onset younger than 65 years), and up to 2%—ie, about half of early-onset cases—will have autosomal dominant inheritance in the family, in which the occurrence of the disease is explained by mutations in one gene with a major effect. A mutation in *APP*, which was shown in 1991 to be associated with a familial form of early-onset AD,[198] was the first known genetic determinant of the disease. Since then, mutations in the

APP, *PSEN1*,[199] and *PSEN2*[200] genes have been shown to account for almost half of all cases of early-onset familial AD. Most of these monogenic hereditary forms of AD follow a mendelian autosomal dominant transmission, affecting at least one individual in each generation.

For the other 98% of AD cases—sporadic AD, with late onset in most patients—clinicians often identify a family history of dementia without any specific mode of transmission, although the precise estimation of family history can be difficult because diagnostic assessments were limited in the past and the patient's parents might no longer be alive. The first susceptibility gene in sporadic AD, the ε4 allele of *APOE*, was discovered in 1993.[201,202] By contrast with *APP* mutations, polymorphism of the *APOE* ε4 allele is frequent in the general population, with a codominant effect on AD risk. The odds ratio (OR) is estimated to be 3·2 and 14·9 for carriers of one or two ε4 alleles, respectively (ie, the odds of having AD is about three times higher in people with one *APOE* ε4 allele than in people without the allele), with a high attributable fraction in the population (between 20% and 40%).[203] Many genetic variants that increase susceptibility to AD have since been identified (table 6).

Genetics plays a major part in understanding the disease mechanisms of AD, and will have an important role in prevention and care in the future. For example, genetic tests can be used to identify and classify individuals with various levels of risk for AD, ranging from low to high, before symptoms have appeared (predictive pre-symptomatic genetic testing), and for early diagnosis in prodromal states of AD. A detailed understanding of the level of AD incidence associated with genetic susceptibility will be important once an effective treatment is available, because genetic testing could then be used to identify and treat at-risk individuals before symptoms of cognitive dysfunction have developed. Genetic discoveries also offer clues to the pathological processes involved in the development of AD, and potential treatment approaches can be developed to intervene in these processes.

For more on the **CHARGE consortium** see http://www.chargeconsortium.com/

For more on the **ADGC collection** see https://www.niagads.org/content/alzheimers-disease-genetics-consortium-adgc-collection

For the **IGAP summary results** see http://www.pasteur-lille.fr/en/recherche/u744/igap/igap_download.php

	Very rare (MAF <0·1%) familial variants	Variants present at low frequency (MAF <1%) in the population	Variants present as common polymorphisms (MAF >10%) in the population
Disease gene	*APP*, *PSEN1*, *PSEN2*	..	..
High impact (OR ≥2)	*SORL1*	*PLD3*, *TREM2* *APP* A673T (protective)	*APOE* ε4 allele *APOE* ε2 allele (protective)
Low impact (OR <2)	..	..	Confirmed loci: *ABCA7*, *BIN1*, *CASS4*, *CD2AP*, *CD33*, *CELF1*, *CLU*, *CR1*, *EPHA1*, *FERMT2*, *HLA DRB5–DRB1*, *INPP5D*, *MEF2C*, *MS4A6A/MS4A4E*, *NME8*, *PICALM*, *PTK2B*, *SLC24A4*, *SORL1*, *ZCWPW1* Unconfirmed loci: *ACE*, *ADAMTS20*, *AP2A2*, *ECHDC3*, *FRMD4*, *HS3ST1*, *IGH*, *NDUFAF6*, rs6678275 (intergenic), *SCIMP*, *SPPL2A*, *SQSTM1*, *TREML2*, *TRIP4*

Identified genes and loci classified according to their effect on the risk for Alzheimer's disease. Generally, causal mutations (associated with early-onset familial disease) are rare and deterministic, which means that they contribute to only a minor fraction of the total number of patients with AD but have a strong impact on the individual (very strong association), being sufficient to cause the disease. These genes are thus classified separately as disease genes. MAF=minor allele frequency. OR=odds ratio.

Table 6: **Identified loci with genetic association to Alzheimer's disease**

Progress of genomics: international collaboration and data sharing

Between 1995 and 2009, more than 500 potential new susceptibility genes were reported, but none of them could be consistently replicated and confirmed.[204] The first achievement of the Human Genome Project[205] and the incredible development of nano-genome-sequencing technologies in the biological sciences[206] were needed to start to decipher the genetic susceptibility to AD.

The genome-wide association study (GWAS) approach that was developed thanks to these new technical developments has enabled the identification of a large proportion of genetic susceptibility to human diseases. Based on high-throughput genomics technologies, the GWAS approach can characterise millions of single-nucleotide polymorphisms (SNPs) covering the entire genome of one individual and offer a comprehensive view of the genomic regions associated with diseases. However, testing millions of variables in a case-control study design can lead to the discovery of false-positive associations. Thus, AD geneticists had to use very stringent p-value thresholds ($<5\times10^{-8}$) and to replicate systematically their discoveries in additional follow-up studies.[207] Consequently, they had to enlarge the size of their samples from hundreds to thousands of cases and controls to increase their statistical power, improving the chances of detecting frequent polymorphisms with small individual effects on disease risk. The only way to collect very large samples of cases and controls was to create large collaborative consortiums that could share their clinical data, biobanks, and genotypes.

In 2009, two such consortiums, the European Alzheimer's Disease Initiative (EADI) and the Genetic and Environmental Risk in Alzheimer's Disease (GERAD) consortium, discovered three new AD susceptibility loci.[208,209] In 2010, the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE), in collaboration with EADI and GERAD, published two new loci,[210] one of which was confirmed. In 2011, the Alzheimer's Disease Genetics Consortium (ADGC) published, back-to-back with a paper from the three other consortiums,[211] five new loci.[212] Thus, the total number of susceptibility loci associated with late-onset AD was ten, including *APOE*. These four consortiums have formed the largest and most efficient genomics collaboration in AD, the International Genomics of Alzheimer's Project (IGAP), which has a combined sample population of 25 580 AD cases and 48 466 controls, and has discovered

and confirmed 11 new loci and proposed 13 potential new loci.[213] Finally, four other genes were identified with different approaches. In 2015, the total number of confirmed genetic effects was 26, with 14 that still need to be validated, located in 39 different loci (table 6; appendix). A substantial proportion of the associated loci have unknown function.

Effects and frequencies of genetic variants

AD-associated loci can be classified into different groups in terms of genetic influence depending on the level of association of the genetic variant with the disease risk (weak or strong) and the frequency of this genetic variant in the general population (table 6). Whereas causal mutations (those associated with early-onset familial AD) are rare and deterministic, contributing to only a minor fraction of cases in the population but having a strong effect on the individual (very strong association), susceptibility genetic variants are usually more common in the population (SNPs with a minor allele frequency [MAF] >10%), and thus an association can have a large effect on the total burden of disease in the population but a small effect on individual risk. Susceptibility loci can have a high impact (OR ≥2) or low impact (<2), depending on how strong the association is to AD.

Causal mutations (disease genes) have been identified in segregation studies of familial forms of AD in which disease inheritance supports the involvement of a single gene mutation as the cause of the disease. Most high-impact susceptibility loci have been identified through hypothesis-driven candidate-gene approaches, targeting one or a few specific genes on the basis of their biological function or systematic sequencing approaches associated with functional studies. Low-impact susceptibility loci have been identified by GWAS, which are based on the association of SNPs to a disease with no a-priori hypotheses. In the absence of any functional or experimental information about the identified loci, GWAS results refer in general to susceptibility loci, largely without any known functional implications in terms of disease aetiology.

Disease genes (causal mutations) and the high-impact susceptibility loci discovered in familial forms of AD form the first two groups of disease loci in table 6. Deterministic mutations in *APP*, *PSEN1*, and *PSEN2*—all of which are involved in Aβ production—in early-onset monogenic forms of AD contributed to the amyloid cascade hypothesis of the disease (section 5), which posits that the Aβ peptide is a key player in AD causation.[214] However, mutations in these three genes are present in only about half of the families with autosomal dominant AD, which suggests that other major genes are still to be discovered. Systematic sequencing of exomes (ie, protein-coding regions) in autosomal dominant early-onset familial forms of the disease led to the discovery of nonsense and missense mutations in *SORL1* that are not detected in large control samples. Following in-silico analyses, the mutations in *SORL1*, which encodes the sortilin-related receptor LR11/SorLA, a protein involved in the control of Aβ peptide production, seem likely to have a pathogenetic effect.[215] This finding provides support for the amyloid cascade hypothesis in early-onset forms of AD. Common polymorphisms of *SORL1* are also associated with sporadic AD.

See Online for appendix

The first and only gene to be consistently associated with sporadic AD with an older age at onset was *APOE*, which constitutes the third group of disease loci, with high frequency in the population and a high impact on disease risk (table 6). *APOE* was already known to be associated with high concentrations of LDL cholesterol and myocardial infarction risk.[216,217] The risk effect of the *APOE* ε4 allele in AD was discovered with candidate-gene approaches.[201,202] More in-depth analyses showed that the *APOE* ε2 allele was, conversely, a protective factor that reduced the risk for AD.[218] In recent studies, lifetime risk for AD, without reference to the *APOE* genotype, at age 85 years was 11% in men and 14% in women. This lifetime risk was 50% for *APOE* ε4 homozygous men and 60% for homozygous women, whereas for heterozygous *APOE* ε3ε4 carriers the lifetime risks were 23% for men and 30% for women. These estimations are consistent with a semi-dominant inheritance of a moderately penetrant gene (penetrance is the proportion of people with the variant who develop the associated disease), similar to the effect of *BRCA1* mutations on risk for breast cancer and other major-effect genes with incomplete penetrance in mendelian diseases.[219] Despite this major susceptibility impact on AD, the role of *APOE* in pathophysiology is open to debate.

Since 2009, several international research consortiums have contributed to the identification of susceptibility loci with high frequency and low impact, the fourth group of loci associated with AD (table 6).[208–213] The total number of confirmed loci is 20, with 14 loci to be determined. The SNPs identified in these loci are frequent (MAF >10%), and are either protective (the minor allele is more common in the control group than in those with AD, and therefore associated with a lower risk) or deleterious (the minor allele is more common in those with AD than in the control group, and is therefore associated with increased risk), but with low impact (OR <2). All the loci in this fourth group need to be investigated to understand through which biological disturbances the genetic variants contribute to the development of AD. Some of the associated loci point to a specific gene, whereas others cover larger regions with several possible candidates. Thus, future research must focus on the identification of the specific genetic variants that cause the increased risk of AD and subsequent functional studies should unravel their biological relevance in pathophysiology.[220]

With the development of next-generation sequencing technologies, the exomes of a given genome can now be sequenced to characterise all the mutations present in the coding regions of patients and to examine their

presence or absence in controls. This sequencing approach was successfully used to discover two new AD genes with low-frequency mutations (MAF <1%) and high impact (almost as high as that observed for heterozygous *APOE* ε4 allele carriers), which constitute a fifth group of susceptibility genes (table 6). The first gene was triggering receptor expressed on myeloid cells 2 (*TREM2*), which had previously been associated with Nasu-Hakola disease, a rare disorder in which patients present with bone cysts and early-onset dementia.[221] While sequencing *TREM2* in a series of AD cases and controls, several low-frequency mutations could be identified and were associated with an increased risk (by more than four times) of sporadic AD.[222] *TREM2* was simultaneously discovered in an Icelandic population and similarly extended to sporadic AD risk in other populations.[223]

The phospholipase D3 (*PLD3*) gene was recently added to this fifth group.[224] A non-synonymous coding mutation was discovered in a whole-exome sequencing study of 14 large families with late-onset AD in four or more individuals. The *PLD3* mutation segregated with AD in two independent families and doubled the risk for AD in a large case-control multicentre study. However, this observation could not be replicated.[225] Functional experiments suggested that *TREM2* is related to the immune pathway, which has previously been implicated in AD pathogenesis. Finally, while searching for rare variants in the *APP* gene with a clinically significant effect on AD risk, Icelandic researchers identified a coding mutation (A673T) that potentially protects against AD and cognitive decline in the elderly population.[226]

From gene discovery to clinical application

Early-onset and late-onset AD genes

For the **Alzheimer Disease & Frontotemporal Dementia Mutation Database** see http://www.molgen.vib-ua.be/ADMutations

More than 200 different mutations in *APP*, *PSEN1*, or *PSEN2* have been identified in cases of early-onset AD. These mutations are usually inherited from an affected parent in an autosomal dominant manner, which suggests that new (de-novo) mutations are rare and penetrance is generally high, reaching almost a 100% lifetime risk. There have also been two reports of recessive *APP* mutations in rare cases.[227,228] Thus, by screening for mutations in *APP*, *PSEN1*, and *PSEN2* in individuals affected by AD who belong to families with dominant inheritance and early onset of disease, the causal mutation can be identified in almost 50% cases. This type of mutation screening in known genes could be applied in clinical practice as a genetic diagnostic test.

If a mutation is identified in an index case from a family with inherited AD, genetic testing can be used to predict the risk in relatives who are still asymptomatic, a procedure known as pre-symptomatic genetic testing. The ability to identify at-risk individuals very early, before the disease process starts and when few comorbidities are present, provides researchers with an important opportunity to increase understanding of AD by tracing the natural history of the disease, the details of which will have implications for treatment and prevention. Several studies of early-onset AD show that the underlying pathophysiological process begins several years before definite clinical symptoms appear. Thus, studies of at-risk individuals from families with early-onset AD caused by mutations in *APP*, *PSEN1*, or *PSEN2* might shed light on the disease process in sporadic AD.[229]

Several research groups have studied the natural history of early-onset familial AD through prospective examinations of healthy, asymptomatic mutation carriers and their healthy non-carrier siblings. In these autosomal dominant AD cases, pathophysiological changes can be detected decades before any cognitive symptoms emerge.[192,230–232] For example, concentrations of Aβ42 in the CSF decline about 25 years before expected symptom onset, and Aβ deposition, as measured by positron emission tomography (PET), is detected 15 years before, as are increased CSF concentrations of tau protein and increased brain atrophy. Given the low frequencies of these familial forms of AD, the DIAN study was launched to examine the temporal progression of biomarker change using, for example, imaging, neuropsychological tests, and CSF analyses.[233] Moreover, in a prospective study of healthy people older than 65 years who were followed up for more than 15 years, the first decline in cognitive performance (eg, measures of semantic memory) was noted 12 years before the diagnosis of AD.[234] Improved understanding of the preclinical and clinical course of sporadic and familial AD could ultimately enable intervention before symptoms emerge.

In addition to *APOE*, the GWAS approach has identified several susceptibility loci whose relative contribution to the total load of AD in the population is high compared with the population attributable fraction of risk associated with the rare genes for early-onset AD (appendix). However, the use of this susceptibility information in any genetic testing at the individual level remains very limited because it does not provide reliable risk estimates.

Finally, other unknown genetic susceptibilities might result from interactions with environmental factors and other genes, and from mechanisms that are as yet unknown. These other potential mechanisms of action include epigenetic modifications of DNA and DNA-binding proteins, such as cysteine methylation and histone acetylation, and somatic mutations in the target tissue (ie, nerve cells).[235] However, insufficient data exist for the relevance of these mechanisms in AD, and future research is needed to address such hypotheses. To decipher these complex genetic mechanisms, increased access to high-quality databases of detailed electronic health records and to biobanks is needed to correlate genotype to phenotype and to estimate interactions between contributing genetic and environmental factors.

Genetic testing

Much work remains to elucidate disease mechanisms in AD. However, the amount of data already accumulated from genetics and genomics prompts thinking about the relevance of this information for translational research and clinical practice. Three important applications in the medium term are risk prediction in research and clinical practice, clinical-trial enrichment (eg, screening for specific susceptibility genes to recruit a more homogeneous sample for drug testing), and precision medicine.

The most obvious application of genomics in clinical practice resides in the use of genetic testing to support early and pre-symptomatic diagnosis. However, the clinical value of preclinical genetic testing for sporadic AD in the absence of proven interventions that can stop or delay the disease process is questionable and raises ethical concerns. Thus, the major use of genomics in AD is to increase scientific knowledge about the disease and to improve translational and clinical research.

In families with a strong history of early-onset AD, clinical genetic testing might be requested by patients themselves. Such cases should be handled in a clinical genetics setting with access to physicians, which would allowing continuing medical, social, and psychological support, rather than by direct-to-consumer genetic testing companies with little medical follow-up and support. Before any type of genetic test can be done, each individual to be tested needs to be fully informed about the consequences of these tests, including information about the disease itself, a-priori risk of inheritance, and consequences of these genetic tests for other family members.

If identification of a causal mutation in a patient with AD results in requests for pre-symptomatic genetic testing in other members of the family, this testing should be done only in the context of genetic counselling provided by teams with experience in neurodegenerative diseases. Such requests might come from family members with autosomal dominant AD, from individuals with a family history compatible with familial AD (the disease occurs in more than one individual, and at least two of the affected individuals are third-degree relatives or closer), or from individuals with an isolated case of sporadic AD.

When genetic testing is requested by a symptomatic individual, the patient should be accompanied by a family member or any declared representative. If the individual is pre-symptomatic, a protocol based on the International Huntington Association and World Federation of Neurology Research Group on Huntington's Chorea Guidelines is recommended.[236] This testing has several weaknesses. In autosomal dominant AD, the search for the causative mutation in a family will focus on *APP*, *PSEN1*, and *PSEN2*. However, half the families will not have any mutations in these three genes. Furthermore, due to the heterogeneity of clinical features in dementia, misdiagnosis of AD in the family has to be considered. In particular, the most common genetic cause of familial frontotemporal lobe dementia, an expansion of the *C9orf72* hexanucleotide repeat, has been identified in families in whom AD has been misdiagnosed.[237] Thus, in families with a clear autosomal dominant inheritance pattern, the possibility of other causative genes should be considered, with an extension of the number of target genes if mutation screening has been requested. A post-mortem neuropathological examination in the family will also help to define the clinical diagnosis.[238] Finally, in families who request genetic testing but lack mutations in the known genes, storage of DNA for future mutation screening in novel genes could be considered, since the risk of recurrence cannot be excluded.

	Deterministic genes	Susceptibility loci
Disease type	Rare	Common
Inheritance	Mendelian, monogenic	Complex, multigenic
Number of genes involved	Few (one)	Many
Prevalence of risk variant	Very rare (<1 per 10 000 individuals)	From rare to common
Test result	Highly predictive	Probabilistic
Individual impact	Strong	Weak
Family impact	High	Low
Potential population impact	Low	High
Risk	Simple (binary: yes or no)	Complex
Lifestyle factors	Do not affect risk in general	Modify risk

Adapted from Wright and Kroese.[239]

Table 7: **Pre-symptomatic genetic testing for deterministic monogenic mutations and susceptibility loci**

Apart from the three causative genes, the other gene that could be tested for is the strongest susceptibility gene for AD, *APOE*. However, despite a high attributable fraction of the *APOE* ε4 allele in the general population (around 20%) and a high lifetime risk in homozygous carriers, the ε4 allele is neither necessary nor sufficient to cause AD. Thus, use of *APOE* genotyping to predict AD risk is not recommended because of its low sensitivity and specificity for diagnosis, the lack of preventive options, and the difficulty of estimating an absolute individual risk.

The genetic testing outcome of the presence of a disease mutation in deterministic genes such as *APP*, *PSEN1*, and *PSEN2* in early-onset AD is very different from a positive test result for a risk gene such as *APOE* or bridging integrator 1 (*BIN1*; appendix) in late-onset AD (table 7).[239] Indeed, for deterministic mutations, the outcome is binary, either the mutation is present and the disease will unequivocally develop at some point in the future, or the mutation is absent and the early-onset form of AD will not develop. By contrast, the presence of a risk allele for a susceptibility gene will result in a lifetime risk-probability score for developing the disease in the future.[239] In most situations, multigenic risk confers only a genetic susceptibility, which will be modulated in a favourable or unfavourable way by gene–gene and gene–environment interactions.

Ethical concerns in genetic testing

Despite the similarities between AD and other neurodegenerative disorders such as Huntington's disease, early diagnosis of a disease whose symptoms might appear years afterwards and for which no treatment is available raises important ethical issues that need to be anticipated. Doing clinical or prevention trials in pre-symptomatic individuals with autosomal dominant mutations or in asymptomatic individuals at risk of developing AD raises ethical questions, because genetic testing will disclose to the individual participating in the trial his or her risk status.

For more on the **US National Alzheimer's Plan** see http://napa.alz.org/

Some ethical concerns were addressed in clinical trials that examined the effect of *APOE* genetic susceptibility testing on asymptomatic individuals: the Risk Evaluation and Education for Alzheimer's Disease (REVEAL) studies.[240] Results of the REVEAL trials suggested that disclosure of *APOE* genetic results by trained professionals using appropriate educational approaches does not generally result in short-term adverse psychological effects. However, these studies were not fully representative of a typical clinical setting. The participants volunteered for the study and they were preselected (had a parent with AD), highly educated, generally female, and received a free-of-charge test, the results of which were not included in their medical record. Nevertheless, these studies provide insight into what can be expected from the various all-in-one personal genomics services that report risk scores for health conditions and usually include results for AD susceptibility genes. Finally, early identification of pre-symptomatic individuals might have major psychological effects and other consequences, not only for the patient but also for family members who might be indirectly informed of their own risk.[241–243]

For more on the **REVEAL studies** see http://www.genomes2people.org/reveal/

The way forward in genetics

The discovery of causative *APP*, *PSEN1*, and *PSEN2* mutations in early-onset autosomal dominant AD paved the way for the amyloid cascade hypothesis of the disease.[214] Less than 20 years after the hypothesis was first published, expansion of the research landscape has been enabled by non-hypothesis-driven genomic approaches, such as whole-genome screening, providing an important entry point into AD research. The 40 genes and susceptibility loci identified so far, whether confirmed or suspected, offer insight into the high level of complexity that underlies the brain pathology of amyloid plaques and neurofibrillary tangles. However, these genetic discoveries now need to be taken forward. We have entered a post-GWAS era, in which all the research methods that are available in biological and computer sciences need to be integrated—bioinformatics, so-called omics technologies, systems biology, epigenetics, molecular and cellular studies, animal models, risk-factor assessments, and social-care and health-care research (figure 4). The future is transdisciplinary and will necessitate well planned and target-oriented development of databases and biobanks that can harbour information from all areas of research and health care, including population-based studies, clinical data, and experimental research results.

In 2012, the USA launched a major sequencing programme in the context of the National Alzheimer's Plan, with the aim of sequencing 10 000 whole exomes and 600 whole genomes in selected patients with AD and healthy controls.[244] Similar European initiatives have been launched in the context of research calls through the EU JPND. Following the example of the GWAS consortiums, sequencing consortiums are now being formed to enable data sharing. However, the magnitude of the information collected will require large data-handling infrastructures.

In parallel, the use of genomics in clinical research must be reinforced. Ready-to-use methods that allow rapid identification of genetic markers in patients attending memory clinics should be developed. These approaches could be used to aid differential diagnoses in dementia and other neurodegenerative disorders. Moreover, they would allow physicians and patients to be educated and prepared for precision medicine, the next revolution in clinical care. However, as long as no effective treatments are available for AD (and even after such treatments become available), social and ethical research must be strongly supported to help patients to cope with the notion of an increased lifetime risk of AD, and to protect them from any negative consequences (eg, access to employment or insurances) of early diagnoses given in the context of clinical research and health care.

To this end, greater efforts must be made in the European health-care systems to enable understanding of the genetic underpinnings of neurodegenerative diseases. To achieve this, professionals should be educated and families and patients should have universal access to qualified genetic counselling. In parallel with the progress in AD genetics and genomics, advances in the genetics of other neurodegenerative dementias, such as frontotemporal dementia, have led to similar challenges.[245]

Tackling AD is no longer in the hands of any one researcher, team, or even country. The first pilot EU JPND research was initiated in 2008. Geneticists and epidemiologists began to share data at the international level and, in less than 5 years, were able to discover more than 20 new AD susceptibility regions.[213] To speed up progress even more, this global collaboration must be extended to even more countries. The JPND initiative now includes 28 countries, including some non-European nations (eg, Canada, Israel). Awareness of the need for global collaborative research is growing, as shown by the G8 summit in London on Dec 12, 2013, which was dedicated to dementia. The ultimate goal is increased global collaboration and data sharing for the greatest benefit of our populations and economies.

Summary and recommendations

The heritability of AD is estimated to be greater than 60%. Several specific gene mutations cause, or contribute to, early-onset familial forms. Gene variants that increase susceptibility to AD have also been identified and large-scale GWAS are in progress. Genetics plays a major part in understanding the mechanisms of AD and will have an important role in the implementation of prevention and care strategies in the future. Well organised biobanks and large collaborative groups that share data are essential to advance understanding of the genetic underpinnings of AD. Insights into the pathogenesis and clinical course of inherited early-onset disease might be generalisable to the development of therapies for sporadic, age-related dementias.

To optimise the use of genetics in the prevention of dementia, pre-symptomatic and early diagnosis of AD, and development and use of present and future treatment approaches, we make the following recommendations.

(1) Data sharing and large-scale national or international collaborative studies should be encouraged.

(2) Clinical and genetic interdisciplinary research should be initiated and supported to advance understanding of the complex and heterogeneous nature of neurodegenerative diseases.

(3) Guidelines are needed for health professionals to support the use of new genetic tests, including information about the clinical value of whole-genome and whole-exome testing (next-generation sequencing).

(4) A legal framework should be developed that regulates the use of personal predictive health information by third parties, protects individuals who undergo genetic testing and their wider family, and facilitates research.

(5) Efforts are needed to increase societal awareness and knowledge of the use and limitations of genetic testing and the ethical concerns associated with such testing.

(6) Genetic counselling should be provided for people who undergo genetic testing. Appropriately trained personnel should provide such counselling within an adapted and professional psychological support system (similar to the genetic counselling provided for Huntington's disease).

(7) Systematic searches should be developed for GWAS and next-generation sequencing data to identify causal variants and biological pathways associated with AD.

(8) DNA and clinical data should be systematically collected and stored in clinical settings, clinical trials, and prevention studies for post-hoc research studies.

(9) The role of gene–gene interactions and gene–environment interactions in disease pathogenesis and progression should be investigated.

(10) Functional studies are needed in the post-GWAS era to unravel the molecular mechanisms of associated genetic variants and the pathways that lead to pathology.

Section 5. Biology of Alzheimer's disease

In 1906, Alois Alzheimer described the pathological changes present in the brain of the first patient with AD, Auguste D. In the past 110 years, substantial knowledge has been gained about the genetic and environmental factors that contribute to the disease (sections 3, 4). However, what triggers the characteristic pathology of AD and which mechanisms drive the progression of the disease remain unknown. Understanding of the basic biology of AD pathogenesis and the way in which clinical dementia relates to the presence of amyloid plaques and tau tangles is urgently needed so that strategies for treatment and prevention can be focused on the correct disease target.

Amyloid β and tau as therapeutic targets

A distinctive feature of AD brain pathology is the accumulation of small (about 0·1 mm) spherical structures called amyloid plaques. These plaques are composed of fibrils formed by the protein fragment Aβ, and are surrounded by dysfunctional neurons. Different variants of Aβ exist; one of the longest forms, Aβ42, is thought to be particularly toxic. The other major hallmark of the disease is the accumulation of tau protein inside neurons, forming fibrillary tangles. Amyloid plaques and tau pathology are present not only in AD, but also in several other neurodegenerative disorders, which suggest a central role for these proteins in neurodegeneration. For example, Aβ is accumulated in cerebral amyloid angiopathy[246] and tau in frontotemporal dementia or Niemann-Pick disease.[247]

In the 1990s, studies of early-onset familial AD identified distinct mutations in *APP*, *PSEN1*, and *PSEN2*

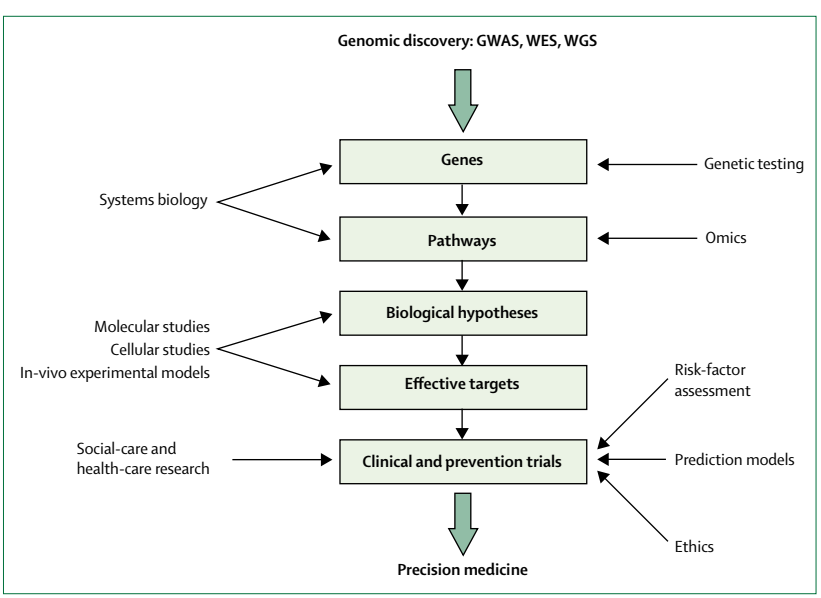

Figure 4: **From genetic and genomic discoveries to precision medicine**
Starting with genetic and genomic discoveries, future research studies need to integrate data from all research areas to construct testable hypotheses and draw meaningful conclusions about the functional consequences of the known Alzheimer's disease genes and loci. These integrated analyses could push the research frontier forward, allow personal risk profiles to be generated, and ultimately help to shape individualised strategies for intervention. GWAS=genome-wide association study. WES=whole-exome sequencing. WGS=whole-genome sequencing.

(section 4). The proteins encoded by these three genes are involved in the production of Aβ, and most (but not all) of the causative mutations cause an overproduction of Aβ peptides.[248,249] These neuropathological and genetic observations led to the amyloid cascade hypothesis, which posited that Aβ initiates a molecular cascade of toxic effects that lead to neurodegeneration and subsequently to the clinical manifestations of dementia.[214] Some forms of Aβ (Aβ42 or Aβ43) are now believed to be trigger factors for AD,[250] although which conformational structure (fibrils,[251] oligomers,[252] soluble forms,[253] or dimers[254]) of these peptides drives neurotoxicity is still debated.

The amyloid hypothesis has dominated the debate about the cause and pathogenesis of AD, and has guided efforts to find treatments (section 7). Although the mechanisms by which the rare mutations in *APP*, *PSEN1*, and *PSEN2* lead to excessive Aβ generation are now well understood, the precipitating factors that lead to Aβ accumulation in the much more common sporadic forms of AD are still unknown, although they probably result from a combination of environmental factors and risk genes. Despite the narrow focus on amyloid in AD, Aβ plaques are ubiquitous in people older than 70 years and about 30% of healthy aged-matched individuals have as much plaque load in their brains as do typical cases of AD.[255]

Following the amyloid cascade hypothesis, explanations have been proposed for the link between Aβ and tau pathology in pathogenesis (figure 5). However, the mechanistic relation is not yet clear, because transgenic animals that carry genes for familial AD and express large amounts of Aβ have little or no tau tangle pathology. The biological functions of APP, the protein precursor of Aβ, and its metabolites, including Aβ, in the healthy individual also need to be explained. Thus, the potential risks of targeting Aβ production for the treatment of AD (in the brain and the periphery) are as yet undetermined.

Aβ is an antioxidant,[256] has antimicrobial activity,[257] activates other signalling proteins,[258–260] and modulates cholesterol transport,[261] but its biological role is largely unknown. β-secretase (including the form known as β-site APP-cleaving enzyme 1 [BACE1]) and γ-secretase are the enzymatic proteins that result in Aβ generation, so efforts have been made to develop inhibitors of these proteins for clinical use. However, these enzymes seem to have roles in the metabolism of multiple substrates, which complicates efforts to achieve selectivity to inhibit only Aβ production. Some of these substrates are fundamental to normal cell biology. For example, BACE1 cleaves β-subunits of voltage-gated sodium channels[262] and neuroregulins, which are crucial for neuronal development and myelination[263,264]—processes that are important not only during development but also in adult life, particularly for the reparation of neuronal damage.

Similarly, γ-secretase is a promiscuous enzyme that cleaves more than 90 protein substrates and regulates various cellular events, such as cell-fate determination, adhesion, migration, neurite outgrowth, axon guidance, and the formation and maintenance of synapses.[265] Besides APP, the most-studied γ-secretase substrate is Notch, a signalling molecule that is crucial for development and cell-fate determination. Development of drugs that can inhibit γ-secretase has not been an issue, but selectivity to inhibit only APP cleavage is difficult to achieve. In addition to decreasing the production of Aβ, γ-secretase inhibitors affect many other proteins and the production of other functionally important peptides, with potentially toxic consequences. Therefore, new strategies are needed to develop drugs that selectively inhibit γ-secretase cleavage of APP without affecting other substrates. These efforts received a boost from the discovery of modulators that control γ-secretase cleavage of specific substrates by binding and recruiting them to γ-secretase for processing—small molecules capable of reducing Aβ42 production without affecting other functionally important γ-secretase products.[266]

Inhibition of the enzymes that produce Aβ also has consequences for the metabolism of APP, which can affect the production of other APP metabolites (eg, soluble APP or the APP intracellular domain [AICD]). AICD has more than 20 interacting protein partners that regulate important signalling pathways and cell functions, such as transcription, apoptosis, and cytoskeletal dynamics.[267,268] Roles for APP have been described in cell migration,[269] trafficking, and signalling;[270] neuronal calcium homoeostasis, synaptic transmission, and networking;[271] and neurotrophic mechanisms.[272] Thus, targeting APP processing to reduce Aβ concentrations could have many biological consequences. Clinical trials of drugs that target Aβ production have not reached their primary clinical endpoints and have, in some cases, caused serious side-effects (section 7).

An alternative way to reduce Aβ concentrations is to increase Aβ clearance from the brain. Since the absence of Aβ does not lead to any loss of physiological function in mice,[273] the elimination of this peptide could be a safe approach for treatment, but whether clearance of this peptide has any benefits in patients with symptoms of AD, such as slowing down disease progression, remains to be seen. Some anti-amyloid immunotherapeutic approaches have been tried in patients with AD, with disappointing results.[274] Thus, the question of whether Aβ (production or clearance) is a good target for treatment is still unknown, and efforts are needed in basic research to understand the possibilities and limitations of this approach.

The other distinguishing feature of AD, the formation of tau tangles in brain neurons, has historically been regarded as a secondary player in disease pathology, despite its direct correlation with neuronal death and disease progression.[275] By contrast with the *APP* gene, mutations in the microtubule-associated protein tau (*MAPT*) gene do not cause AD, but do cause familial frontotemporal dementia.[276] Some biological functions of

tau are well known—the protein regulates microtubule assembly, dynamics, and spatial organisation, and participates in the axonal transport of organelles and vesicles.[277] The biological activity of tau is regulated by its degree of phosphorylation, and tau in neurofibrillary tangles is abnormally hyperphosphorylated.[278] Hyperphosphorylation converts tau from a microtubule-stabilising to a microtubule-disrupting protein.[279] Evidence strongly suggests that neurodegeneration in many tauopathies results from loss of the biological function of tau, together with the initiation of toxic events. Hyperphosphorylation promotes the aggregation of tau into paired helical filaments, leading to the formation of tangles inside neurons and corresponding impairments of neuronal cytoskeletal organisation and of the transport of proteins and organelles.

Efforts have been made to develop inhibitors of the enzymes, tau kinases, which phosphorylate the protein. However, several kinases are involved in the generation of hyperphosphorylated tau, raising the question of whether specific or multiple tau-kinase inhibitors would be more effective as potential treatments for AD.[280] Individual tau-kinase inhibitors, mainly glycogen synthase kinase 3β (GSK3β) inhibitors or lithium, successfully reduce tau pathology in animal models of AD.[281] However, the GSK3 inhibitor tideglusib failed to meet the primary cognitive endpoint in a 26 week phase 2b trial in more than 300 patients with mild-to-moderate AD.[282]

As an alternative to kinase inhibition, activation of phosphatases has been proposed as a strategy to reduce tau phosphorylation. Protein phosphatase 2A (PP2A), the main brain phosphatase involved in the dephosphorylation of tau, has received special attention. Treatment of tau transgenic mice with the PP2A activator sodium selenate reduced tau hyperphosphorylation and tangle formation, improved memory, and prevented neurodegeneration.[283] However, PP2A has multiple substrates, which might lead to multiple side-effects, and the activation of this enzyme to reduce tau phosphorylation specifically is not an easy task.

Several other anti-tau treatments effectively prevented or intervened in the process of tau hyperphosphorylation in animal models, thereby improving neuronal function or cognition. For example, the microtubule-stabilising drug davunetide showed promise in preclinical studies,[284] but a 12 week placebo-controlled study of intranasal davunetide failed to show significant benefits in 144 patients with amnestic mild cognitive impairment.[285]

Other anti-tau strategies, such as tau anti-aggregants or tau immunotherapy, are being tested in preclinical and clinical studies (section 7). Among them are methylene blue (methylthioninium chloride), a drug identified in 1891 as a possible anti-malaria agent,[286] which might inhibit tau aggregation.[287] Efforts are being made to design an effective vaccine against tau pathology, but few studies of passive immunisation (transfer of ready-made antibodies against a target protein to enhance its clearance) against tau protein are in progress.[288] Several studies suggest that active immunisation (induction of immunity after exposure to an antigen—the recipient develops antibodies that can be stored permanently) might be effective against tau in animal models.[282] As for anti-amyloid approaches, several key questions remain to be answered in relation to tau-based immunotherapeutic approaches. The exact species to be targeted (aggregation states, fragments, and subtypes of tau) and the mechanisms by which antibodies clear target molecules are unknown.

Whether current anti-tau immunotherapeutic approaches will be effective in patients or lost in translation, as has been the case for many previous strategies targeting Aβ, remains to be seen.

The reasons for the lack of successful translation from preclinical to clinical studies in treating AD are unknown. For both Aβ-based and tau-based approaches, the scarcity of good predictive animal models, good biomarkers for disease progression, and well-defined target populations in clinical trials have been major challenges in demonstrating potential benefits in AD. The use of simple animal models that reflect a single aspect of AD might not be enough to capture the complexity of the disease and develop new treatments.

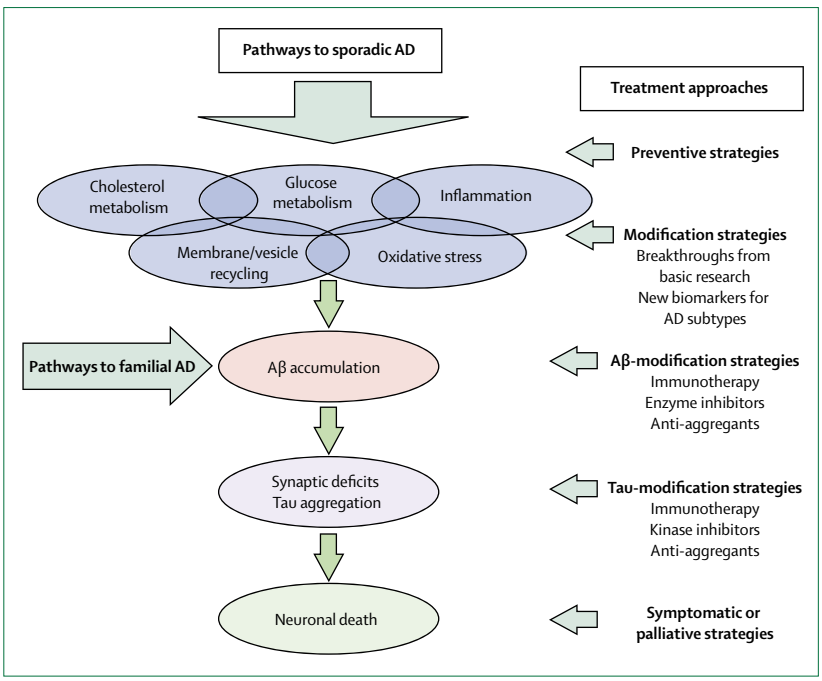

Figure 5: **Pathways to Alzheimer's disease**
Epidemiological and genetic studies of people with non-genetically determined (ie, sporadic) AD have identified mechanisms that might underlie brain Aβ accumulation, neuronal tau hyperphosphorylation, and synaptic deficits, ultimately leading to cognitive impairment and dementia. In familial AD, the disease begins with Aβ pathology. It seems likely that different causative pathways result in distinct disease subtypes, which should be treated differently. The identification of subtypes of patients, with homogeneous pathogenesis and prognosis, will facilitate research and result in more accurate and personalised treatments for sporadic and familial AD. AD=Alzheimer's disease. Aβ=amyloid β.

Animal models of AD

Transgenic animals, in which genetic engineering techniques are used to mimic some aspect of the disease, are important for studies of the molecular basis of neurodegenerative disorders and the mechanisms of disease progression. Many organisms, including mice, zebrafish, worms, and fruit flies, have been used to model aspects of AD. Most of these models are based on the overexpression of one, two, or in some cases several human mutations that result in the accumulation of Aβ or hyperphosphorylated tau in the brain. Despite many promising results in animal experiments, drugs that have made it to human clinical trials have so far failed to reach the primary objectives of these studies, and have in some cases had serious adverse effects. Thus, although existing animal models can be highly informative about the molecular processing of Aβ and tau, they do not fully capture the pathophysiology of sporadic AD in humans.

Despite some efforts to generate disease-relevant experimental animal models,[289,290] new models of AD are urgently needed for drug development. Some inherent problems exist with transgenic mice models: the foreign gene is inserted at unknown locations in the genome and other genes could be disrupted, non-natural promoters of gene transcription (the first step in gene expression) are used, and gene expression (the synthesis of a functional gene product) is unnaturally high. A knock-in mouse has been developed in which the endogenous mouse *App* gene is substituted with a human version of *APP* carrying a familial AD mutation. The main advantage of these mice compared with previous mouse models is that they show ageing-dependent amyloid pathology, neuroinflammation, synaptic alterations, and memory impairment, all in a manner more like the human disease.[291] However, these mice do not develop tau pathology, and although they offer promise for future studies of amyloidosis (accumulation of Aβ in brain tissue), they still have weaknesses as a model of AD.

Research breakthroughs are needed for the development of animal models that recapitulate the complexity and heterogeneity of the disease. Such models of AD will be crucial not only in testing potential treatment approaches, but also in advancing understanding of basic disease biology.[292] One possibility is that, in most cases of AD, Aβ and tau pathologies are endpoints of other disease-driving mechanisms that have not been captured in animal models. Thus, successful inhibition of Aβ or tau pathologies might not necessarily mean finding a successful drug for AD. In view of the heterogeneity of AD, a multi-target approach will probably be necessary.

Mechanisms of AD

Epidemiological evidence emphasises the importance of vascular health and diabetes in the development of sporadic AD, and hypertension and high blood cholesterol concentrations have been shown to increase risk in many studies (section 2).[293] Additionally, several other pathways have been identified that can contribute to disease development, such as mild TBI,[294] ischaemia and hypoxia,[295] neuroinflammation,[296] environmental toxin β-*N*-methylamino-L-alanine from cyanobacteria,[297] and metabolic abnormalities associated with decreased brain glucose uptake.[298] Although, at present, the use of risk indicators increases the reliability of predicting who will develop AD only slightly, their greater importance is that they identify pathways and processes that lead to AD. Large GWAS and systematic exome-sequencing approaches have confirmed some of the previously known pathways and have identified new pathways (section 4). However, the new susceptibility loci have only moderate effects on risk (with ORs in the 1·1–2·0 range).[299] Analyses with pooling of larger numbers of samples might provide further insight into the pathways leading to AD.

In broad terms, GWAS identified cholesterol metabolism, the innate immune system, and endosomal vesicle recycling as important contributors to AD. The strongest known genetic risk factor for sporadic AD is the presence of the ε4 allele of the cholesterol carrier APOE (section 4).[202] Since the discovery of the APOE4 protein as a major risk factor for AD, efforts have been made to link this molecule to Aβ metabolism, aggregation, and deposition. Increased plaque deposition has been noted in individuals with APOE4 and in animal models of brain amyloidosis.[300] APOE4 can potentiate Aβ toxicity in vitro[301,302] and in animal models,[303] and it has been suggested that Aβ clearance is less efficient in carriers of the *APOE* ε4 allele.[304] By contrast, the contribution of APOE4 to tau pathology remains poorly understood.

Reduced capacity for neuronal delivery of cholesterol in *APOE* ε4 allele carriers is thought to have consequences for the development of new synapses and for neuronal repair mechanisms. The brain is the major cholesterol-containing organ in the body,[305] and efficient cholesterol metabolism is crucial for recovery of damaged membranes. Furthermore, neuronal axons are surrounded by cholesterol-rich myelin, which protects axons and facilitates neurotransmission. Thus, impaired cholesterol synthesis, delivery, or metabolism is likely to contribute directly to disease progression.[305] This notion is supported by GWAS, in which genes related to cholesterol synthesis, transport, uptake, or metabolism were shown to be linked to AD (eg, ATP-binding cassette subfamily A member 7 [*ABCA7*], *ABCA1,* clusterin [*CLU*], and cytochrome P450 family 46 subfamily A member 1 [*CYP46A1*]).[299] However, further efforts are needed to understand the mechanisms by which APOE4 and other cholesterol-related molecules contribute to AD pathology, and to clarify whether experimental manipulation of brain cholesterol metabolism has therapeutic potential.

Studies in the late 1980s suggested a role for the innate immune system and the complement cascade (part of the

immune system that helps antibodies and phagocytic cells to clear toxins or pathogens) in the pathogenesis of AD,[306] and inflammation has been proposed as an early pathogenetic event in the disease.[307] The brain has its own innate immune system, which can maintain a low-grade, systemic inflammatory reaction. Presumably, the innate immune system of the brain has a defensive, protective role, but a chronic inflammatory process might damage neuronal cells. The brains of patients with AD harbour activated immune cells (microglia and macrophages) and various proteins that result from inflammatory reactions. Proteins of the classic complement cascade might also be of particular importance, because studies have shown that they are largely expressed in the cortical pyramidal neurons, which are severely affected in AD.[308] However, whether complement-producing neurons are particularly vulnerable to immune-system attack is unknown. GWAS have clearly shown that variability in innate immunity confers risk for AD.[208,209] The S isoform of the complement component receptor 1 (CR1) protein, has been associated with AD[212] and might be linked to increased complement activation.[309] Furthermore, the complement cascade is activated by Aβ,[310] which would stimulate phagocytic mechanisms to remove Aβ deposits. If this process were to fail, persisting complement activation would cause excessive inflammation that could damage neurons.

Another inflammation-associated gene uncovered by exome sequencing in AD is *TREM2*.[223] TREM2 suppresses the inflammatory response in microglial cells,[311] and it might participate in the regulation of phagocytic processes to remove amyloid.[312] Thus, loss of function of TREM2 might result in chronic inflammation and amyloid accumulation. APOE has been identified as a ligand for TREM2,[313] but the biological consequences of this association and its relation to AD pathology remain to be defined. Despite the links between inflammatory and immune components of AD pathology, the mechanisms by which they affect the onset of amyloid deposition and tau phosphorylation need to be elucidated. Longitudinal data are missing, and since inflammatory responses can have both beneficial and detrimental effects, to understand how to regulate inflammation effectively is an important challenge for AD research.

GWAS approaches have also identified endosomal vesicle recycling as one of the pathways in AD pathogenesis.[208,209] Endosomes are a dynamic vesicular network that provide an environment for material to be sorted in a cell before it is degraded. Some material from endosomes is recycled to the plasma membrane of cells, and SORL1, phosphatidylinositol-binding clathrin assembly protein (PICALM), and BIN1 all probably have a role in this process. Little is known about the functional implications of this discovery. However, it is worth noting that some of the metabolism of APP occurs in the endosomal pathway,[314] and impairments in the machineries used to secrete or degrade unwanted proteins could plausibly affect the survival of neurons.

Another hypothesis is that AD has a prion-like pathology. According to this model, Aβ or tau,[315] misfolded or aggregated, is produced in one cell, secreted to the extracellular space, and gains entry into neighbouring connected cells, where it triggers further Aβ or tau aggregates. Thus, Aβ and tau inclusions begin in specific regions of the brain and are spread to other areas.[316,317] Intracerebral or intraperitoneal injections of Aβ or extracts from the brains of patients with AD induce brain amyloidosis in animal models.[316,317] In 2015, Jaunmuktane and colleagues[318] reported an autopsy study of individuals who received human cadaveric supplementary pituitary hormone when young, and showed brain Aβ pathology at the age of death (36–51 years). The authors suggest that cadaveric pituitary hormone could contain "seeds" of Aβ that transmitted the pathology. Further research is necessary to clarify the mechanisms and possible risks associated with transmissible Aβ or tau.

Consensus exists among researchers that Aβ aggregation and accumulation is the cause of familial AD. However, this view is not consensual for sporadic AD. Aβ is important in the pathology of such cases, but might not be the cause of AD. The identification of multiple pathways to AD is a mark of the heterogeneous causes of the disease. To discern which overlapping, intersecting, or synergistic mechanisms in these pathways induce brain Aβ and tau pathology remains an important challenge for the future.

Future goals

Despite impressive efforts in the past three decades, the causal mechanisms of AD remain to be elucidated. Furthermore, the assumption that molecular mechanisms that underlie genetically determined forms of the disease are identical to those resulting in late-onset AD needs to be tested. Non-European initiatives such as the API study (of a kindred carrying a mutation in *PSEN1*) and the DIAN study (of individuals with mutations in *APP*, *PSEN1*, or *PSEN2*)[234] will determine, in the near future, whether clearance of Aβ from the brain is effective in the treatment of familial AD (section 7). One possibility is that targeting Aβ will be successful only for these autosomal dominant forms of AD, in which increased Aβ production occurs from birth. For most AD cases, amyloid accumulation is probably a later event that results from other metabolic disruptions. We have substantial information on different pathways that contribute to the disease, and a priority for the future is to discern the causative forces and overlapping mechanisms among them, and to determine how these mechanisms result in (or from) Aβ accumulation and tau hyperphosphorylation.

The identification of subtypes of patients with disease of homogeneous aetiology (cause or pathogenesis) and prognosis will enable the development of more effective, personalised treatments. Intensification of innovative basic research will also result in the identification of new

biomarkers for the subtyping of AD (section 6), which will open possibilities for precise medical interventions (figure 5).

Summary and recommendations

The brain pathology of AD is distinct from that of other neurodegenerative diseases. Amyloid plaques are made up of deposits of Aβ, a derivative of the precursor protein APP, and neurofibrillary tangles result from the abnormal accumulation of a protein called tau. Most therapeutic strategies for AD are focused on the direct reduction of these protein deposits, or on other proteins and enzymes that regulate their concentrations in the brain. However, epidemiological and genetic studies have identified a range of factors that contribute to AD, including insulin resistance, hypertension, deficits in cholesterol transport, and neuroinflammation. Improved understanding of the mechanisms that link these factors to Aβ and tau pathways, and how clinical dementia relates to the presence of amyloid plaques and tau tangles, is urgently needed so that prevention and therapy can be focused on the correct disease targets.

Preventive strategies to target risk factors for AD are likely to be successful in delaying by a few years the onset of disease. However, in an ageing population, the need to find a cure or an effective therapy for AD is imperative. Without new breakthroughs in understanding the basic biology of disease pathogenesis, the development of a cure seems unachievable. We make the following recommendations.

(1) Identification of novel disease-modifying strategies (ie, thinking outside the box) needs to be intensified. A strong commitment to the support of innovative basic research is needed to advance understanding of the biology of AD—a prerequisite for the identification of new, valid targets and the development of new treatments.

(2) Efforts to understand disease mechanisms need to be expanded, encompassing systems biology, vascular research, neuroplasticity, and inflammation. Programmes that support multidisciplinary, collaborative studies should be encouraged.

(3) Relevant animal models of AD need to be developed to study disease mechanisms and to test potential new treatments. Understanding of the biology of AD is increasing rapidly, and new models should aim to capture the complexity and heterogeneity of the disease. Specific lines of support should be provided for the development of relevant animal models, with a view to accelerating therapeutic development.

Section 6. Diagnosis and clinical assessments in Alzheimer's disease

The consequences of a diagnosis of AD for patients and their families are complex. AD is one of the diseases most feared by the general public, and the disclosure of a dementia diagnosis can result in severe mental distress, with evidence of an increased risk of suicide after diagnosis.[319] However, with the right approach, evidence suggests that a diagnosis can relieve symptoms of anxiety in patients because it explains a frightening loss of cognitive capacities.[320] At more advanced stages of AD, self-reflection is often impaired and the meaning of the dementia diagnosis might not be understood fully by the patient, which prevents severe mental distress. For caregivers, the disclosure of an AD diagnosis is also stressful and associated with fear and grief, but it can trigger seeking and receiving of help to cope with the situation.

Overall, the process of providing information on diagnostic procedures and the meaning of outcomes, applying and interpreting diagnostics, disclosing the diagnosis, and providing counselling on prognosis and treatment options is a very complex and individualised procedure, which is becoming even more complex with earlier diagnosis and the increasing availability of new biomarkers and treatment options. This complexity increases demands on the diagnosing physician and requires increased specialist knowledge.

Health services and professionals involved in diagnosis

The services and professionals involved in dementia diagnosis in different European countries depend on the health-care system and the reimbursement structure. In many countries—eg, Germany—a large proportion of patients with AD is seen only by general practitioners (GPs), and a diagnosis is often not firmly established. Some patients are referred to neurologists or psychiatrists in private practice, but only a very small proportion of patients is diagnosed in specialised centres, such as memory clinics, which are usually linked to large hospitals and universities.No specific reimbursement structure exists for guideline-based dementia diagnosis.

Several EU countries now have national plans or guidelines for dementia diagnosis, the chain of care, and recommended treatment. In the UK, policies to increase the recognition of dementia have introduced limited screening (linked to reimbursement for diagnosis) into hospitals and some dementia practices. However, the introduction of such policies without trial evidence of benefit has been controversial and, some would argue, has led to further delays in access to diagnostics services because of the large volume of referrals.

Benefits of a dementia diagnosis

Diagnosis of a dementia syndrome and clinical diagnosis of AD are usually the basis for pharmacological and non-pharmacological treatment, and can provide access to support for the person with dementia and their caregivers. Especially in younger people, differential diagnosis of the cause of dementia will be important for treatment decisions and estimation of individual prognosis. In older people, in whom most dementia is mixed (eg, co-occurrence of AD with other causes of cognitive decline), this differential diagnosis

is arguably less helpful. Rarely are fully reversible causes of cognitive decline detected, but most guidelines do highlight those that should be ruled out, such as hypothyroidism.

Diagnosis and clinical assessments: challenges and priorities

In the absence of substantial improvements in quality of life and effective treatments for people with dementia, there might be few incentives for family doctors to pursue a diagnosis of AD. However, patients and their families can benefit if a diagnosis is made appropriately and continuing care and support are made available.

AD is a slowly evolving disorder with a long preclinical period, followed by a prodromal phase with mild symptoms before the dementia stage is reached. At present, the clinical diagnosis of AD in clinical care and in most clinical trials is made at the dementia stage. Overlapping but slightly different sets of criteria for AD dementia are provided by the *International Classification of Diseases*, tenth revision (ICD-10),[321] which is used in Europe, and the US *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition (DSM-5).[322] These criteria list clinical features needed to make the clinical diagnosis of typical AD, such as memory deficit at initial presentation and slowly progressive onset and disease course. They also acknowledge atypical presentations of AD, such as the language variant (logopenic aphasia), the visuospatial variant (posterior cortical atrophy), and the variant with executive dysfunction (frontal variant).

The reliability of criteria has been established in clinical settings (ie, different physicians agreed reasonably well when applying the same set of criteria to the same patients).[323] However, people with a clinical diagnosis of AD, when followed to post mortem, do not always have AD-type pathology, with around 20% suggested to be misclassified during life in one report.[324] Also, many older people who fulfil neuropathological criteria for AD do not have dementia when they die, creating a continuing and largely unaddressed conundrum for the specialty of AD and early detection.

Research diagnostic criteria include the National Institute of Neurological Disorders and Stroke–Alzheimer's Disease and Related Disorders Association (NINCDS–ADRDA) criteria, the National Institute on Aging–Alzheimer's Association (NIA–AA) criteria, and the revised criteria of the International Working Group (IWG-2). Two major conceptual changes in recent years have been the introduction of biomarkers in combination with clinical syndrome definitions to the NIA–AA[325–327] and IWG[328–330] criteria, and the inclusion of criteria for pre-dementia stages of AD, which can be diagnosed on the basis of mild symptoms plus biomarkers or even in the absence of symptoms on the basis of biomarkers alone (table 8). These approaches are being applied in research, including validation studies and clinical trials in dementia, and although not yet used in clinical practice, they will be adapted for clinical use in the future.

The main challenge in the clinical assessment of patients with AD is the transfer of concepts and methods that were developed mainly for advanced dementia to earlier stages of the disease. The focus on pre-dementia stages is crucial, because future treatments will probably have to be initiated at early stages to be effective (section 7). This transition can be achieved by viewing AD as a slowly progressive disorder of cognition that starts gradually before full dementia is reached. Identification of very early symptoms of disease, the effects of treatment on these symptoms, and predictors of treatment outcomes at the very mild symptomatic stage are urgent priorities. Recognition of the very early stage of AD as a disorder with distressing impairment of memory that affects the patient's wellbeing even in the absence of severe impairment in daily functioning is also important.

At present, the standard instruments used in clinical care and clinical trials include comprehensive and detailed cognitive test batteries, rating scales of functional impairment, informant-based questionnaires about IADL and basic ADL, and assessments of neuropsychiatric symptoms, quality of life, and disease-related burden. Most methods have been developed for the assessment of patients with dementia between the mild and the severe stage. Even though these measurements are widely accepted and understood in terms of their performance in clinical and population settings, they are acknowledged as being somewhat insensitive for people with high levels of education. Furthermore, such instruments sometimes lack sensitivity for very mild symptoms of the disease. Many measurements as applied will have uncertain reliability (ie, the same result might not be achieved when applied several times in the same person).

Cognitive assessment

Three main challenges exist with regard to improved assessment of cognition. First, it is common in clinical practice and clinical trials to describe the cognitive performance of patients with a single global score: the commonly used MMSE expresses the level of cognitive performance with a single number ranging from 0 to 30, and the standard scale for cognitive testing in clinical trials, the Alzheimer's Disease Assessment Scale–cognitive subscale (ADAS-Cog), expresses cognitive function as a single number between 0 and 70. This approach needs to be extended, especially for use in clinical trials, by measuring individual components of cognition (eg, memory, attention, language) to increase understanding of how these components are affected over time by the disease, how they relate to biomarkers as indicators of AD pathology, and how they individually respond to treatment. This information would also be of use in describing clinical subtypes.

	NIA–AA criteria[325-327]	IWG criteria[328-330]	Comments
Diagnosis in the absence of symptoms	Preclinical AD: Stage 1: asymptomatic cerebral amyloidosis (CSF Aβ or amyloid imaging) Stage 2: asymptomatic cerebral amyloidosis with evidence of neuronal injury (volumetric MRI, CSF tau, or ^{18}F-FDG PET) Stage 3: cerebral amyloidosis with evidence of neuronal injury and subtle cognitive decline	Asymptomatic at risk: Normal cognition with one pathophysiological marker of AD (CSF Aβ and tau or P-tau, or amyloid imaging) Pre-symptomatic AD: Normal cognition with an autosomal dominant AD-causing mutation	The disease process, including accumulation of amyloid and tau pathology, can begin years or decades before symptoms emerge. The NIA–AA criteria specify three stages of preclinical AD, whereas the IWG criteria specify two different conditions in cognitively healthy individuals
Diagnosis of cognitive impairment due to AD (prodromal stage)	MCI due to AD—high likelihood: Biomarkers of amyloidosis (CSF Aβ or amyloid imaging) and neuronal injury (volumetric MRI, CSF tau, or ^{18}F-FDG PET) present MCI due to AD—intermediate likelihood: Biomarker of amyloidosis or neuronal injury present MCI—possibly due to AD: Biomarkers gave conflicting results MCI—unlikely due to AD: Biomarkers of amyloidosis and neuronal injury absent	Prodromal AD: Amnestic syndrome of the hippocampal type or a specific phenotype compatible with atypical AD, with one pathophysiological marker of AD (CSF Aβ and tau or P-tau, or amyloid imaging)	The IWG-2 criteria propose a specfic type of memory impairment for AD and a confirmation of the diagnosis by biomarkers. The NIA–AA criteria do not propose a specfic type of cognitive impairment in MCI and discuss different biomarker patterns in terms of different likelihoods of the presence of AD.
Diagnosis of dementia due to AD	Probable AD dementia: AD dementia with documented clinical decline AD dementia with an autosomal dominant AD-causing mutation Possible AD dementia: AD dementia with an atypical course AD dementia with evidence of mixed aetiology Probable AD dementia with evidence of the AD pathophysiological process: High likelihood of AD aetiology (biomarkers of amyloid abnormalities and neurodegeneration present) Intermediate likelihood of AD aetiology (biomarker of amyloid abnormalities or neurodegeneration present) Possible AD dementia with evidence of the AD pathophysiological process: High likelihood of AD aetiology (biomarkers of amyloid abnormalities and neurodegeneration present) Intermediate likelihood of AD aetiology (biomarker of amyloid abnormalities or neurodegeneration present) Pathophysiologically proved AD dementia: Clinical phenotype of probable AD with neuropathology findings indicative of AD	AD dementia: Episodic memory impairment or atypical AD phenotype with impaired activities of daily living and a pathophysiological marker of AD (CSF Aβ and tau or P-tau, or amyloid imaging)	The IWG criteria view the disease as a clinicobiological entity, so a diagnosis of AD dementia can be made in patients with typical or atypical clinical features only if a pathophysiological marker of AD is present

These research criteria are important in establishing a very early diagnosis of AD and in defining participants for clinical trials. After sufficient validation, these criteria could provide the basis for early, pre-dementia AD diagnosis in clinical practice. NIA–AA=National Institute on Aging–Alzheimer's Association. IWG=International Working Group. AD=Alzheimer's disease. CSF=cerebrospinal fluid. Aβ=amyloid β. MRI=magnetic resonance imaging. ^{18}F-FDG PET=^{18}F-fluorodeoxyglucose positron emission tomography. P-tau=phosphorylated tau. MCI=mild cognitive impairment.

Table 8: **Classification of Alzheimer's disease subtypes across NIA–AA and IWG criteria**

The second main challenge is detection of the earliest symptoms and symptomatic changes below the detection threshold of tests used at present. Several studies have described decline in different cognitive domains at the preclinical stage in individuals at risk of AD.[330] However, measures of such changes have not been standardised and are not applied on a large scale across studies. Furthermore, they are not being tested in all the different patient groups to which they might be applied in the future (eg, patients in GP practices or memory clinics). New tests will need to incorporate techniques that allow reliable detection of the very subtle early changes in AD.

Subjective cognitive decline (SCD), which is defined by the experience of worsening of cognitive abilities, is often reported by elderly people.[331] It is associated with increased risk of progression to dementia in population studies.[332,333] Some studies have shown that subjective cognitive decline adds predictive power about the risk of future dementia in an individual of a similar magnitude to that provided by impairment in performance on a memory test.[334] People with SCD are reported to have biomarkers that indicate the presence of AD pathology, such as reduced concentration of Aβ42 or increased concentration of tau in the CSF,[335] or AD-typical changes on brain imaging.[336,337] Those with SCD and evidence for AD pathology measured by CSF biomarkers are at increased risk of dementia.[338] According to a 2014 international consensus publication,[331] research is needed to develop improved and standardised assessments of SCD, and to investigate the relation of SCD to objective decline in cognition and psychiatric disorder such as depression and anxiety.[339]

The third main challenge is the minimisation of intra-individual and inter-individual variance and rater-related or rating-related confounds in cognitive assessments. Intra-individual variance refers to the fact that, in some tests, the performance of an individual changes from day to day (eg, because of differences in alertness or concentration) and is subject to learning

effects when the test is repeated (repetition effect). Problematic inter-individual variance can occur—eg, in the case of a verbal recall test that aims to assess memory, in which individuals with greater language abilities might have an advantage over those with poorer skills.

The rater-related or rating-related confounds describe the observation that patients score differently on a test depending on how it is administered (eg, in terms of task instructions), but also with regard to behaviour of the person who is doing the test (the rater). In particular, at the early disease stage (the late asymptomatic at-risk stage and the early prodromal AD stage),[330] the decline in cognitive performance is small and often cannot be detected, because the normal day-to-day variation in performance on a particular test is larger than the subtle decline related to early AD. Thus, tests with less variation need to be developed as a matter of urgency. These tests should have standardised task instructions to reduce rating-related confounds and should minimise components that increase inter-individual variance (eg, being independent of language skills). Intra-individual variance can be reduced by applying the test without repetition effects.

Functional assessment

ADL scales have low sensitivity for early functional changes in the course of AD. However, early cognitive impairment can affect IADL at the pre-dementia stage of the disease, and IADL impairment actually predicts decline to dementia.[334] At present, some diagnostic criteria acknowledge the presence of mild impairment of IADL and define the threshold for dementia by a level of impairment that interferes with independence. Because mild impairment already contributes to disease burden in affected individuals, improved assessment of IADL is needed, as are studies to examine the impact of early interventions on ADL impairments to establish whether such approaches have effects that are relevant and meaningful for patients. Current scales for IADL impairment in very early AD rely largely on observations reported by the informant. Innovative IADL assessments therefore need to include direct measures of the time taken and number of errors made by the patient while performing IADL.[340,341]

Closely associated with IADL assessment is the approach of individualised outcomes of treatment, in which specific IADL (eg, using a telephone) are identified and defined with each patient as a goal of treatment (goal attainment), rather than applying an identical scale to all patients.[342] This approach is appealing because it focuses on the most relevant areas of impairment for the individual patient. It also mirrors clinical practice, in which patients discuss and work on individual goals with the treating physician. However, standardisation of the goal-attainment approach for clinical trials is challenging.

Quality-of-life assessment

Evidence of the effects of treatment on the quality of life of patients is increasingly required by decision makers for reimbursement in some countries—eg, in Germany—as a measure of the patient-related benefit of an intervention. However, the reliability and validity of most of the scales used for the assessment of quality of life in AD are poor.[343] New instruments for refined, disease-specific quality-of-life assessment in AD, including early disease stages, are being validated and will increasingly be integrated into observational studies and clinical trials.[344,345]

Post-mortem diagnosis of AD

Despite biomarker discoveries in the clinical diagnostics of AD and other neurodegenerative dementias, neuropathological confirmation is still needed for a definitive diagnosis, which necessitates a post-mortem examination to confirm the presence of extracellular Aβ deposits and intraneuronal aggregates of neurofibrillary tangles in brain tissue (figure 6) according to the NIA–Reagan Institute criteria.[346] Unfortunately, in many European countries and the USA, the number of autopsies has decreased by at least half since the 1970s. This trend could mask diagnostic errors that reduce the power of research studies and thereby hamper progress. Moreover, reduced autopsy rates could lead to less reliable records of cause of death, which is of even greater concern in an ageing population with chronic disorders, in which multiple morbidities could make the cause of death uncertain. The low autopsy rate for neurodegenerative diseases is particularly alarming, because the reported cause of death from dementia in Sweden, for example, has quadrupled since 1987. In a study of 176 consecutive

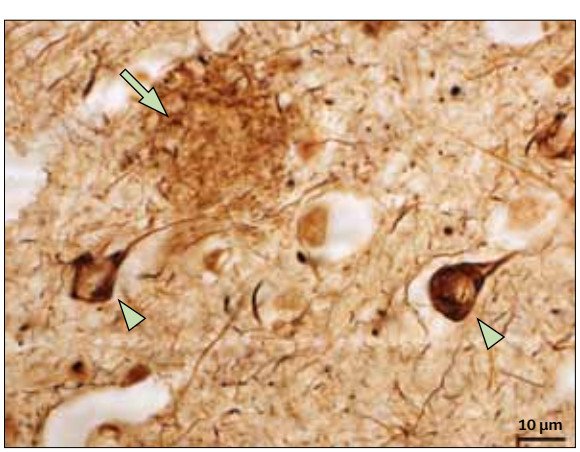

Figure 6: **Neuropathological hallmarks of Alzheimer's disease**
Post-mortem Bielschowsky silver staining of frontal cortex from a patient with Alzheimer's disease, showing the presence of a neuritic amyloid plaque (arrow), consisting of aggregated extracellular amyloid β fibrils, and intraneuronal neurofibrillary tangles (arrowheads), consisting of hyperphosphorylated tau protein. Neuritic plaques and neurofibrillary tangles are hallmarks of the disease, but more work is needed to understand the pathways that lead to pathology and the contributions of amyloid and tau pathology to neurodegeneration and the emergence of cognitive impairment and dementia.

neuropathological examinations of patients with clinically diagnosed dementia, the clinical and pathological diagnoses were in agreement in only 86 cases (49%).[238] More standardised clinical and neuropathological diagnostic methods are under development.

Collaborative and specific efforts are needed to reverse the global decline in autopsy rates, with a particular focus on the neuropathological examination of patients included in clinical research studies or clinical trials. Indeed, advances in the neuropathological characterisation of neurodegenerative diseases suggest that a complex interplay of several pathologies underlies the clinical presentation of most common dementias, including AD,[347] which has resulted in new guidelines for assessment.[348,349] Of equal importance is the need for basic research studies on human brain tissue as a complement to in-vitro and in-vivo animal studies, which will be possible only if human brain and spinal cord tissue are collected after death.

Studies of other disorders suggest a correlation between autopsy rates and how strongly physicians recommend a post-mortem assessment.[350] Thus, one strategy to increase autopsy rates is to train physicians and health-care professionals to understand and communicate the value of neuropathological confirmation of the diagnosis of AD and the need for researchers to have access to human post-mortem tissue for basic research. Another strategy is to build and facilitate national and international brain biobanking infrastructures to ensure that tissue is collected in line with standardised and harmonised protocols, as achieved in the BrainNet Europe initiative.

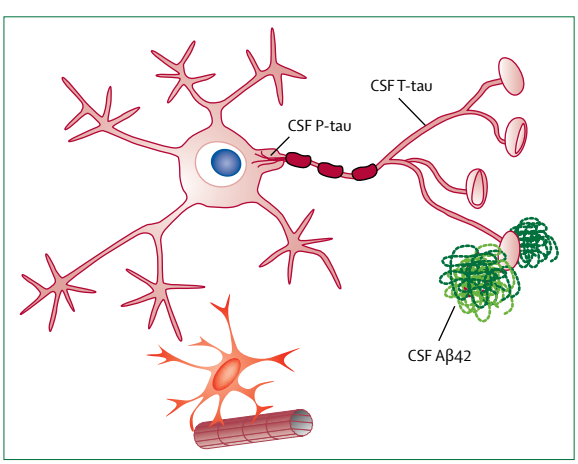

***Figure 7*: Pathological changes associated with cerebrospinal fluid biomarkers for Alzheimer's disease**
Schematic representation of a neuron, showing the pathological changes associated with the three core CSF biomarkers of Alzheimer's disease. Increased CSF concentration of T-tau is a marker of axonal degeneration, increased CSF concentration of P-tau suggests the presence of neurofibrillary tangles, and decreased CSF concentration of the 42-aminoacid form of Aβ (Aβ42) relates to senile plaque pathology. In future, newly discovered CSF, blood, or brain imaging (eg, MRI, PET) biomarkers could allow early diagnosis, including the subtyping of Alzheimer's disease, and personalised-medicine approaches to treatment and prevention. CSF=cerebrospinal fluid. T-tau=total tau. P-tau=phosphorylated tau. Aβ=amyloid β. MRI=magnetic resonance imaging. PET=positron emission tomography.

Use of biomarkers in AD diagnosis

Biomarkers

The pathological hallmarks of AD—neuritic plaques composed of aggregated extracellular Aβ fibrils and intraneuronal neurofibrillary tangles of hyperphosphorylated tau (figure 6)—are associated with neurodegeneration and brain atrophy (section 5). Various methods can be used to monitor these brain changes as the disease progresses. Brain volume and structure can be investigated by computed tomography (CT) and magnetic resonance imaging (MRI). The size of particular (disease-relevant) brain regions, such as the temporal lobe (hippocampus), is used to assess brain atrophy in AD.[351] To study the functional activity of the brain, imaging techniques such as PET are used to measure cerebral brain glucose metabolism and cerebral blood flow, both of which correlate with cognitive function.[352] Molecular PET also allows detection of AD pathology manifested as amyloid plaque deposition.[352] Several PET tracers are under development for the imaging of tau deposition in AD and non-AD dementia disorders.[353] CSF can easily be obtained by lumbar puncture, which is a well established and safe procedure in clinical neurology.[354] A CSF test result that shows increased concentrations of total tau (T-tau) and phosphorylated tau (P-tau), and decreased concentrations of Aβ42,[355] suggests AD-like neurodegeneration in conjunction with Aβ pathology.

Several diagnostic biomarkers have been developed to detect AD neuropathology even in individuals at preclinical stages of the disease. Diagnostic biomarkers are markers of in-vivo pathology that are present at all stages of the disease, and they can therefore be used to detect AD pathological changes even in the asymptomatic state. PET of amyloid plaques in the brain and measurement of Aβ42 and P-tau in the CSF are examples of diagnostic markers (figures 7, 8). By contrast, a progression marker, which might have poor disease specificity and might not be present at early stages, indicates clinical severity (ie, changes as the disease progresses). PET of cerebral glucose metabolism, measurement of T-tau in the CSF, and brain atrophy measured by MRI can be viewed as markers of disease progression (figure 9).[356]

Amyloid imaging and CSF biomarkers thus enable early detection of AD and, most importantly, discrimination of patients with mild cognitive impairment who have underlying AD pathology (prodromal AD) and are therefore at a high risk of progression to AD dementia (appendix).[357,358] Three amyloid PET tracers—florbetapir (Amyvid; Eli Lilly, Indianapolis, IN, USA), florbetaben (Neuraceq; Piramal, Berlin, Germany), and flutemetamol (Vizamyl; GE Healthcare, Waukesha, WI, USA)—have been approved

by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for use in the clinical assessment of memory disorders to exclude AD.[359]

The International Federation of Clinical Chemistry and Laboratory Medicine and the Global Biomarker Standardization Consortium are making progress to create certified reference methods and materials to standardise CSF biomarkers,[360,361] and a fully automated assay of CSF Aβ42 with very low inter-laboratory coefficients of variation (1–4%) was described in 2015.[362] Although structural imaging is well established in the clinical assessment of memory impairment, the use of CSF and PET biomarkers of tau and Aβ pathology are becoming part of the clinical routine in memory assessments at specialist clinics in Europe. However, in many countries, important questions remain about the reimbursement from health insurance for such procedures.

The use of these biomarkers in longitudinal studies of cognitively healthy individuals at risk of AD has shown that the pathophysiological process of AD begins a decade or more before the appearance of symptoms. A prospective cohort study[363] suggested that Aβ deposition is slow and that it takes around 20 years before the onset of clinical symptoms. Meta-analyses show a correlation between amyloid positivity and clinical diagnosis, age, and *APOE* genotype.[364,365] Because a patient with clinical symptoms of mild AD will already have a substantial loss of neurons in specific brain regions, such as the entorhinal cortex,[366] the reversal or slowing down of symptomatic decline at this disease stage is extremely difficult. Disease-modifying approaches will probably work best in clinical trials that aim to prevent the progression of the clinical syndrome in individuals with very mild or no clinical symptoms, but with a genetic predisposition to AD or positive CSF or radiological AD biomarkers (ie, preclinical or prodromal AD).[330]

In trials already underway,[367] biomarkers will be assessed before and after treatment initiation to ascertain whether any drug-related clinical benefit correlates with biomarker evidence of a change in the underlying disease process. By such an approach, the drug's effect on the target would be validated, and the validity of the biomarkers would be established, which would help in the design of new trials. Specifically, biomarkers could be used to establish whether negative trial results are a result of the absence of drug effects on the intended target, or whether the intended target changed in the expected direction but without any clinical benefit. Similarly, a finding of clinical benefit in a positive trial would be strengthened if it was backed by expected biomarker changes.

Proteomic studies of plasma biomarkers in AD have so far been disappointing, with only a few replicated positive results.[368] A study of lipid profiles in the plasma of older adults (age ≥70 years) suggested that it might be possible to discriminate older adults with AD from cognitively healthy individuals by the use of a blood test,[369] but independent replication of these results is needed. Novel approaches, such as analysis of the profile of the different sugars (ie, glycans attached to proteins) in CSF or plasma might be helpful. Defects in the glycosylation of proteins involved in pathogenesis, such as tau, have been reported.[370] The stratification of patients on biomarker grounds—eg, by amyloid and tau PET or by the use of CSF Aβ and tau markers to establish whether they have Aβ-predominant or tau-predominant disease—might become possible when methods for the PET imaging of tau deposition in the brain are available. Methods for the detection of other processes, such as neuroinflammation or cerebrovascular dysfunction, by MRI, PET, or CSF biomarkers might also be useful. The aim will be to personalise the selection of drugs for individual patients on objective grounds.

Finally, novel generic markers of neurodegeneration (eg, markers of synaptic dysfunction) that might be relevant to a broad range of neurodegenerative disorders would be helpful to assess the effects of disease-modifying treatments intended to slow down neurodegeneration. Novel ultrasensitive measurement techniques have just opened up the possibility of measuring such biomarkers in serum and plasma.[371]

Clinical use of biomarkers

Biomarkers of Alzheimer's disease are in a transitional state between research and clinical practice. Widespread application to enable accurate, early, and differential

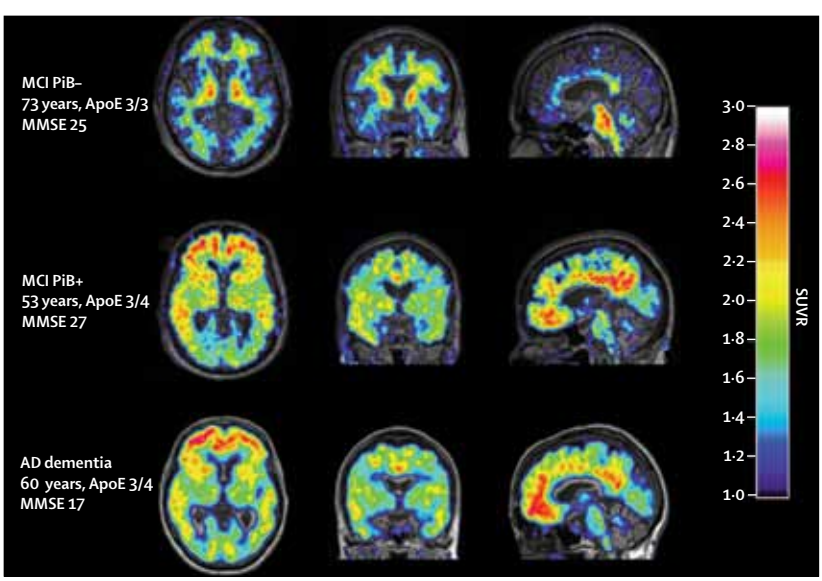

Figure 8: **Deposition of fibrillar amyloid plaques in patients with mild cognitive impairment and Alzheimer's disease**

Deposition of fibrillar amyloid plaques measured with PiB (a radioactive compound that binds to amyloid β peptide) PET in two patients with MCI and one patient with AD. Fusion images from coregistered PET and MRI scans are presented as transverse (left), coronal (middle), and sagittal (right) sections. The patients with MCI were clinically followed up for 2·5 years. The condition of the patient with MCI and low ^{11}C-PiB retention (PiB–) remained as MCI and did not convert to AD, whereas the patient with MCI and high ^{11}C-PiB retention (PiB+) converted within 2·5 years to AD dementia. Standard ^{11}C-PiB uptake values are expressed in relation to the cerebellum on a colour scale. Image courtesy of A Nordberg, Karolinska Institute, Huddinge, Sweden. PiB=^{11}C-Pittsburgh compound B. PET=positron emission tomography. MCI=mild cognitive impairment. AD=Alzheimer's disease. MRI=magnetic resonance imaging. ApoE=apolipoprotein E. MMSE=Mini-Mental State Examination score. SUVR=standard uptake value cerebellum ratio.

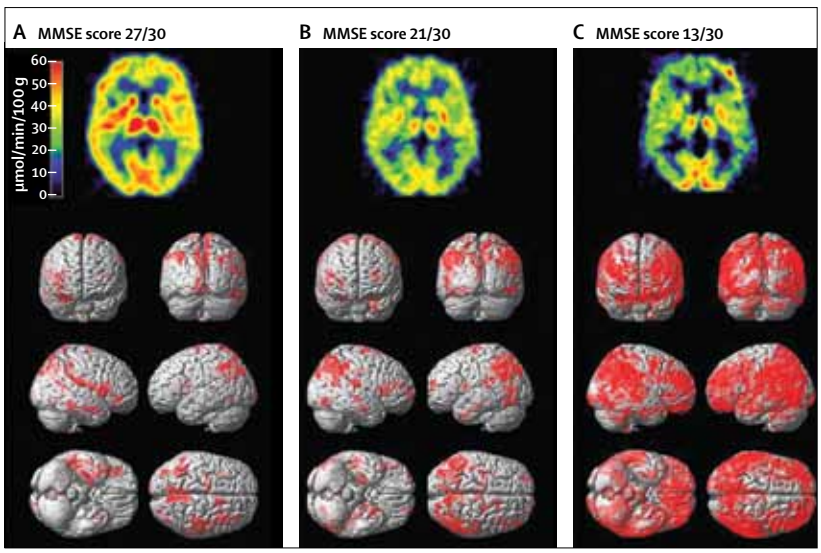

Figure 9: **Progressive reduction in regional cerebral glucose metabolism in a patient with Alzheimer's disease**
The upper row shows PET images of regional glucose metabolism (µmol/min/100 g), as measured by ^{18}F-FDG uptake, in a woman with a diagnosis of Alzheimer's disease at the age of 53 years (A), 56 years (B), and 58 years (C). ^{18}F-FDG uptake values are expressed on a colour scale (red indicates high uptake, yellow medium, and blue low). The lower row shows a three-dimensional rendering of the brain from the same patient (a representation of statistical parametric mapping of ^{18}F-FDG PET images), where red depicts areas in which regional cerebral glucose metabolism was significantly reduced during the progression of Alzheimer's disease compared with that in a group of healthy participants (p=0·001). Reproduced from Kadir and colleagues,[356] by permission of Oxford University Press. PET=positron emission tomography. ^{18}F-FDG=^{18}F-fluorodeoxyglucose. MMSE=Mini-Mental State Examination.

diagnosis of AD is being delayed by several methodological, economic, and political factors. Particularly, their practical usefulness is questioned in the absence of interventions to substantially delay the progression of neurodegeneration. The main methodological factor is related to standardisation. The economic and political factors relate to costs of sample acquisition and analysis, and how biomarker results affect the clinical management of patients.

Many AD biomarkers are not sufficiently standardised to be applied routinely in clinical practice, but standardisation initiatives are underway.[360,372,373] Europe is not homogeneous in terms of technology (eg, neuroimaging scanners and laboratory equipment) and personnel with the necessary expertise; diagnosis of neurodegenerative diseases in memory clinics is, at present, made largely on clinical grounds, with brain imaging (CT or MRI) and clinical chemistry tests (CSF tau and Aβ) to exclude other potential causes of cognitive decline, such as depression, normal pressure hydrocephalus, or cerebrovascular changes. Recently proposed diagnostic algorithms that incorporate AD biomarkers—the NIA–AA[325–327] and IWG[328–330] research diagnostic criteria (table 8)—are being adapted to clinical realities across Europe. For example, the EU JPND Biomarkers for Alzheimer's Disease and Parkinson's Disease (BIOMARKAPD) project is a pan-European network of memory clinics and laboratories engaged in the uniform implementation and standardisation of diagnostic algorithms in the assessment of patients who seek medical advice because of cognitive symptoms.

The development and standardisation of biomarkers as practical and affordable tools for clinical use will be essential to prepare for the next generation of preventive and disease-modifying AD drugs. The diagnostic use of biomarkers will be given a substantial boost by the availability of treatments proven to be effective at the pre-dementia stages of AD. If the ongoing secondary prevention trials with anti-amyloid therapies are successful (section 7), patients could be selected for treatment during the preclinical stages of AD on the basis of biomarker detection.[367] Treatment should be initiated at specialist clinics until more information about the clinical use of such therapies has been obtained. From a safety and cost perspective, exclusion of individuals from some treatments will also be important—eg, an amyloid-negative patient should not be treated with an anti-amyloid drug.

Summary and recommendations

Diagnosis of AD and other dementias is complex, requiring cognitive and functional assessment, sometimes with serial evaluations, and exclusion of other morbidities that can cause dementia. New, robust, and affordable methods are needed for the diagnosis of AD, especially at early (pre-dementia) stages. The use of biomarkers—from blood, CSF, and brain imaging such as MRI or PET—is not yet widespread, except in the setting of clinical trials in specialist clinics. Better approaches are needed for subjective cognitive testing, in addition to validated objective diagnostic criteria for AD. We make the following recommendations for much-needed improvements in diagnosis.

(1) At a time when no effective treatment exists, an accurate appraisal of the value of diagnosis for society and for the care of individual patients is needed if decision makers are to allocate public funds to relatively expensive diagnostic procedures. Virtually no studies of this aspect of diagnosis have been done so far.

(2) Methods are needed to measure the cognitive characteristics of prodromal AD. New methods should be sensitive to minor impairment and subtle changes, and should be robust in application and informative in the populations for whom they are intended. Knowledge of the cognitive components of AD at very early disease stages could be used to predict cognitive and functional decline, to assess the effectiveness of interventions, and for stratification of patients in clinical trials.

(3) Biomarkers need to be further developed into standardised and affordable tools that can be used routinely in clinical practice to select patients for appropriate care and treatment. The diagnostic use of biomarkers will increase as treatments proven to be effective at the pre-dementia stages of AD become available.

(4) Some biomarkers are already being used in memory clinics. However, guidelines are needed for the routine

application of biomarkers in the diagnosis of AD to avoid uncontrolled, poor, or non-cost-effective use. Overuse could lead to the identification of AD-related pathological changes with uncertain relevance to the symptoms presented; underuse could lead to the misdiagnosis of AD as depression or other non-degenerative brain disorders.

(5) Data are needed on the added diagnostic value of individual biomarkers and the cost-effectiveness of different sequences of biomarker assessment, in addition to a detailed characterisation of patients in whom biomarkers are assessed, including age, comorbidities, and social factors (eg, education level).[374]

(6) The search for novel biomarkers with higher predictive value at pre-dementia stages of the disease should be continued, and simple, low-cost assays (preferably in blood) that could be used in general practice should be developed.

Section 7. Pharmacological treatment of Alzheimer's disease

The increasing number of people with AD is leading to substantially more use of pharmacological treatments and greater medication costs. For example, in Sweden, the total drug costs for people with dementia constituted about 1·1% of the societal costs of dementia in 2000, 1·6% in 2005, and 1·8% in 2012.[375] Although drug costs are a small proportion of the total societal cost of dementia (the largest proportion of costs, around 80%, is within the municipal sector, for long-term care), they constitute a noteworthy proportion of health-care costs for people with dementia. In Sweden, the cost of dementia drugs as a proportion of the costs of dementia care in the health sector increased from 23% in 2000, to 39% in 2012.[375] This trend indicates that the incentives to provide treatment from the perspective of health-care budgets might differ from a societal viewpoint, because the economic impact of dementia drug costs on the health sector is so large. Moreover, the drift in diagnostic boundaries of AD towards earlier diagnosis might lead to greater use of marketed drugs even in the absence of efficacy evidence in pre-dementia cognitive impairment.

Marketed drugs for Alzheimer's disease

Approved drugs marketed in Europe are the acetylcholinesterase inhibitors donepezil, galantamine, and rivastigmine, and the *N*-methyl-D-aspartate (NMDA) receptor antagonist memantine. They are indicated for mild-to-severe AD or moderately-severe-to-severe AD, respectively. All are approved for the dementia of AD, and rivastigmine is approved for Parkinson's disease dementia. In Europe, no drugs are approved for preclinical AD, prodromal AD, or mild cognitive impairment, or for at-risk conditions (prevention). In the USA, however, these drugs are provided for patients at pre-dementia stages.

As all approved drugs are now available as generics, the price has dropped substantially. For example, the price of donepezil has fallen by 98% in Sweden, by 97% in the UK, and by 84% in Germany, similar to previous price drops for drugs such as enalapril, simvastatin, and citalopram. However, although total prescriptions have risen because of the increasing number of people with AD, prescription rates have not necessarily increased, perhaps because information campaigns from drug companies have decreased or because the known and approved target population has already been reached. Proprietary formulations of donepezil 23 mg, memantine 28 mg, and higher-dose rivastigmine patch (transdermal formulation) are being marketed in Europe to compete with the generics, despite the absence of evidence that higher doses of proprietary drugs are more effective than the lower recommended doses.

Effectiveness of marketed drugs

The evidence we present comes from clinical and efficacy studies of marketed drugs for the treatment of AD, and does not address other disorders, such as cognitive impairment due to mixed AD, dementia with Lewy bodies, or ageing in the oldest old. Although AD influences many functional domains, the main focus of, and primary outcome in, most AD trials has been cognitive function. Other potential meaningful outcomes, such as global measures of functionality, ADL, and behaviour, are in most studies secondary outcomes, and are more relevant in advanced dementia than in early phases of the disease. Studies in mild AD cases should include outcomes that focus on memory functions, whereas in later stages of the disease, effects on ADL and psychiatric and behavioural disturbances are more clinically relevant.

Efficacy based on cognitive tests and inventories of daily activities can be assessed reliably in clinical trials of drugs for AD. However, the effects of the marketed acetylcholinesterase inhibitors have been statistically small, and just how effective, and cost effective, they are remains controversial. The few RCTs in which data for resource use and costs have been collected have not shown any significant cost savings or cost-effectiveness for the brand-name drugs.[376] However, these clinical trials have not been designed for economic evaluations and their duration has been short (6–12 months) in relation to the period over which long-term cost-effectiveness is of interest. Thus, several simulation approaches have been used, in which inputs of effectiveness and data for mortality and costs can be applied to, for example, the expected period of survival.[377] The conclusion from such simulations (largely sponsored by drug companies) is that treatment is cost effective.[376,378] Notably, these models assume long-term use of the drugs over several years, even though most patients take them in the shorter term.

Outcomes from trials of approved drugs cannot easily be generalised to clinical practice or to effectiveness. Study populations in RCTs are generally highly selected in terms of inclusion and exclusion criteria. Very old people (eg, age ≥85 years), who constitute a great proportion of the population with AD, and people with

medical comorbidities (which are common in the oldest old) are underrepresented, making generalisations from trials to the clinical practice of dementia care problematic. Duration of treatment in clinical trials is generally up to 6 months, with only a few trials extending beyond this period. In clinical trials, acetylcholinesterase inhibitors can be tapered and withdrawn without loss of function over 8 weeks; there is no need to substitute memantine. Most patients can be withdrawn from treatment when uncertainty exists about its effects.[379] Little unbiased information exists on long-term use or safety. Rather, there is a reliance on medical records from research centres, research cohorts, and prescribing data.

Long-term effective therapy for cognitive impairment is a major unmet need. A drug that provides even 1–2 years of stable function or quality of life would be useful and cost effective,[380] irrespective of whether the underlying pathology of AD is affected. Indeed, clinical trials of drugs in development for prodromal AD and mild AD dementia are 18–24 months in duration to show longer-term effects.

For policy makers and stakeholders, long-term cost-effectiveness might be of greater interest than efficacy in trials or clinical effectiveness. Since such long-term data are unlikely to be available from clinical trials, other sources such as economic simulations, registry data, or results from epidemiological studies might be of interest.

	Donepezil		Rivastigmine		Galantamine		Memantine	
	Approval	Reimbursement	Approval	Reimbursement	Approval	Reimbursement	Approval	Reimbursement
Austria	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Belgium	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Bulgaria	Yes	No	Yes	No	Yes	No	No	No
Croatia	Yes	No	Yes	No	No	No	Yes	Yes
Cyprus	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Czech Republic	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Denmark	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Estonia	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Finland	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
France	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Germany	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Greece	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Hungary	Yes	Yes	Yes	Yes	No	No	Yes	Yes
Iceland	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Ireland	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Italy	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Jersey	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Latvia	Yes	No	Yes	No	Yes	No	Yes	No
Lithuania	Yes	Yes	No	No	No	No	Yes	Yes
Luxembourg	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Malta	Yes	No	Yes	No	Yes	No	Yes	No
Netherlands	No	No	Yes	Yes	Yes	Yes	Yes	Yes
Norway	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Poland	Yes	Yes	Yes	Yes	Yes	No	Yes	No
Portugal	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Romania	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Slovakia	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Slovenia	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Spain	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Sweden	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Switzerland	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Turkey	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
UK	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Approval and reimbursement in European countries for drugs with European Medicines Agency approval for marketing for Alzheimer's disease: the acetylcholinesterase inhibitors donepezil, rivastigmine, and galantamine (indicated for mild-to-severe Alzheimer's disease) and the *N*-methyl-D-aspartate (NMDA) receptor antagonist memantine (indicated for moderately-severe-to-severe Alzheimer's disease). Information obtained from Alzheimer Europe.[388]

Table 9: **Approval and reimbursement for drugs on the market for Alzheimer's disease in Europe**

These alternative sources have lower credibility than RCTs in terms of quality of evidence. Thus, no single design can be used to judge effectiveness, and a synthesised approach in which results from several sources are used might be a feasible way forward. Furthermore, instead of focusing on single drugs, combined drug treatment (and the combination of drug treatment with various non-pharmacological options) in various settings is perhaps the best approach. The total effect of an intervention package is of primary importance, rather the effects of single interventions, as shown in the FINGER study.[189]

Effectiveness of drugs for disruptive behaviours

RCT evidence does not show donepezil or memantine to be effective for patients with significant behavioural disruption (ie, agitation or aggression).[381,382] In patients with mild-to-moderate AD, measurable changes in response to these drugs can be measured on behaviour rating scales, but such patients do not have marked agitation, and the significance of the small mean change is unclear.[383]

Effective pharmacological treatment of behavioural symptoms is a challenge. Modest advantages of antipsychotics for delusions or aggression are offset by their considerable toxicity, and they should be used cautiously or avoided.[384] Antidepressants have not been shown to be effective for depression in AD, but in some cases are modestly efficacious for behavioural symptoms (eg, citalopram for agitation in dementia).[385] However, cardiovascular adverse effects and worsening cognition restrict their use as well.[386] Anticonvulsants should not be used. Newer drugs with different mechanisms of action might eventually be helpful. The combination of non-pharmacological and pharmacological treatment is important—the total effect is of primary interest, not the effect of a single treatment component per se.[387]

Inequalities in treatment in Europe

Reimbursement is crucial to the availability of many drugs. Substantial inequalities exist in AD treatment across Europe, despite the presence of common standardised diagnostic and treatment procedures. The proportions of people with AD who receive treatment with approved drugs and treatment durations vary across Europe[19] (table 9) and globally.[389] These differences can be explained partly by variations in prescribing practices and reimbursement policies among European countries. In some countries, reimbursement requires decisions to be made by specialist doctors or in specialist centres; in other countries a continuous evaluation by a specialist of the treatment decision is also necessary (table 10). Reimbursement might not be made available to people with AD living alone or in nursing homes. Other systems require specific examinations before a reimbursement decision is made. Finally, substantial differences exist between European countries in the specified cognitive test scores that guide the initiation and discontinuation of treatment. Although the situation varies across Europe, the drugs are both approved and reimbursed in most countries (table 9).

The centralisation of the market authorisation process at the level of the EMA has solved the problem of delays among European countries for the marketing of drugs for neurodegenerative disorders. However, the launch dates of products continue to vary across countries, as

	Initial prescription by specialists	Initial prescription by GPs	Continued treatment decisions by specialists	Continued treatment decisions by GPs
Austria	Yes	No	Yes	Yes (for 6 months)
Belgium	Yes	No	Yes	No
Bulgaria	..	..	..	..
Croatia	Yes*	No	Yes*	Yes*
Cyprus	..	Yes	..	..
Czech Republic	Yes	No	Yes	No
Denmark	Yes	No	Yes	Yes
Estonia	..	..	..	..
Finland	Yes	Yes†	Yes	Yes†
France	Yes	No	Yes	Yes
Germany	Yes	Yes	Yes	Yes
Greece	Yes	No	Yes	Yes
Hungary	Yes	No	Yes	No
Iceland	..	..	..	..
Ireland	Yes	Yes	Yes	Yes
Italy	Yes	No	Yes	No
Jersey	..	..	..	..
Latvia	..	..	..	..
Lithuania	..	..	..	..
Luxembourg	Yes	Yes	Yes	Yes
Malta	Yes	Yes	Yes	Yes
Netherlands	Yes‡	No	Yes‡	Yes‡
Norway	Yes§	Yes§	Yes§	Yes§
Poland	Yes	Yes	Yes	Yes
Portugal	Yes	No	Yes	No
Romania	Yes	No	Yes	No
Slovakia	Yes	No	Yes	No
Slovenia	Yes	No	Yes	Yes
Spain	Yes	No	Yes	No
Sweden	Yes	Yes	Yes	Yes
Switzerland	Yes	Yes	Yes	Yes
Turkey	Yes	No	Yes	Yes
UK	Yes	No	Yes	Yes

Prescription regulations for drugs approved for marketing in European countries: the acetylcholinesterase inhibitors donepezil, galantamine, and rivastigmine (indicated for mild-to-severe Alzheimer's disease) and the *N*-methyl-D-aspartate (NMDA) receptor antagonist memantine (indicated for moderately-severe-to-severe Alzheimer's disease). GP=general practitioner. *Memantine only. †Support with statement from specialist. ‡Not donepezil. §Restrictions for donepezil. Information obtained from Alzheimer Europe.[388]

Table 10: **Prescription regulations of drugs on the market for Alzheimer's disease in Europe**

	Mechanism	RCTs	Participants	Duration
Reduced production of amyloid				
Pioglitazone	PPARγ agonist that acts as a β-secretase inhibitor: inhibits first protease needed for Aβ production	TOMMORROW (NCT01931566; phase 3)	3500 people aged 65–83 years with healthy cognition at risk of developing MCI due to AD, with risk stratification including age and *TOMM40* and *APOE* genotype; a masked extension is planned with the aim of recruiting 316 participants who complete TOMMORROW with a diagnosis of MCI due to AD (NCT02284906; phase 3)	5 years (completion by 2019); extension study 2 years (completion in 2021)
Increased clearance of amyloid				
Solanezumab	Anti-amyloid monoclonal antibody: passive immunotherapy	A4 study (NCT02008357; phase 3)	1150 people aged 65–85 years with healthy cognition, 500 of whom show evidence of brain amyloid accumulation	3 years plus 2 years' follow-up (completion by 2020)
Solanezumab	Anti-amyloid monoclonal antibody: passive immunotherapy	DIAN-TU (NCT01760005; phase 2/3)	210 members of families with early-onset familial AD (age 18–80 years), 105 of whom have an autosomal dominant AD-causing mutation in one of three genes (*APP*, *PSEN1*, *PSEN2*)	2 years plus 3 years' follow-up (completion by 2019)
Gantenerumab	Anti-amyloid monoclonal antibody: passive immunotherapy	DIAN-TU (NCT01760005; phase 2/3)	210 members of families with early-onset familial AD (age 18–80 years), 105 of whom have an autosomal dominant AD-causing mutation in one of three genes (*APP*, *PSEN1*, *PSEN2*)	2 years plus 3 years' follow-up (completion by 2019)
Crenezumab	Anti-amyloid monoclonal antibody: passive immunotherapy	API—autosomal dominant AD (NCT01998841; phase 2)	300 members of Colombian families with early-onset familial AD (age 30–60 years), including 200 carriers of an autosomal dominant AD-causing mutation in *PSEN1*	3 years plus 2 years' follow-up (completion by 2020)

Only selected phase 2 or 3 RCTs due for completion after 2015 are listed. Information obtained from ClinicalTrials.gov. RCT=randomised controlled trial. PPARγ=peroxisome proliferator-activated receptor γ. Aβ=amyloid β. MCI=mild cognitive impairment. AD=Alzheimer's disease. A4 study=Anti-Amyloid Treatment in Asymptomatic Alzheimer's study. DIAN-TU=Dominantly Inherited Alzheimer Network Trial Unit. API=Alzheimer's Prevention Initiative.

Table 11: **Drugs in late-stage clinical development for Alzheimer's disease in people at risk of developing the disorder**

do the timings for integration of approved drugs in the reimbursement system. Thus, inequalities in access to new drugs still exist. As the demand for social and medical care increases, successful medications that are priced fairly need to be introduced such that access to them is fair and equitable. Any effective treatment anticipated for people with pre-symptomatic, preclinical, or prodromal AD will increase the size of the market, and the numbers of patients should be estimated and provided for. Discussions are ongoing between the EMA and the FDA to harmonise the rules for drug approvals, because drug trials for approval are often done separately in the USA and Europe. A harmonised approach would be desirable because fewer trials would be required for approval across the USA and Europe.

For more on **drugs in development** see http://www.alzforum.org/therapeutics

Challenges and priorities

Several issues need to be considered with regard to the pharmacological treatment of AD at present: the diagnosis of AD, the selection of patients to be offered treatment (eg, which groups are likely to benefit), the use of evidence-based prescribing standards and patient-preference-based standards to assist in treatment decisions, and the need for reimbursements across health-care systems that are fair to patients and valid, including decisions to start and stop treatment and more consistent access and reimbursement policy across Europe. Patient-centred and family-centred standards for pharmacological treatment have yet to be developed. The use of current drugs needs to be linked to their ability to show better health outcomes, including better function. Continuing assessments of effectiveness are needed, including of the circumstances under which marketed drugs are most helpful, and whether groups or individual patients can be recognised who might benefit from particular approaches.

Drugs in late-stage development

AD is a complex disease and several drug targets are under investigation. The amyloid cascade hypothesis has dominated the specialty for the past two decades, with an emphasis on Aβ pathways, but tau and small molecules are also the focus of investigation (section 5). The targets for AD are not yet validated and are potentially numerous, so alternatives to Aβ-targeting and tau-targeting drugs might be important in the future. Tables 11–13 list drugs that are in late-stage clinical development (phase 2–4), including mechanisms of action. The diagnostic targets for new drugs include at-risk populations (prevention) and preclinical or pre-symptomatic AD (table 11),[326,330] prodromal AD[330] (ie, mild cognitive impairment due to AD;[325] table 12), or mild-to-moderate AD (table 13).[390]

Drugs that target Aβ

The most active research is taking place in the disruption of the amyloid pathway, because changes in Aβ production or clearance are thought to be among the earliest pathological changes and to lead to neurodegeneration in AD. New drugs include vaccines and antibodies to Aβ, and inhibitors and modulators of β-secretase and γ-secretase (section 5). The first vaccine to be tested in patients removed amyloid plaques, but caused brain toxicity and had no clinically significant benefits.[391,392] Active trials of Aβ immunotherapies, which aim to increase the clearance of amyloid, are taking place with the monoclonal anti-amyloid antibodies solanezumab (Eli Lilly), gantenerumab

(Hoffmann-LaRoche), crenezumab (Genentech), and aducanumab (Biogen) (tables 11, 12), and with several Aβ vaccines, including CAD106 (Novartis; NCT02565511) and ACC-001 (Janssen, Pfizer; NCT01284387).

γ-secretase cleaves the precursor protein APP intracellularly to produce Aβ fragments, which are thought to be toxic and crucial to the pathogenesis of AD. This enzyme was regarded as a valid therapeutic target, but clinical trials of γ-secretase inhibitors (avagacestat[393] and semagacestat[394]) failed, with an unexpected degree of toxicity and worsening of cognition, possibly because of off-target effects, the particular drugs used, or dosing.[395]

β-secretase, including the form known as BACE1, cleaves APP extracellularly to produce Aβ peptides. The development of BACE1 inhibitors is being avidly pursued and several have entered clinical trials in people with prodromal AD or AD dementia, including E2609 (Eisai; tables 12, 13), AZD3293 (AstraZeneca; tables 12, 13), HPP854 (High Point Pharmaceuticals; NCT01482013), and LY3202626 (Eli Lilly; NCT02323334); others are in preclinical stages of development. The most advanced is verubecestat (MK-8931; Merck), which is in combination phase 2/3 trials for either prodromal AD (table 12) or mild-to-moderate AD dementia (table 13). In phase 1, it reduced CSF concentrations of total and soluble Aβ by up to 84% and 88%, respectively. The phase 2/3 trials (NCT01739348 and NCT01953601) will include about 1800 participants, each treated over 18–24 months. Outcomes and marketing authorisation (if successful) are expected in 2018.

Drugs that target tau

Although the mechanistic link between Aβ deposition and tau pathology—and their contributions to neurodegeneration and the clinical manifestations of AD—remain unclear, treatment approaches that aim to downregulate tau-related toxicity might be of clinical benefit. Drugs that reduce the pathological hyperphosphorylation of tau protein, or the fibrillation or deposition of tau, are in development (section 5). These effects have been shown in vitro for several drugs, often inhibitors of GSK3β,[280,281] a kinase involved in the generation of hyperphosphorylated tau. Several companies have been developing similar tau-related approaches, including AbbVie, Bristol-Myers Squibb, Lundbeck, Pfizer, and TauRx Therapeutics.

	Mechanism	RCTs	Participants	Duration
Reduced production of amyloid				
E2609	BACE1 inhibitor: inhibits first protease needed for Aβ production	NCT02322021 (phase 2)	700 people aged 50–85 years with prodromal AD or mild AD dementia	18 months (completion in 2016)
AZD3293	BACE1 inhibitor: inhibits first protease needed for Aβ production	AMARANTH (NCT02245737; phase 2/3)	2202 people aged 55–85 years with MCI due to AD or mild AD dementia	2 years (completion in 2019)
Verubecestat (MK-8931, MK-8931-009)	BACE1 and BACE2 inhibitor: inhibits proteases needed for Aβ production	APECS (NCT01953601; phase 3)	1500 people aged 50–85 years with prodromal AD	2 years (completion in 2018)
JNJ-54861911	BACE1 inhibitor: inhibits first protease needed for Aβ production	NCT02260674 (phase 2)	100 people aged 50–85 years with early (pre-dementia) AD; an extension study of 100 people with early AD (50–85 years) who participated in previous phase 1 and phase 2 RCTs with the drug is ongoing (NCT02406027; phase 2)	10 months (completion in 2016); extension study 2 years (completion in 2024)
Reduced aggregation or oligomerisation of amyloid				
PQ912	Glutaminyl cyclase inhibitor: counteracts production of amyloid peptides highly prone to aggregation (ie, pyroglutamate-modified Aβ peptides)	SAPHIR (NCT02389413; phase 2)	110 people aged 50–89 years with MCI or mild dementia due to AD	3 months (completion in 2016)
Increased clearance of amyloid				
Gantenerumab	Anti-amyloid monoclonal antibody: passive immunotherapy	NCT01224106 (phase 3)	799 people aged 50–85 years with prodromal AD	2 years (completion in 2015)
BAN2401	Anti-amyloid monoclonal antibody: passive immunotherapy	NCT01767311 (phase 2)	800 people aged 50–90 years with MCI due to AD or mild AD dementia	18 months (completion by 2018)
Aducanumab (BIIB037)	Anti-amyloid monoclonal antibody (originally derived from healthy older adults): passive immunotherapy	EMERGE (NCT02484547; phase 3) and ENGAGE (NCT02477800; phase 3)	2700 people (1350 per trial) aged 50–85 years with MCI due to AD or mild AD dementia	About 18 months (completion in 2020)
Intravenous immunoglobulin derived from healthy donors	Passive immunotherapy (contains naturally occurring polyclonal anti-Aβ antibodies)	NCT01300728 (phase 2)	50 people aged 50–84 years with MCI	2 years (completion in 2017)
Reduced production of P-tau or reduced fibrillation or deposition of tau				
Exenatide (exendin-4)	GLP1 receptor agonist (diabetes drug): restores intracellular transport of tau, prevents tau phosphorylation, and improves insulin signalling	NCT01255163 (phase 2)	100 people aged ≥60 years with MCI or mild AD dementia	About 18 months (completion in 2016)

(Table 12 continues on next page)

	Mechanism	RCTs	Participants	Duration
(Continued from previous page)				
Modulation of neurotransmission				
Atomoxetine	Noradrenaline reuptake inhibitor (licensed): increases brain concentrations of noradrenaline	ATX-001 (NCT01522404; phase 2)	40 people aged 50–90 years with MCI	6 months (completion in 2017)
Ladostigil (TV-3326)	Acetylcholinesterase inhibitor and MAO inhibitor: increases cholinergic neurotransmission and transmission mediated by monoamines; a derivative of rasagiline and rivastigmine, it also has antioxidant properties and can modulate APP processing and cellular signalling pathways	NCT01429623 (phase 2)	200 people aged 55–85 years with MCI	3 years (completion in 2015/2016)
DAOIB	NMDA receptor regulator: enhances NMDA-receptor-mediated glutamatergic neurotransmission	NCT02239003 (phase 2)	50 people aged 50–90 years with MCI	6 months (completion in 2016)
PXT00864*	Regulates GABAergic neurotransmission (depending on the receptor, it can have antagonistic or agonistic effects)	PLEODIAL-I (NCT02361424; phase 2)	45 people aged ≥60 years with mild AD dementia; an open-label extension study, PLEODIAL-II, is ongoing (NCT02361242; phase 2)	12 weeks (completion in 2015); extension study 24 weeks
Other mechanisms of action				
Benfotiamine	Thiamine derivative: supports brain glucose metabolism and can reduce amyloid accumulation	NCT02292238 (phase 2)	76 people aged ≥65 years with MCI or mild AD dementia	1 year (completion in 2018)
Insulin (including rapid-acting insulin analogue glulisine)	Regulates glucose metabolism and can reduce amyloid accumulation	SNIFF (NCT01767909; phase 2/3)	240 people aged 55–85 years with MCI or mild AD dementia	18 months (completion in 2016)
Glulisine	Rapid-acting insulin analogue: regulates glucose metabolism and can counteract amyloid accumulation	NCT02503501 (phase 2)	90 people aged 50–90 years with MCI or mild AD dementia	6 months (completion in 2017)
Cilostazol	PDE3 inhibitor (licensed antiplatelet drug): can reduce amyloid toxicity	COMCID (NCT02491268; phase 2)	200 people aged 55–84 years with MCI	About 2 years (completion in 2018)
BI 409306 (SUB 166499)	PDE9 inhibitor: enhances synaptic plasticity and reduces amyloid toxicity	NCT02240693 (phase 2) and NCT02337907 (phase 2)	624 people aged ≥55 years with MCI due to AD	12 weeks (completion in 2016)
Simvastatin	Cholesterol-lowering drug (licensed) with antioxidant and anti-inflammatory properties: can lower brain Aβ production and reduce Aβ-mediated neurotoxicity	SIMaMCI (NCT00842920; phase 4)	520 people aged 55–90 years with amnestic MCI	2 years (completion in 2018)
VX-745	p38 mitogen-activated protein kinase inhibitor: modulates inflammation	NCT02423200 (phase 2) and NCT02423122 (phase 2)	32 people aged 60–85 years with MCI due to AD or mild AD dementia	6–12 weeks (completion in 2016)

Only selected phase 2, 3, or 4 RCTs due for completion in or after 2015 are listed. Information obtained from ClinicalTrials.gov. RCT=randomised controlled trial. BACE1=β-site APP-cleaving enzyme 1. Aβ=amyloid β. AD=Alzheimer's disease. MCI=mild cognitive impairment. BACE2=β-site APP-cleaving enzyme 2. APECS=β Amyloid Production and Effects on Cognition Study. P-tau=phosphorylated tau. GLP1=glucagon-like peptide 1. MAO=monoamine oxidase. APP=amyloid precursor protein. NMDA=*N*-methyl-D-aspartate. GABA=γ-aminobutyric acid. SNIFF=Study of Nasal Insulin in the Fight Against Forgetfulness. PDE=phosphodiesterase. SIMaMCI=Simvastatin in Amnestic Mild Cognitive Impairment. *A combination of acamprosate and baclofen (both licensed drugs).

Table 12: **Drugs in late-stage clinical development for Alzheimer's disease in people at symptomatic, pre-dementia stages**

Among other targets[396] is the dynamic *O*-linked *N*-acetylglucosamine (*O*-GlcNAc) post-translational modification of tau, which might relate to tau hyperphosphorylation. Concentrations of *O*-GlcNAc are decreased in the brains of patients with AD. Merck and Alectos Therapeutics have collaborated to inhibit the enzyme involved in removal of *O*-GlcNAc sugars, with some preclinical evidence that this approach can slow neurodegeneration and reduce tau and amyloid pathology.[397,398] Antibodies can target the *MAPT* gene or tau protein, and several approaches are in development.[282,288,396] For example, in January 2015, AC Immune partnered with Johnson & Johnson to develop the liposome-based anti-tau vaccine ACI-35.[399] A phase 1 study of active vaccination against tau with AADvac1 (Axon Neuroscience; NCT01850238 and NCT02031198) is also in progress. Another drug that is being developed with the aim of increasing tau clearance—on the basis of the view that tau clearance in general must be achieved to modify disease progression—is methylene blue, an FDA-approved compound that can inhibit tau aggregation. A formulation of methylene blue, TRx0237 (LMTX; TauRx Therapeutics; table 13), is being tested in a phase 3 trial of 833 patients with mild-to-moderate AD, with patients followed up for 12 months (NCT01689246), and a phase 2 trial of 500 patients with mild frontotemporal dementia, followed up for 18 months (NCT01626378). Outcomes of both trials are expected in 2016. Other drugs in late-stage clinical development for prodromal AD or AD dementia include exenatide (tables 12, 13) and liraglutide (table 13).

The way forward in therapeutic development

Since the advent of the acetylcholinesterase inhibitors, drug development for AD has been disappointing. All drugs in completed phase 2 and phase 3 trials have failed. Pursuit of the amyloid cascade hypothesis has not so far been rewarding, and clinical research efforts are now being directed more broadly. Drug development is moving towards earlier stages of the disease, with RCTs

in people with preclinical and prodromal AD. This approach raises important questions about the future of drug development for AD, including the issues of ethics, cost sustainability of new treatments, validity and costs of diagnostics (biomarkers) and analyses, and durations of trial participation for people with AD and their families. To accelerate the process of drug development, new trial designs are needed, with expedited programmes for the testing and approval of drugs to address the unmet needs of patients. Moreover, improvements in basic and translational research are needed for the discovery of new targets and new drugs for clinical development.

The shift to earlier stages of AD

In future, if drugs are approved for AD and marketed as disease modifying or as long-term treatments, diagnostic

	Mechanism	RCTs	Participants	Duration
Reduced production of amyloid				
E2609	BACE1 inhibitor: inhibits first protease needed for Aβ production	NCT02322021 (phase 2)	700 people aged 50–85 years with prodromal AD or mild AD dementia	18 months (completion in 2016)
AZD3293	BACE1 inhibitor: inhibits first protease needed for Aβ production	AMARANTH (NCT02245737; phase 2/3)	2202 people aged 55–85 years with MCI due to AD or mild AD dementia	2 years (completion in 2019)
Verubecestat (MK-8931, MK-8931-009)	BACE1 and BACE2 inhibitor: inhibits proteases needed for Aβ production	EPOCH (NCT01739348; phase 2/3)	1960 people aged 55–85 years with mild-to-moderate dementia due to AD	18 months (completion in 2017) with 5 year double-blind extension phase
Bryostatin-1	Macrocyclic lactone (has been investigated as an antineoplastic drug): stimulates α-secretase and reduces brain amyloid burden	NCT02431468 (phase 2)	150 people aged 55–85 years with moderate-to-severe dementia due to AD	7 months (completion in 2017)
Reduced aggregation or oligomerisation of amyloid				
Carvedilol	Non-selective β-adrenoceptor blocker (approved for congestive heart failure and hypertension): prevents formation of amyloid oligomers	NCT01354444 (phase 4)	50 people with mild dementia due to AD*	6 months (completion in 2016)
PQ912	Glutaminyl cyclase inhibitor: counteracts production of amyloid peptides highly prone to aggregation (ie, pyroglutamate-modified Aβ peptides)	SAPHIR (NCT02389413; phase 2)	110 people aged 50–89 years with MCI or mild dementia due to AD	3 months (completion in 2016)
Increased clearance of amyloid				
Solanezumab	Anti-amyloid monoclonal antibody: passive immunotherapy	EXPEDITION 3 (NCT01900665; phase 3)	2100 people with mild AD dementia; an open-label extension study, EXPEDITION EXT, is underway to assess safety in 1275 people with dementia due to AD (≥55 years) who previously participated in phase 3 RCTs with solanezumab (NCT01127633; phase 3)	18 months (completion in 2018); extension study 2 years (completion in 2018)
Gantenerumab	Anti-amyloid monoclonal antibody: passive immunotherapy	NCT02051608 (phase 3)	1000 people aged 50–90 years with mild AD dementia	About 2 years (completion in 2018)
BAN2401	Anti-amyloid monoclonal antibody: passive immunotherapy	NCT01767311 (phase 2)	800 people aged 50–90 years with MCI due to AD or mild AD dementia	18 months (completion by 2018)
Aducanumab (BIIB037)	Anti-amyloid human monoclonal antibody (originally derived from healthy older adults): passive immunotherapy	EMERGE (NCT02484547; phase 3) and ENGAGE (NCT02477800; phase 3)	1700 people aged 50–85 years with MCI due to AD or mild AD dementia	About 18 months (completion in 2020)
Crenezumab	Anti-amyloid monoclonal antibody: passive immunotherapy	NCT01723826 (phase 2)	A long-term, open-label safety extension study in 360 people with mild-to-moderate dementia due to AD who previously participated in phase 2 RCTs of the antibody	About 2 years (completion in 2017)
Albumin and immunoglobulin associated with plasmapheresis	Passive immunotherapy	AMBAR (NCT01561053; phase 2/3)	350 people aged 55–85 years with mild-to-moderate AD dementia	14 months (completion in 2016)
Reduced production of P-tau or reduced fibrillation or deposition of tau				
TRx0237	Tau aggregation inhibitor: reduces abnormal tau accumulation	NCT01689246 (phase 3) and NCT01689233 (phase 3)	About 1533 people aged <90 years with mild-to-moderate AD dementia	About 18 months (completion in 2016)
Exenatide (exendin-4)	GLP1 receptor agonist (diabetes drug): restores intracellular transport of tau, prevents tau phosphorylation, and improves insulin signalling	NCT01255163 (phase 2)	100 people aged ≥60 years with MCI or mild AD dementia	About 18 months (completion in 2016)
Liraglutide	GLP1 receptor agonist (approved diabetes drug): improves insulin brain signalling and can prevent tau hyperphosphorylation	ELAD (NCT01843075; phase 2)	206 people aged 50–85 years with mild dementia due to AD	12 months (completion in 2017)

(Table 13 continues on next page)

	Mechanism	RCTs	Participants	Duration
(Continued from previous page)				
Modulation of neurotransmission				
Donepezil	Acetylcholinesterase inhibitor (already approved for dementia due to AD): increases brain levels of acetylcholine	NCT01129596 (phase 4), NCT01251718 (phase 4), and NCT02162251 (phase 4)	Post-marketing surveillance studies of 1600 people with mild-to-severe AD dementia*	Up to 4 years (completion in 2015/2016)
Encenicline (MT-4666, EVP-6124)	α7 nicotinic acetylcholine receptor agonist (increases cholinergic neurotransmission)	NCT02246075 (phase 2), NCT02327182 (phase 3), NCT01969136 (phase 3), and NCT01969123 (phase 3)	1930 people aged 50–85 years with mild-to-moderate AD dementia; an extension study is planned with the aim of recruiting 1000 participants from these studies (NCT02004392; phase 3)	6–12 months (completion in 2016/2017); extension study 6 months (completion in 2017)
MK-7622	Allosteric modulator of muscarinic acetylcholine receptors (postulated): enhances response to acetylcholinesterase inhibitors, increasing cholinergic neurotransmission	NCT01852110 (phase 2)	830 people aged 55–85 years with mild-to-moderate dementia due to AD	Up to 1 year (completion in 2020)
Rasagiline	MAOB inhibitor (licensed for Parkinson's disease): increases neurotransmission mediated by monoamines	R2 (NCT02359552; phase 2)	50 people aged 50–90 years with mild-to-moderate dementia due to AD	6 months (completion in 2016)
RG1577 (RO4602522	MAOB inhibitor: increases neurotransmission mediated by monoamines	NCT01677754 (phase 2)	544 people aged 50–90 years with moderate AD dementia	1 year (completion in 2015)
Idalopirdine (Lu AE58054, SGS 518)	5-HT_6 receptor antagonist: can enhance cholinergic, glutamatergic, noradrenergic, and dopaminergic neurotransmission	STARSHINE (NCT01955161; phase 3), STARBEAM (NCT02006641; phase 3), and STARBRIGHT (NCT02006654; phase 3)	2490 people aged ≥50 years with mild-to-moderate AD; an extension study, STAR Extension, with 1770 people from STARSHINE AND STARBEAM is ongoing (NCT02079246; phase 3)	6 months; extension study 8 months (completion in 2015/2016)
Riluzole	Decreases glutamatergic neurotransmission by inhibiting both glutamate release and postsynaptic glutamate receptor signalling	NCT01703117 (phase 2)	48 people aged 60–85 years with mild dementia due to AD	6 months (completion in 2017)
DAOIB	NMDA receptor regulator: enhances NMDA receptor-mediated glutamatergic neurotransmission	NCT02103673 (phase 2)	90 people aged ≥50 years with AD or vascular dementia at stages from mild to moderate–severe	6 weeks (completion in 2016)
Methylphenidate	Dopamine and noradrenaline reuptake inhibitor (licensed): acts as a stimulant by promoting dopaminergic and noradrenergic neurotransmission	ADMET2 (NCT02346201; phase 3)	200 people with mild-to-moderate AD dementia and apathy	6 months (completion in 2019)
Other mechanisms of action				
Sagramostim	Licensed synthetic form of the haemopoietic growth factor GM-CSF: promotes amyloid removal by stimulating phagocytosis	NCT01409915 (phase 2)	40 people aged 55–85 years with mild-to-moderate AD dementia	6 months (completion in 2016)
Formoterol	Longacting β_2-adrenoceptor agonist (approved for asthma and chronic obstructive pulmonary disease): can improve synaptic plasticity and reduce amyloid burden	NCT02500784 (phase 2)	60 people aged 50–85 years with mild-to-moderate dementia due to AD	1 year (completion in 2016)
Benfotiamine	Thiamine derivative: supports brain glucose metabolism and can reduce amyloid accumulation	NCT02292238 (phase 2)	76 people aged ≥65 years with MCI or mild AD dementia	1 year (completion in 2018)
ATP (small molecule)	Enhances metabolism and can protect against amyloid-mediated cytotoxicity	NCT02279511 (phase 2)	20 people aged 55–85 years with moderate-to-severe AD dementia	3 months (completion in 2016)
Azeliragon (PF-04494700, TTP488; small molecule)	RAGE inhibitor: can counteract brain amyloid accumulation and modulate inflammation	NCT02080364 (phase 3)	800 people aged ≥50 years with mild AD dementia	18 months (completion in 2018)
T-817MA (small molecule)	Has neurotrophic and neuroprotective properties: can protect against amyloid-mediated and tau-mediated toxicity	NCT02079909 (phase 2)	450 people aged 55–85 years with mild-to-moderate AD dementia	About 1 year (completion in 2016)
Cerebrolysin†	Peptide mixture with neurotrophic-like properties related to regulation of cell signalling: can control amyloid metabolism and has anti-apoptotic effects mediated by expression of endogenous neurotrophic factors	NCT01822951 (phase 4)	510 people aged ≥50 years with mild-to-moderate dementia due to AD	6 months (completion in 2016)
Nilvadipine	Dihydropyridine calcium channel blocker (licensed antihypertensive): can enhance brain circulation, prevent amyloid accumulation, and increase amyloid clearance	NILVAD (NCT02017340; phase 3)	500 people aged ≥50 years with mild-to-moderate AD dementia	18 months (completion in 2017)
Insulin (including rapid-acting insulin analogue glulisine)	Regulates glucose metabolism and can counteract amyloid accumulation	SNIFF (NCT01767909; phase 2/3)	240 people aged 55–85 years with MCI or mild AD dementia	18 months (completion in 2016)

(Table 13 continues on next page)

	Mechanism	RCTs	Participants	Duration
(Continued from previous page)				
Glulisine	Rapid-acting insulin analogue: regulates glucose metabolism and can counteract amyloid accumulation	NCT02503501 (phase 2)	90 people aged 50–90 years with MCI or mild AD dementia	6 months (completion in 2017)
AZD0530 (saracatinib)	Fyn-kinase inhibitor: attenuates amyloid-mediated and tau-mediated neuronal damage	NCT02167256 (phase 2)	152 people aged 55–85 years with mild AD dementia	1 year (completion in 2016)
Masitinib (AB1010)	Selective tyrosine-kinase inhibitor: modulates neuroinflammation by regulating mast cell activity, and promotes neuroprotection by targeting Fyn kinase	NCT01872598 (phase 3)	396 people aged ≥50 years with mild-to-moderate AD dementia	6 months (completion in 2016)
VX-745	p38 mitogen-activated protein kinase inhibitor: modulates inflammation	NCT02423200 (phase 2) and NCT02423122 (phase 2)	32 people aged 60–85 years with MCI due to AD or mild AD dementia	6–12 weeks (completion in 2016)

Only selected phase 2, 3, or 4 RCTs due for completion in or after 2015 are listed. Information obtained from ClinicalTrials.gov. RCT=randomised controlled trial. BACE1=β-site APP-cleaving enzyme 1. Aβ=amyloid β. AD=Alzheimer's disease. MCI=mild cognitive impairment. BACE2=β-site APP-cleaving enzyme 2. AMBAR=Alzheimer's Management by Albumin Replacement. P-tau=phosphorylated tau. GLP1=glucagon-like peptide 1. ELAD=Evaluating Liraglutide in Alzheimer's Disease. MAOB=monoamine oxidase B. 5-HT=5-hydroxytryptamine. NMDA=*N*-methyl-D-aspartate. ADMET2=Apathy in Dementia Methylphenidate Trial 2. GM-CSF=granulocyte-macrophage colony-stimulating factor. ATP=adenosine triphosphate. RAGE=receptor for advanced glycation end-products. NILVAD=Nilvadipine in Mild to Moderate Alzheimer's Disease. SNIFF=Study of Nasal Insulin in the Fight Against Forgetfulness. *Age not provided. †A previous meta-analysis of six RCTs suggested beneficial symptomatic effects in people with mild-to-moderate dementia due to AD.[390]

Table 13: **Drugs in late-stage clinical development for Alzheimer's disease in patients with dementia**

work-ups will probably shift from mild AD and prodromal AD to preclinical AD (section 6). This shift is likely to have two implications, first for the validity of early-stage or preclinical diagnoses, and second for the long-term cost-effectiveness of treatment.

Biomarkers will be crucial for diagnosis, but have yet to be validated. Even if they were validated, available biomarkers would need to have high levels of sensitivity and specificity (eg, 95–99%) to be clinically useful. The risk of false-positive and false-negative cases needs to be considered carefully.[400] Predictive biomarkers are needed to facilitate the diagnostic process. For example, no evidence exists to suggest that a patient with mild memory impairment will evolve differently from one with worse impairment, or that one with a small hippocampus or low CSF Aβ concentrations will respond to treatment better than a patient with a larger hippocampus or higher concentrations. Furthermore, the prognostic value of biomarkers such as Aβ and tau is unclear in very advanced age, and 70% of dementia cases in the general population are in people aged 75 years or older.

Estimating the long-term cost-effectiveness of available drugs is a challenge (section 1), and the duration for expected effects of treatment will be prolonged by many years with a shift to earlier-stage diagnoses, such as preclinical and prodromal AD. Furthermore, resource use and costs during the pre-dementia period are low, and conventional trials such as RCTs will not be useful for cost-effectiveness assessments. Other strategies, such as simulations or the use of registry data, will probably be better options for such assessments.

Population ageing is occurring worldwide, led by the demographic transition that has already happened in many European countries and in Japan. Ageing adds additional challenges in terms of early diagnosis, because of our unclear understanding of the threshold between age-related and disease-related cognitive decline. Another problem in developing drugs for AD dementia is the multifactorial nature of dementia in old individuals, including concurrent vascular dementia and different types of neurodegenerative lesions. Physical comorbidity is also frequent in advanced age, generally accompanied by poly-pharmacotherapy, with non-optimum use of drugs for patients with AD (eg, anticholinergic and sedative effects are common and undesirable in geriatric patients with AD).[401,402]

These challenges highlight the importance of offering a comprehensive geriatric assessment to every elderly patient—a multidisciplinary diagnostic and treatment process that could identify medical, psychosocial, and functional limitations of a frail elderly person, with the aim of developing a coordinated care plan to maximise overall health with ageing.[403,404] Comprehensive geriatric assessment can support the assessment and management of people with dementia, improving pharmacological treatment decisions. Additionally, optimum management of multimorbidity can have benefits for cognition.

Existing and future regulatory processes

The unique challenges inherent in the development of drugs for AD and other dementias have driven regulatory policy. Guidance documents from the EMA[405,406] and the FDA[407–409] in the area of AD and other neurodegenerative diseases have considered a range of relevant issues: the potential effect of new diagnostic criteria for AD (the NIA–AA[325–327] and IWG[328–330] criteria) on trial design, and the development of drugs for treatment of early-stage disease; the choice of outcome parameters in clinical trials and the need for distinct assessment methods at different disease stages; the validation and potential use of biomarkers for different phases of AD in different stages of drug development; the design of long-term efficacy and safety studies; the design of studies of the usefulness of combination therapy; and the use of expedited

programmes for new treatments in drug development, such as fast-track designation or accelerated approval. Lessons learned from the challenges and successes of ongoing and future clinical trials in well-defined groups of participants at the preclinical, prodromal, or dementia stages of AD should lead swiftly to appropriate changes in regulatory policy. Moreover, harmonisation of the rules for drug approvals by the EMA and the FDA could help to accelerate the availability of promising new drugs.

Challenges in drug development

The evidence generated so far from clinical trials of drugs for AD is limited by the underlying assumptions and theories implicit in the generation of the data. The conceptual models for age-associated cognitive impairment, dementia syndrome, and AD need to be developed further, with a consideration of their effects on drug development. The causes of AD have yet to be elucidated: it is a complex disease, and formidable barriers to treatment research need to be overcome.

The several AD-related clinical diagnoses, including mild cognitive impairment due to AD, prodromal AD, and AD dementia, result in biologically and clinically heterogeneous groups of patients. In each group, patients vary in their cognitive profiles, severity of early memory impairments, genotypes, and expression of putative biomarkers. This heterogeneity makes drug discovery and development more complicated, and efforts are needed to subtype patients (eg, on the basis of biomarker profiles) such that groups with homogeneous aetiology and outlooks can be included in clinical trials. Similar efforts should be made for the range of age-associated conditions of cognitive impairment and other neurodegenerative disorders beyond AD.

Diagnostic criteria can have a substantial effect on the numbers of people recognised as having AD or other dementias, including those who are treated in clinical trials. The absence of validated drug targets and the large number of targets can lead to ethical challenges in clinical drug development. Many drug targets might be applicable to cognitive ageing or brain ageing, and to cognitive decline associated with AD. Moreover, substantial numbers of people in subgroups of the AD population probably won't be helped by any particular treatment. The identification of targets and development of safe therapeutics that can be used for very early intervention to prevent dementia in at-risk people is a priority.

So far, drugs in development for AD have each targeted and altered one aspect of the disease or one facet of brain function, but they have also adversely or unpredictably altered other aspects of brain function. Relating mechanisms of drug action to clinical outcomes is one challenge that needs to be addressed. The designs and outcomes of clinical trials have so far tended to be nearly identical from one programme to the next, and not necessarily relevant to the modelled action of the drug in question. Long clinical trials that use soft or uncertain clinical and biological endpoints are obstacles to progress; targeted, efficient trial designs with optimum assessment of outcomes are needed to enable the individualisation of treatment. Decisions on the right drug for development, for the relevant groups in society, should be taken carefully, and not before the ultimate aims of treatment in the general population have been set.

A new clinical trials infrastructure is needed to avoid delays and barriers to recruitment, which are a major problem at present. Samples of convenience (eg, those that are not typical of everyday clinical practice) might not constitute valid trial samples for many purposes. For example, the median age at onset of dementias and AD is 80 years or older, in people who have substantial concomitant illnesses, and neuropathology is usually mixed.[410,411] However, clinical trials are frequently done with much younger patients (eg, around 70 years) who have little concomitant illness and are taking few drugs, and attempts are made in recruitment to exclude other causes of cognitive impairment. The real benefit of anti-AD drugs for elderly patients needs to be established in clinical trials that take into account the mixed nature of the brain damage and neurodegeneration causing dementia, the impact of other illness, and the effects of poly-pharmacotherapy on cognition. The careful selection of participants would make trial results more generalisable to the general population.

Major barriers to progress include the limitations of current animal models of disease and translation of findings from preclinical studies to humans (section 5). New approaches to prevention trials, stratified medicine, and smaller phase 2a trials to gain early signals of potential efficacy might be helpful. In clinical research, the risks faced by participants are higher in the early phases of trials than in late phases, so a concentration of risk assessment and resources on early-phase research is essential. The substantial challenges involved in drug development for AD and other dementias demand a collaborative rather than a competitive effort, and all data from clinical trials should be made publicly available. Panel 5 provides a summary of steps that could be taken to improve the clinical-development enterprise.

Many reasons for the failures of clinical trials and drug-development programmes in AD have been advanced, but the most likely explanation for the absence of effective medications is that the drugs do not work. When truly effective drugs are tested, their effects will overcome the current inefficiencies in clinical development.

Prospects and goals for experimental treatments

Establishment of validated drug targets necessitates greater understanding of neurodegenerative diseases, other age-related syndromes of cognitive impairment, cognitive impairment associated with other disorders, and the numerous processes that lead to illness in these

conditions. Advances in basic and clinical science, including better knowledge and selection of drug targets, will drive future drug development. Although the amyloid cascade hypothesis of AD has dominated the specialty, basic and clinical research efforts need to assess the promise of other targets in different subgroups of patients at different disease stages. Advances in drug development and clinical trials will be incremental and iterative. Several failures in clinical development for AD have led to progress, with improved prospects for the identification of effective drugs. However, predictions of an effective treatment in the near future can be based only on the drugs in development at present, preclinical evidence, and the interest of experts and investors.

Summary and recommendations

An effective treatment for AD is perhaps the greatest unmet need facing modern medicine. An organised and concerted effort among governmental agencies, academic researchers, and industry will be needed to develop effective and affordable therapies. The overall success rate of drug development for AD has been poor. A few drugs are approved for the symptomatic treatment of dementia, and several drug candidates are in clinical trials, but novel paradigms are needed to incorporate advances in early diagnosis, genetic factors, and epidemiology into the design of clinical trials for new drug candidates. Major long-term financial commitment to clinical development will be essential.

(1) Improvements in the clinical-development infrastructure are needed, with increased collaboration between governments, public and private institutions, AD associations, and the pharmaceutical industry to facilitate clinical research. Substantial redundant research in AD drug development should be avoided.

(2) Increased research budgets are needed for drug discovery, drug development, and clinical trials. International cohorts, standardised methods, and ethical and regulatory frameworks should be established to facilitate clinical studies. Clinical drug development and clinical trials should be coordinated internationally. New approaches to drug development (eg, for different treatment aims) should be recognised and supported.

(3) Public, private, and corporate funding decisions should be based on evidence and scientific merit, rather than being driven by advocacy, opinion, persuasion, or corporate considerations.

(4) The voice of patients should be strengthened in risk-based approaches to the conduct of early first-in-human clinical trials in which the preclinical evidence base is weak. Options should be discussed for earlier entry of patients into clinical-development programmes, enabling the collection of valuable pharmacokinetic and pharmacodynamic information from participants. This approach would help to refine adaptive clinical trials and enable early failure.

***Panel 5:* Clinical-development enterprise for Alzheimer's disease**

- Drugs are needed to both prevent and treat the cognitive and functional symptoms of preclinical Alzheimer's disease (AD), prodromal AD, and AD dementia.
- Plans are needed to decide which drugs to support in clinical development and to identify the determinants of successful translation of experimental drugs to AD treatment.
- More resources are needed for early clinical development so that more potential treatments can be assessed. Resources should be directed to areas where there is evidence of efficacy. Clinical development should be justified by previous knowledge that indicates the likelihood of success.
- Detailed results and outcomes of clinical trials should be made broadly available immediately after studies have been completed in a manner that is accessible to the general public. Protocols for clinical trials should be published.
- Preclinical research and early-phase clinical trials need to be replicated before drug development moves to later phases. People at risk of AD and patients with the disease should not be enrolled in trials that have a high risk of failure. The emphasis on phase 3 without fulfilling the objectives of phase 2 is wasteful and not justifiable from a societal perspective (although high-risk, high-rewards business arguments have been made for these wagers).
- Careful assessments are needed to decide whether or not clinical research is worth pursuing. For example, is an expected 1·5 point change on the Alzheimer's Disease Assessment Scale–cognitive subscale after 2 years of treatment worthwhile, or might efforts be better spent elsewhere? The capital put into the unsuccessful bapineuzumab and solanezumab phase 3 programmes could have funded perhaps 20 focused phase 2 development programmes for a range of compounds with different mechanisms, the outcomes of which would have provided more information than those for just two drugs.
- Collaborative risk-sharing among governments and industry should be considered. Failures of very large programmes can have devastating effects. Treatment approaches with common mechanisms could be developed collaboratively rather than competitively. There is a societal need to reduce redundant approaches and competition between similar approaches.

(5) More patients should be invited to participate in research. Registries of elderly patients with and without cognitive impairment are needed to facilitate recruitment into trials.

(6) A more synchronised approach is needed for the implementation of regulatory processes for the conduct of clinical trials in national laws.[412,413]

Section 8. Non-pharmacological interventions for dementia and mild cognitive impairment

Although considerable efforts have been made to improve understanding of the neurobiology of AD (section 5) and to identify and evaluate candidate disease-modifying therapies (section 7), far less effort has been focused on the development and implementation of non-pharmacological interventions. Insufficient focus on these approaches represents a missed opportunity, because the identification of effective non-pharmacological interventions for key indications is a much more tractable short-term target than is the development of effective drugs, and efforts in this area are likely to lead to tangible benefits that will help people

to live better with dementia. Specialist terms used in this section are defined in panel 3.

Non-pharmacological interventions for dementia

Cognitive training and brain-training games

The aim of cognitive training and brain-training games is to provide individuals with strategies to improve cognition. Generally, such interventions follow one of two approaches: strategies based on theoretical neuropsychological models of cognition or learning (eg, errorless learning), or the teaching of skills to improve specific aspects of cognition (eg, mnemonic strategies to improve new learning). These interventions, which include computer-based approaches, can be delivered to individuals or to groups. A meta-analysis of ten (mainly small) RCTs that focused on healthy older individuals (age 60–76 years across the studies) indicated a small but significant benefit (effect size 0·15, 95% CI 0·103–0·194), which was generally limited to the specific cognitive domain targeted by the training.[414] A common weakness of many such studies is that the comparison has been no treatment—ie, no active control. In such circumstances, the comparison group will not benefit from the non-specific advantages associated with any intervention due to placebo and Hawthorne effects. The consequence is that the comparative benefits of the intervention under investigation can be exaggerated.

The largest and most extensive study, the Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) trial,[415] followed up more than 2500 cognitively healthy older adults aged 65 years or older (mean age 74 years) during 5 years at six US sites. Participants received training focused on attention, memory, or reasoning in ten group sessions, with follow-up booster training over the course of the study. Participants learned specific mnemonic (organisation, visualisation, and association) strategies and reasoning strategies (eg, teaching strategies to find a pattern in a letter or word series) to improve cognitive performance in the respective intervention groups. Benefits were reported in the cognitive domain that was the focus of the specific training package, with improvements in memory after memory training, and improvements in attention after attention training. Only reasoning training had the added benefit of more general improvements in memory and attention as well as reasoning, and conferred additional benefits on IADL.[415] Further work is needed to examine the cost-effectiveness of cognitive training in healthy older people.

Findings from studies of the benefits of cognitive training in people with memory impairment or dementia are more conflicting. In the ACTIVE study, memory training conferred no benefit in the subgroup of individuals with memory impairment (based on a threshold of 1·5 SD below normative values on the Rey Auditory Verbal Learning Test). Cognitive training in people with AD has been assessed in 11 RCTs, which mainly had fewer than 50 participants. Out of eight studies reviewed for general cognitive outcomes (MMSE or ADAS-Cog) in a systematic review, three showed significant benefits.[416] However, neither of the trials that were judged to be high quality by the reviewers reported a significant advantage of cognitive training. Several studies reported benefits in at least one specific aspect of cognition, but without any consistency in cognitive domains across studies. The authors of the systematic review did not do a meta-analysis because of the huge variability in the cognitive outcomes measured across the studies, so the effect size and overall significance of reported cognitive benefits have not been elucidated. They concluded that there was sufficient evidence of benefit provided by cognitive training to merit further, larger intervention studies.[416]

Many commercial companies have developed and marketed brain-training games. Despite the publicity surrounding the benefits of such games, little evidence exists to support the value of any of the commercially available products. By far the largest intervention study of brain training is Brain Test Britain,[417] a 6 week online study with 11430 participants aged 18–60 years who were randomly assigned to receive brain training in reasoning (with an emphasis on training games involving executive function), general brain training (similar to commercially available brain-training games), or control (internet search tasks). On average, participants completed 24 training sessions during the 6 weeks of the intervention. Participants showed a large and significant improvement in performance in the actual brain-training games (Cohen's *d* standardised effect size 0·73, 99% CI 0·68–0·79, and 0·72, 0·67–0·78, respectively, for the two active interventions), but these improvements were not translated to significant benefit in standardised cognitive assessments of executive function, attention, or working memory.[417] Longer-term outcomes have been reported for the older participants in the study (6742 adults older than 50 years), including significant benefits in reasoning, verbal learning, and IADL over 6 months with reasoning training and general brain training compared with the control treatment, but with substantial numbers of dropouts after 12 weeks.[418]

The largest RCT of cognitive rehabilitation assessed 69 people with AD or mixed AD and vascular dementia who had MMSE scores of more than 18.[419] Participants were randomly assigned to three arms for 8 weeks: the first group (n=23) received a cognitive-rehabilitation intervention to improve individualised outcomes, an active control group (n=24) received relaxation and stress management, and the third group (n=22) received no treatment. The multifaceted cognitive-rehabilitation approach consisted of weekly individual sessions with use of teaching strategies and techniques for learning new information, maintaining attention and concentration, managing stress, and using appropriate aids. The cognitive-rehabilitation intervention was associated with significant improvement in ratings of goal performance and satisfaction, whereas scores were unchanged in the control groups. Smaller case series

have also shown improvements in global ADL measures with the use of interventions based on implicit memory.[419]

Although the idea of cognitive stimulation for people with dementia is not new, Spector and colleagues were the first to develop this approach into a standardised treatment.[420] Their intervention, cognitive stimulation therapy (CST), is a group-based approach for people with mild-to-moderate dementia that is based on the theoretical notions of reality orientation and cognitive stimulation. The therapy takes a very specific, operationalised approach, with 14 sessions of themed activities that typically run twice a week during a 7 week period.[420] In a single-blind RCT of CST in 201 people with dementia (115 receiving CST and 86 controls),[421] significant improvements in MMSE (p=0·04) and ADAS-Cog (p=0·01) scores were reported in the treatment group compared with the control group, with additional benefits in quality of life. These initial cognitive improvements after CST were sustained with maintenance CST.[422]

The cost-effectiveness of CST was examined in an RCT in people with mild-to-moderate dementia, in which 91 people received CST and 70 were given care as usual. Costs were calculated for the 8 weeks before and the 8 weeks after treatment. Cost-effectiveness analyses usually calculate the cost of improving quality of life, with outcomes such as QALYs (section 1). A health-economic analysis[423] indicated that CST has quality-of-life advantages without incurring additional cost, suggesting that CST is a cost-effective intervention. The positive effect of CST on quality of life has been further supported by qualitative studies.[424] Other research groups have adopted a broader definition of cognitive stimulation, and developed other interventions that are less operationalised than the package of CST developed by Spector and colleagues. However, the overall evidence base for these alternative approaches is less clearcut than that for the original package of CST.[425,426]

The important role of caregivers

Caregivers have a crucial part to play in the treatment of patients with AD. Caregivers' reports about patients' cognitive impairment correlate better with objective neuropsychological assessments than do patients' own complaints.[427] Furthermore, people with pre-symptomatic or preclinical AD whose caregivers identify that they have cognitive complaints are more than twice as likely to progress to dementia than are people with caregivers who do not report such complaints (OR 2·2, 99% CI 1·2–3·9; p<0·001), suggesting that carers can accurately identify significant levels of cognitive dysfunction.[428] Caregivers generally provide a more accurate longitudinal history and more precise information about daily function than can be gleaned from an office consultation with the patient. Importantly, they can often provide proxy consent for treatment and for trials when patients are insufficiently competent to give consent themselves. All drug trials for AD require an informant with a specified minimum amount of weekly contact. Caregivers can help to ensure compliance, monitor outcomes, and report adverse effects.

In addition to being part of the therapeutic team, caregivers can become therapists themselves through the use of cognitive stimulation techniques,[429] and by managing behavioural and psychological symptoms of dementia.[430] Drug treatment for patients with AD can secondarily benefit carers in reducing their time commitment for supervision and assistance with daily care.[431–433] Nevertheless, caregivers often experience substantial subjective and objective burden, with high levels of stress and mood disorder, and they are at increased risk of alcohol-related problems and medical comorbidity. Provision of support for caregivers is therefore essential for their wellbeing and to enable the best care for people with dementia. Non-pharmacological interventions play a key part in reducing stress and improving wellbeing in caregivers themselves. Several small RCTs of group cognitive behavioural therapy for caregivers and educational programmes that include skill training have shown significant improvements in the mental health and coping skills of caregivers.[434,435] Educational interventions without these components, carer support groups that do not use cognitive behavioural therapy, and information provision without other key elements are associated with less convincing evidence of benefit.[436]

For more on **cognitive stimulation therapy** see http://www.cstdementia.com/

Information provision

Information is a key aspect of service provision to people with dementia and those caring for them, and the importance of information and signposting is often presented as a benefit of early diagnosis. Information can cover a broad range of topics, including the symptoms and causes of dementia, drug therapies and other treatment approaches, and more detailed information about specific symptoms and their treatment and management. Other topics include the effects of dementia on caregivers, financial information (eg, available financial support), key legal issues, and guidance about advance directives. Some sources also address local service provision, providing information about charities and local groups that can signpost caregivers and people with dementia to the support that they need.

In a systematic review,[436] 13 RCTs were identified that focused predominantly on the provision of information, although many included additional elements such as skills training, telephone support, and direct help to navigate the medical and care system. Two of the three studies in which quality of life was measured indicated modest but significant benefits of information provision in people with dementia, and significant benefits were also evident for neuropsychiatric symptoms. However, a meta-analysis of the same 13 studies did not show any significant benefit for caregivers with respect to caregiver burden. Although this evidence provides some support for the value of information services, further studies are

needed to determine the specific elements that are effective and to optimise interventions. The design of such studies will be challenging, because it would not be ethical to deprive individuals of the usual sources of information. However, these studies, including a health-economic component, will be essential to enable international standards to be set for the development and implementation of optimum and cost-effective information-provision services.

Treatment of neuropsychiatric symptoms

The three main types of difficult-to-manage neuropsychiatric symptoms in patients with dementia are agitation, psychosis, and mood disorder. Agitation includes symptoms of aggression, irritability, restlessness, shouting, and pacing, usually in the context of distress or anxiety. The most frequent psychotic symptoms are visual hallucinations, auditory hallucinations, and persecutory delusions. First-rank symptoms of schizophrenia almost never occur in individuals with dementia, and the psychotic symptoms seen in dementia are much less complex than those associated with functional psychoses—usually visual or second-person auditory hallucinations of people or animals, and simple persecutory delusions such as believing that possessions have been stolen. Mood disorders include depression, anxiety, and apathy.[437]

A review of neuropsychiatric symptoms in AD was done in 2010 under the auspices of the Neuropsychiatric Syndromes (NPS) Professional Interest Area of the Alzheimer's Association International Society to Advance Alzheimer's Research and Treatment (ISTAART).[437] The review stated that "treatment development should not be limited to pharmacological interventions... Treatment developments must take into consideration neurobiological and psychological contexts of the development and manifestations of NPS in AD."[438–441]

For more on **ISTAART** see https://act.alz.org/site/SPageServer?-pagename=ISTAART_homepage

In a systematic review[442] of the value of personalised psychosocial interventions to address behavioural and psychological symptoms in people with dementia living in care-home settings, the substantial evidence in favour of pleasant activities with or without social interaction for the treatment of agitation was highlighted. Well established interventions include the Seattle protocols, which focus on the assessment of person-centred activities and the introduction of a care plan to ensure that individuals receive at least 60 min a week of enjoyable activities, with an additional focus on problem solving to maximise implementation;[443] and the approach for person-centred social interaction developed by Cohen-Mansfield and colleagues.[444] The review also showed the value of reminiscence therapy to improve mood.[442]

A meta-analysis of RCTs of person-centred care training also showed the value of specific training approaches to improve agitation and reduce antipsychotic medication use in people with dementia living in care homes.[445] The Improving Well-being and Health for People with Dementia (WHELD) trial,[446] which combined person-centred care with person-centred activities and exercise, also showed the potential for this intervention to reduce mortality and antipsychotic use and improve neuropsychiatric outcomes. However, in the studies published so far, such training interventions did not improve measures of wellbeing and quality of life for people with dementia.[445] Further work is therefore needed to optimise training interventions to deliver significant quality-of-life improvements, perhaps by using specific elements for the implementation of evidence-based non-pharmacological interventions, in addition to more generic training to promote person-centred care.

Wellbeing and quality of life in nursing-home care

The numbers of people with dementia living in care homes have not been calculated on a Europe-wide basis. In the UK, about 250 000 of the 750 000 people with dementia reside in care homes.[447] As the age and dependency characteristics of people with dementia are similar across Europe,[447] it seems likely that roughly 1·6 million European citizens are living with dementia in care homes, with a median spend of 1% of GDP on long-term care across Europe.[448] Admission to a nursing home for old people with AD is associated with a reduction in the range of life roles. For example, people are usually less involved in the management of their financial affairs and might be less engaged with family, friends, and hobbies outside the care-home environment. Individuals might also find that engagement in meaningful activities within the care home is diminished. Life in nursing homes is often depicted in terms of boredom, loneliness, and a disconnect between previous roles and interests and ongoing engagement in meaningful activities.

In a large observational study[449] that used dementia care mapping to assess the quality of care in private-sector and UK National Health Service facilities, participants spent less than 2 min of a 6 h daytime observation period engaged in direct social interaction, and spent much of the time withdrawn. Contemporary nursing-home care in Europe and North America is often criticised for being task oriented and strongly focused on functional and biomedical needs, despite research suggesting that best-practice nursing-home care involves a health-promoting approach that addresses psychosocial and existential needs through resident engagement in individualised, meaningful activities.[450–453] Research shows that people with AD and other dementias in nursing homes generally have little opportunity to participate in such activities.[449]

In the previous subsection, we briefly described the potential benefits of personalised activities as a treatment approach for neuropsychiatric symptoms. A strong body of evidence also points to beneficial outcomes from interventions that promote engagement in activities adapted to the patient's cognitive and functional abilities, including improved quality of life and wellbeing, reduced anxiety, better attention, and increased alertness.[451,454–460] The essence of nursing-home care is to compensate for

cognitive and functional losses by assisting patients in meeting basic human needs, including active or passive social engagement and participation. From an existential perspective, engaging in meaningful activities also helps to represent and define individuality, and to support a sense of self. Such engagement might simply mean passive participation in, or observation of, familiar and everyday activities, rather than the use of wide-ranging activity programmes. Interventions that promote activities and an increase in vocational tasks improve wellbeing and quality of life, in addition to neuropsychiatric symptoms.[450,461–464]

Natural products and medical foods

Studies of the potential benefits of natural products and medical foods in AD have not yielded positive results. Initial studies of ginkgo biloba, the most extensively studied product, suggested modest but significant improvements in cognition, but the results were not replicated in larger and more robust studies, and the overall evidence does not suggest that the product offers any significant benefit.[465]

Intervention studies of vitamin supplements or medical foods containing vitamins have generally been disappointing. In a study of Souvenaid (Nutricia, Zoetermeer, Netherlands),[466] a nutritional drink that contains vitamins and other components with the aim of neuroprotection, 225 patients with mild AD were randomised to Souvenaid or a control drink, taken once daily for 12 weeks; the primary outcome measure was a composite neuropsychological assessment battery. Souvenaid did not confer significant benefit on overall cognitive performance, and was associated with only very slight benefits on select areas of cognition, mainly memory. Additionally, Souvenaid did not offer any improvements in everyday functioning compared with placebo.[466] Thus, the evidence of benefit for Souvenaid did not meet the usual standards for a recommended therapy.

The Homocysteine and B Vitamins in Cognitive Impairment (VITACOG) study[467] examined vitamin B12, vitamin B6, and folic acid supplementation in 271 people with mild cognitive impairment. No significant benefit with respect to neuropsychological performance or the rate of brain atrophy was found for the whole group. However, some evidence of benefit was noted in a post-hoc analysis that focused on the subgroup of people with high plasma concentrations of homocysteine (a homologue of the aminoacid cysteine) at baseline. Benefits in this subgroup seem biologically plausible, because raised homocysteine is associated with low concentrations of vitamin B12 and folic acid, and has been linked to increased risk of vascular damage and dementia.[467] Further studies are needed to confirm whether or not B vitamins and folic acid are beneficial in people with pre-symptomatic or preclinical AD and raised homocysteine concentrations.

Vitamin E is the only other vitamin-based treatment with some clinical trial evidence of potential benefit. The Trial of Vitamin E and Memantine in Alzheimer's Disease (TEAM-AD)[468] examined the efficacy of memantine and vitamin E (α-tocopherol; 2000 IU per day), alone or in combination, in people with mild-to-moderate AD who were already taking acetylcholinesterase inhibitors. A significant and potentially important overall clinical benefit, equivalent to 6 months of natural decline, was shown for vitamin E compared with placebo for the primary outcome, ADL. However, no benefit was reported for the group receiving both vitamin E and memantine, or for any of the secondary measures, including cognition.

Previous RCTs of vitamin E have also produced mixed results. A large RCT in people with preclinical or prodromal AD (diagnosed on the basis of criteria for mild cognitive impairment without biomarkers) suggested no benefit.[469] However, the Alzheimer's Disease Cooperative Study (ADCS)[470] of 341 patients with moderate-to-severe disease did show significant benefits for vitamin E on the primary outcome, a composite measure of poor outcome. However, although two well done RCTs (ADCS and TEAM-AD) have shown benefits of vitamin E on the primary outcome measure, the interpretation or understanding of global benefit is difficult in the absence of evidence for specific benefits on cognition or function. Additionally, because the dose of vitamin E used in these studies is ten times higher than that usually sold as a food additive, potential safety issues need to be considered. For these reasons, the use of vitamin E as a clinical treatment for AD is not recommended at present.

For more on the **ADCS initiative** see http://adcs.org/

Fatty acids have also been a focus of interest in AD. Two large multicentre RCTs, each with more than 150 participants, showed no significant benefits of omega-3 fatty acid treatment, including docosahexaenoic acid supplementation, on cognition, everyday activities, or global outcomes.[471,472] Although there has been media interest in ketogenic treatments such as Axona (Accera, Broomfield, CO, USA), the only published clinical trial—a multicentre phase 2 RCT in 152 people with mild-to-moderate AD—did not show any significant benefits on cognition or other outcomes after 90 days.[473] The theory that ketones could provide an alternative energy source for the brain is predicated on the unproven assumption that the brain's ability to use glucose is impaired in AD.

Generally, very little efficacy or safety evidence is required for the marketing of food additives, which can have an unfortunate role in creating false expectations among consumers, and could potentially lead to unforeseen safety issues. For example, a meta-analysis showed that antioxidant supplements might be associated with increased mortality risk,[474] and another meta-analysis of RCTs provided evidence that vitamin E supplementation is associated with increased mortality and an increased risk of haemorrhagic stroke.[475]

Although promising results have been reported in cohort studies of the potential benefits of the Mediterranean diet,[476] these results might be confounded

by other elements of healthy living, and a randomised intervention study is needed in people with mild cognitive impairment and mild dementia.

Non-pharmacological interventions for people at risk of dementia

Many studies of lifestyle and other non-pharmacological interventions to prevent or delay the onset of dementia in people with preclinical AD have been done (section 3), mostly in people with amnestic impairments in whom AD biomarkers have not been assessed. Evidence for any benefit of social activity, weight maintenance, or diet is inconsistent or very preliminary.[477] The pivotal FINGER study of people aged 60–77 years[189] showed significant benefits of a multidomain intervention (diet, exercise, cognitive training, and management of vascular risk factors) on overall cognitive function, compared with a control treatment (general health advice), with the largest benefits seen for attention and executive functions. This 2 year RCT provides key proof of concept that multidomain trials are feasible and that such approaches can confer cognitive benefit. However, further studies are needed to ascertain which elements contributed to the reported benefits, and to understand and improve the cost-effectiveness of the intervention, which was originally delivered as three separate interventions with a total of more than 30 therapy sessions, in addition to self-directed interventions.

For more on the **ENLIGHTEN trial** see http://sites.duke.edu/enlighten/

For more on the **AETMCI study** see https://www.nia.nih.gov/alzheimers/clinical-trials/aerobic-exercise-training-mild-cognitive-impairment

For more on the **POEM study** see https://www.nia.nih.gov/alzheimers/clinical-trials/pioglitazone-or-exercise-treat-mild-cognitive-impairment

For more on the **My Buddy Study** see http://www.wakehealth.edu/Research/Gerontology-and-Geriatrics/Kulynych-Center/Buddy.htm

Strong evidence exists to support smoking cessation in people at risk of AD,[477] which is already widely implemented, and the benefits of cognitive reserve,[478] although this would need to be implemented as part of educational policy across the life course because the development of cognitive reserve is based largely on childhood cognition and educational attainment, together with occupation in adult life.

Several small and medium-sized trials have investigated the effects of exercise specifically in people with subjective memory problems, mild cognitive impairment, or preclinical or prodromal AD. The main studies have identified participants on the basis of amnestic deficits or subjective reports of memory difficulties in the absence of AD, and alterations in AD biomarkers were not required. The largest trial,[479] which was undertaken in Australia and included 170 adults with subjective memory complaints, 92 of whom had mild cognitive impairment, showed a significant advantage of a 6 month programme of physical activity on cognitive function (the primary outcome was change in ADAS-Cog score at 6 months' follow-up). Benefits were maintained for 18 months and were more pronounced in people with mild cognitive impairment. Additional benefits were noted in global outcome.[479] Several exploratory trials of aerobic exercise in people with mild cognitive impairment, most of which assessed a range of measures without stipulating a primary outcome, have also reported significant improvements in cognition, function, cardiovascular fitness, motor performance, brain plasticity, and AD biomarker concentrations,[480–483] and a systematic review has concurred that aerobic exercise provides cognitive benefits in people with preclinical or prodromal AD.[484]

The evidence is already strong, but larger and better-powered RCTs are now needed in people with preclinical or prodromal AD to determine whether exercise can delay conversion to symptomatic AD, provide evidence about cost-effectiveness, and inform practice. Several studies are examining the potential of multicomponent interventions, including exercise, to prevent dementia in people with cognitive impairment and vascular disease or vascular risk factors—eg, Exercise and Nutritional Interventions for Cognitive and Cardiovascular Health Enhancement (ENLIGHTEN; NCT01573546), Aerobic Exercise Training in Mild Cognitive Impairment Study (AETMCI; NCT01146717), Pioglitazone Or Exercise to Treat Mild Cognitive Impairment (POEM; NCT00736996), and Community-Based, Buddy-Supported Exercise in Patients with Mild Cognitive Impairment (My Buddy Study; NCT01561820). These trials will improve understanding of the cost-effectiveness of interventions, the potential additive benefits of multicomponent interventions, and the specific groups of individuals who might derive optimum benefits. However, exercise already has a better evidence base than any other pharmacological or non-pharmacological intervention for people with preclinical AD, and a strong case can be made that we should be offering exercise interventions routinely as a core part of the clinical management of individuals at risk of dementia. The public health impact could be substantial: a review[111] of the relative risk of incident dementia in 16 longitudinal cohort studies calculated that a 25% reduction in inactivity could prevent up to 1 million people from developing AD worldwide.

Implementation of non-pharmacological interventions

One of the most disappointing aspects of non-pharmacological interventions to treat or prevent dementia is that they are rarely systematically implemented in clinical and care practice, even when there is clear evidence of benefit from RCTs. For example, although opportunities exist to further optimise the benefits of person-centred care training in nursing homes, clear evidence already shows that several specific interventions to improve person-centred care (eg, focused intervention training and support [FITS] and dementia care mapping) can help with neuropsychiatric symptoms and enable a reduction in antipsychotic use. However, a 2014 survey of available person-centred care interventions in the English language showed that only three of 170 interventions (1·8%) were supported by clinical-trial evidence of benefit.[445] Many training programmes have been developed by private companies and have not been assessed to establish whether or not they benefit people with dementia. Interventions that are known to be

effective all involve a therapist working with care-home staff for a period of at least 4 months to reinforce the training, and although some of the unevaluated training programmes follow good educational principles, they do not generally have this additional component. Tighter criteria are needed that demand evidence of benefit for approved training programmes.

Further examples of failure to implement a non-pharmacological intervention with good clinical-trial evidence of benefit relate to the promotion of person-centred activities for people with dementia in nursing homes, and interventions to promote aerobic exercise in people at preclinical stages of disease, with general recommendations often being made without attention to detail or structure for implementation. A programme to train and support CST therapists has been developed by University College London, UK, and has enabled some use of CST in routine clinical practice within the UK, but further development of the training and support is needed to enable full international implementation of this intervention.

Challenges and opportunities

The 2013 G8 dementia summit emphasised the need for non-pharmacological interventions that are effective and safe and can be used worldwide.[173] Accordingly, our future vision is the routine implementation of evidence-based effective and cost-effective non-pharmacological therapies for the treatment of cognition, function, and neuropsychiatric symptoms, and caregiver support, coupled with a better understanding of the optimum combination of non-pharmacological and pharmacological interventions as a routine part of clinical care. Related to these aims is the need to fully harness the potential of caregivers as cotherapists to improve outcomes for people with dementia (section 9).

Further systematic review and international consensus are required to enable a blueprint for best practice and to identify the non-pharmacological interventions that should be routinely available as part of clinical care and key research gaps. The absence of a strong commercial interest in the development of non-pharmacological interventions has meant that funding for RCTs is difficult to obtain. Moreover, studies to examine the additive benefits of non-pharmacological and pharmacological interventions are time consuming, expensive, and difficult to undertake, as are large, adequately powered RCTs of personalised non-pharmacological interventions. There might be opportunities to streamline other non-pharmacological interventions, such as cognitive training and exercise, by using self-directed online interventions.

In the treatment of neuropsychiatric symptoms, the absence of clear research definitions for key symptoms, such as agitation, is an additional challenge, with different definitions used in different studies and with different assessment methods. A working group of the International Psychogeriatric Association has been convened to develop an improved international consensus. High placebo response rates in clinical trials of neuropsychiatric symptoms—often higher than 40% and reflecting non-specific benefits, increased social and clinical interaction as part of study protocols, and spontaneous resolution of symptoms—are an additional challenge that needs to be addressed. Proposed solutions include the introduction of a less intense non-pharmacological intervention lead-in period for all participants, an increased symptom threshold for entry into trials, and the use of novel approaches (eg, central rating through video links) to reduce the number of raters and increase the inter-rater reliability for primary outcome measures.

Personalised activities for people with dementia living in nursing homes require a shift in culture, from doing for to doing with. The overall philosophy of care, organisational demands, and priorities can enable or obstruct resident engagement in activities and health promotion. Good-quality information must be widely available in Europe, and understanding of the added components of information and educational interventions that are necessary to confer benefit to people with dementia and those caring for them is essential.

For more on the **International Psychogeriatric Association** see http://www.ipa-online.org/

Summary and recommendations

Non-pharmacological interventions and the active, early involvement of caregivers should be an integral part of AD treatment strategies. The diagnosis and treatment of associated conditions, neuropsychiatric symptoms, and psychosocial deterioration are key elements in improving the quality of life of patients with AD and their families. Lifestyle changes, exercise, and nutritional support might have a role at all phases of the disease, but more research is needed to guide the implementation of intervention programmes.

(1) Systematic reviews are needed and must be supported by an international Delphi consensus to establish which evidence-based non-pharmacological interventions should be available for patients in Europe and for what indications.

(2) European recommendations and an infrastructure to enable the use of non-pharmacological interventions for which clear evidence of benefit already exists should be put into practice with appropriate training, support, and maintenance of fidelity. Examples of such interventions include exercise, CST, personalised activities, person-centred care training in care homes, and activities (with or without social interaction) for the treatment of agitation.

(3) A European consensus on the highest-priority non-pharmacological interventions would be helpful in guiding reimbursement decisions in individual countries.

(4) Additional RCTs are needed to address key gaps in understanding and unmet needs of patients (eg, non-pharmacological management of sleep disturbance, pain, psychosis, and apathy in people with dementia).

(5) Partnerships are needed between public funders and commercial organisations to address the funding challenge in studies of non-pharmacological interventions, to enable studies of the combination of key non-pharmacological and pharmacological interventions, and to facilitate academic–commercial collaborations.

(6) Open access to data from RCTs of non-pharmacological treatments is needed to support systematic reviews and meta-analyses based on individual patient data.

(7) Treatment manuals and caregiver training programmes for effective non-pharmacological interventions should be made generally available—eg, as part of dissemination by research groups involved in the development and assessment of such programmes.

(8) Non-pharmacological interventions and activities can have an inherent ethical value in high-quality care, even if the detection of measurable group-level outcomes is sometimes difficult. Ethical evidence, such as observed signs of wellbeing while a personally meaningful activity is ongoing, needs to be systematically collected, discussed, and used in clinical care.

Section 9. Formal and informal care for people with dementia

People with dementia need care and support in many areas of their lives. This support might be provided by health-care, social-care, housing, transport, leisure, or other sectors. Irrespective of the provider, support can be grouped into three main domains: support in basic ADL, support in IADL, and supervision to safeguard individuals from harm.[485] In addition to these forms of care and support, individuals with dementia might receive care from specific medical services, such as injections, infusions, and medications to alleviate dementia symptoms. ADL are basic personal activities that include dressing, eating, toilet visits, personal-care activities, and moving around the home or a care facility. IADL relate to more complex activities with a social component, such as preparing food, shopping, managing money, laundry, cleaning the house, managing public transportation, and communication (eg, using the telephone). One challenge with IADL is that they are affected by context and more closely linked to technical abilities, such as use of mobile phones, the internet,[486] or technical equipment in care.

The care and support provided for people with dementia often spans several sectors and does not fit easily into typical health-care delivery structures. The optimum approach for patients is not always in harmony with traditional ways of organising and financing formal care into distinct health-care and social-care categories. Traditional health care takes place in hospitals, specialist-care settings, and primary-care settings, and is provided by doctors, nurses, physiotherapists, occupational therapists, psychologists, and health-care assistants. Long-term care in nursing homes (or similar) or in the patient's home can be delivered by health-care or social-care providers, or both. Similarly, day care can focus on social activities (social care) or physical rehabilitation (health care). Care at home is conventionally classified as formal (delivered by paid staff) or informal (delivered by unpaid family members or other carers), although the meaning and separation of these concepts is changing.

Most people with dementia will receive both formal and informal care during the course of their illness. Indeed, no health-care or social-care system in the world could meet the needs of people with dementia without these informal-care inputs. Consequently, the substantial contributions made by family members and other unpaid carers should be fully recognised in strategic policy discussions and in case-level planning and assessments, with a consideration of the opportunity costs for carers and the consequences for their health and quality of life.[487]

The distinction between paid staff and unpaid carers has been blurred as informal caregivers have become increasingly active in many parts of the care system, not only as providers of personal care but also as advocates, participants in care planning, and holders of devolved (personal) budgets (section 8).[488] The growth of different forms of self-directed support has been a notable feature of many social-care and health-care systems; personal budgets pass responsibility for the management of care resources to the patient or carer, often with both effectiveness and cost-effectiveness advantages.[489] However, by contrast with other chronic disorders, care planning and self-directed support are complicated in the case of dementia by the effects of cognitive decline (eg, loss of mental capacity, lack of insight, legal issues of impaired autonomy, and risks of financial abuse). Thus, strategies to close the gaps between all involved factors and participants—including clear political strategies (eg, national dementia care plans), case-management plans, counselling, and education—are crucial for quality of care.

The needs and demands of patients and their families cannot all be met by public-sector health-care and social-care agencies alone, even though the public sector tends to dominate in most European countries. Organisations in the voluntary sector (often called the charitable, non-profit, or third sector) and in the private (for-profit) sector have an important part to play. The voluntary and private sectors deliver mainstream services and engage in other activities, such as information provision, lobbying for better care or more research, and case-level brokerage. Some of these activities might be funded by government under contract or via (general) grant aid, but many will be funded through charitable donations or private-market transactions, in which care services are sold directly to people with dementia or their families. Whether such services can serve as complements to, or substitutes for, available public-sector resources will depend on national structures and local conditions. Moreover, how the quality and cost-effectiveness of such services compare with those of the public sector is unclear.[490–492]

Formal (paid) care

Panel 6 provides a list of formal-care resources and activities, including support provided by staff in various settings, aids and adaptations, and newer technical support (eg, alarms and other forms of telecare). For the purposes of policy development, local planning and commissioning, and the regulation and monitoring of care, each activity should be measurable and quantifiable in some way (eg, hours, days, or number of visits). The definition of institution (as an alternative to home) varies widely. It could be a small, specialised group home for six to eight people with dementia, with staff trained in dementia care to provide round-the-clock support, a supervised facility with low staff-to-patient ratios, or a large nursing home with several hundred people with dementia and an emphasis on medical care. The wider concept of long-term care also includes comprehensive care at home.

The ultimate aim of high-quality formal care for people with dementia is the creation of an environment in which the individual's needs are met—where they are respected and have a sense of dignity, meaningfulness, and wellbeing, despite the various limitations imposed by the disease. Care needs to go beyond the provision of basic physical tasks and procedures (eg, eating, dressing, and hygiene) to include the creation and maintenance of a positive, person-centred environment and the support of patients' relationships. However, there is a risk that, of these two important dimensions of formal care, basic care tasks are given almost exclusive priority in financially constrained contexts, and that organisational decisions are so heavily influenced by financial considerations that only the minimum resources are made available to guarantee the most basic physical care. Ethical dimensions also need to be considered, even if outcomes such as dignity, meaningfulness, and wellbeing are difficult to assess. The processes of planning, organising, funding, delivering, and assessing formal dementia care need to support the completion of basic care tasks and enable high-quality care to meet the psychosocial and existential health needs of patients with dementia.

Informal (unpaid) care

Analysis of the circumstances of informal carers is complex (eg, including assessments of the needs and preferences of carers), and economic analyses often take a pragmatic and narrowed approach by focusing simply on the time spent on care. As in formal care, the range of activities included in informal care needs to be clarified, otherwise comparisons between various studies of care are not possible or meaningful. Classification of care into three domains—support in basic ADL, support in IADL, and supervision—provides a useful overview of how informal carers' time is used. The quantity of informal care can be measured in different ways. Direct and continuous timed observation provides clear measures of time spent on informal care, but for practical reasons it is useful only in validation and exploration studies.[493] Diaries and recall are the most frequently used methods to quantify informal care, although recall might lead to overestimates of caregiver time.[494]

Panel 6: **Formal resources to include in economic assessments of dementia care**

- Formal care
- Living situation (at home or in institutions)
- Respite care
- Home social-care visits
- Home medical-care visits
- Home rehabilitation-care visits
- Visits to clinics: physician specialists
- Visits to clinics: general practitioner specialists (or similar)
- Visits to clinics: registered nurses (or similar)
- Visits to clinics: rehabilitation (similar)
- Hospital care (various specialities and departments)
- Day hospital care (eg, day surgery)
- Day care (special care for dementia)
- Day care (not specifically for dementia)
- Use of drugs
- Technical devices and equipment
- Food support (eg, meals on wheels)
- Transport services

Instruments to assess the amount of dementia care can be generic or specific to a diagnosis. Data can be gathered in different ways—eg, from interviews, diaries, medical records, or registries—but legal and ethical issues, which can vary between and within countries, need to be considered when gaining access to data. In dementia and AD, the Resource Utilization in Dementia (RUD) instrument[495,496] and the Client Service Receipt Inventory (CSRI)[497] are comprehensive and frequently used methods to gather data on resource use. When combined with appropriate unit costs, these instruments aim to calculate the costs of dementia care from a societal viewpoint, including the use of health-care and social-care resources and informal-care time. Examples of other instruments are the Caregiver Activities Time Survey (CATS),[498] the Caregiver Activity Survey (CAS),[499] and the Resource Use Inventory (RUI).[500] The CATS captures time use by formal and informal caregivers across a range of tasks and activities, whereas the CAS measures caregiver time and some aspects of caregiver burden. The US RUI, which asks about resource use in the past three months, is designed for AD prevention trials.

How formal-care and informal-care resources are used by people with dementia worldwide is difficult to establish. Data from high-income countries are readily available for the most part, and Alzheimer's Disease International (ADI) and the 10/66 Dementia Research Group, the Alzheimer's Association, and Alzheimer Europe have attempted to broaden the picture to include low-income and middle-income countries. The ADI

For more on **Alzheimer's Disease International** see http://www.alz.co.uk/

For more on **Alzheimer Europe** see http://www.alzheimer-europe.org/

World Alzheimer Report 2010,[56] and linked publications,[3,72] were based on a comprehensive review of the use of formal and informal resources worldwide.

Informal care, which was very often deemed to be comprehensive and burdensome (providing all the physical and psychosocial care required by patients), was the most important form of care in low-income and middle-income countries. In low-income countries, the social-care sector (home care, nursing homes, and day care) was almost non-existent, and 90–100% of people with dementia were estimated to live at home (compared with 50–90% in high-income countries). Across all regions, 55–91% of carers were women, although the proportion tended to be lower in high-income regions.[56] However, the ADI report concluded that the education of women in low-income and middle-income countries, and their increasing participation in the workforce (which should generally be viewed as a positive indicator of human development), tend to reduce their availability for informal caregiving. Spouses were the most common informal caregivers, but this factor varied substantially (eg, daughters or daughters-in-law more frequently serve as caregivers in some countries or cultures). Data for the formal and informal care of people with dementia in eastern Europe are also scarce, but data from Hungary were presented as part of the EuroCoDe project,[501,502] and similar resource-use figures from Romania were provided as part of the ICTUS study.[24] Although few studies have been done (and figures from eastern Europe must therefore be viewed with caution), the contribution of informal care seems to be higher in eastern Europe than in western Europe. Accordingly, the proportions of people with dementia who are living and cared for in nursing homes might be lower in eastern Europe.

For more on the **ACTIFCare project** see http://actifcare.eu/

End-of-life care

Compassionate end-of-life care should respect social norms (ie, the cultural context in which care is provided). When end-of-life care is provided at home by an informal carer (often a spouse or another family member), perhaps with formal carers available for part of the day, the quality of care will depend on information provision and communication between the patient, family members and those responsible for practical care and important end-of-life decisions. The aim should be to respect the preferences of the patient. The challenges of providing high-quality end-of-life care are discussed in more detail in section 10.

Challenges and future goals

In the absence of effective treatments for dementia, high-quality, person-centred care is essential to meet the health needs of patients and to promote dignity, meaningfulness, and wellbeing as the disease progresses. Two of the main challenges that need to be addressed are how to achieve the vision of timely care,[503] and how to ensure the effectiveness and cost-effectiveness of care systems. National strategies for dementia—such as those in the USA, France, the UK, the Netherlands, Sweden, and many other countries—all emphasise the need for a timely diagnosis.[504] More generally, these national policy frameworks aim to set out how to improve care and support, including strategies for implementation across health-care, social-care, and other sectors.

For many people with dementia and their families, timely access to care is the main priority. The EU-funded RightTimePlaceCare[503] and Access to Timely Formal Care (ACTIFCare) projects show how a timely diagnosis and timely care planning can facilitate care and help patients and their families to take control of their situation. Care that is inadequate or arrives too late is ineffective and can be a burden to some families, whereas too much care too early can create dependency and waste resources. The main arguments for diagnosis at an early stage are linked to care planning for the immediate future (providing appropriate care and support in the short term) and to planning across the life course (working with patients and their carers to prepare for the long-term consequences of the diagnosis).

A timely diagnosis of dementia[504] is necessary to arrange timely care; however, timely does not necessarily mean as early as possible (such as in a preclinical state) and it does not indicate mass screening programmes, which could lead to false-positive cases.[377] Indeed, one enduring challenge in the diagnostic process is accuracy, particularly in the transitions from normal cognition to mild cognitive impairment to very early dementia (section 6). Misdiagnoses can be enormously distressing: a false positive can have negative psychological consequences, whereas a false negative can lead to delayed support and care planning. At present, opportunistic screening for dementia might be a good alternative to mass screening—eg, by offering cognitive testing in a primary health-care centre.[504] The diagnosis rate of dementia varies within and between countries, but the tip-of-the-iceberg metaphor[505] seems appropriate. Increasing the rate of diagnosis is not only an issue of resources, but also a question of public awareness and attitudes.[12]

Although care is organised and financed differently across Europe, early detection of dementia and timely access to post-diagnostic support demands the presence of some kind of care infrastructure, including diagnostic resources, support programmes for people living at home, and resources for long-term care in (ideally) home-like institutions with staff available around the clock or as needed. Better understanding is needed about the multidimensional needs and related preferences of people with dementia and their families. Information and advice can help affected individuals to gain some understanding of the disorder and its consequences, and self-directed support—if it is available within a particular national or local context—can empower patients and their families to become active partners in care. The principles of person-centred care, in which the individuality of the person with dementia is acknowledged in all aspects of care and

treatment, are essential to improve quality of life for patients and their family members.[506]

The long-term formal care of people with dementia is demanding on staff time and therefore very costly. Long-term care refers not only to institutional provision, but also to (often quite intensive) support in community settings.[507] Most people with dementia, especially as their condition gets more severe, need support in IADL, basic ADL, and more general supervision, which overall can amount to a much heavier need than that in other chronic disorders in which cognition is not affected.[508] As the number of people with dementia grows and the funding of long-term care becomes a greater challenge, national governments will be forced to seek new strategies for sustainable long-term care.[507] However, an obvious tension exists between the need to contain future costs and the desirability to provide better education and training for care staff to improve the quality of care. Offering better working conditions and higher salaries to attract and retain high-quality care staff will push up costs unless that investment in human resources can reduce the risk of expensive admissions into institutions. A Swedish study showed that day care for people with dementia, provided by trained staff, reduced nursing-home admissions.[509] Formal-care support for family members and informal caregivers—such as day care,[510] respite care,[511] counselling,[512] and various case-management programmes[513,514]—is not only crucial for their quality of life, but can also represent a cost-effective use of resources.

Because most care at home is provided by family members, and in view of the high cost of maintaining current patterns of formal care into the future, efforts are needed to ensure the continued availability of unpaid carers. Recent and expected future demographic, social, and economic trends that have led to smaller families (and hence fewer potential child carers), greater geographical dispersion of families, and higher employment rates for women will add to the challenge of providing informal care for patients with dementia.[505] In addition to formal-care support, interventions are needed to help informal caregivers to manage the heavy personal burden of caring. Encouraging results have emerged from a support programme in England that offered a coping intervention to family carers of people with dementia: the intervention improved carer mental health and quality of life, and was cost effective.[516,517] The basic components of support from these studies ought to be reproducible in other country contexts. Counselling programmes can also help to improve the quality of life of informal caregivers and to postpone nursing-home admission.[512]

Policy statements such as those from WHO,[3,4] the G8 dementia summit,[173] and the European Parliament[5] are important for raising the profile of dementia and ensuring that it is high up on the political agenda, and national strategies and local dementia plans are important for turning high-level aspirations into the reality of care and support as experienced by individuals with dementia and their families. However, despite developments in recent years, research evidence to support the implementation of effective and cost-effective dementia care plans is scarce. More data are needed on the interaction between formal and informal care, on the interactions between different elements of health-care and social-care systems, on the funding challenges of integrated care, and on how best to ascertain and meet the preferences of individuals with dementia and their caregivers.

Summary and recommendations

The care of patients with AD and other dementias does not fit easily into typical health-care delivery systems, especially those that rely on the active involvement of patients. The long-term care of people with dementia often begins at home with a collaborative partnership between informal and formal caregivers. Institutional care for patients with severe dementia is demanding and costly, and little information is available about the transition (eg, in terms of costs and cost-effectiveness) between informal family care and institutional care. Patients' autonomy and ethical considerations (eg, meeting the potentially conflicting needs of patients and their caregivers) are challenges that need to be addressed as part of clinical decision making in dementia care. Worldwide, the burden of care often falls on family members, but effective assisted care and nursing homes with skilled staff will become increasingly important, especially in Europe, with shifting age demographics.

National policy strategies and implementation guidelines for dementia care—with the development of EU or global guidelines as a longer-term aim—are needed in all countries. Such frameworks should address at least the following points.

(1) Timely diagnosis of dementia should be a priority in the planning of care for patients. A timely diagnosis can help to ensure that people with dementia receive the right care at the right time.

(2) Wider availability of evidence-based post-diagnostic support and information programmes—such as counselling, day care, and respite care—is needed for people with dementia and their families and other carers.

(3) The aim of dementia care plans—including informal and formal care—should be to meet not only the basic physical needs of patients, but also the psychosocial and existential needs of people with dementia. Respect for patients' autonomy and acknowledgment of the contributions and needs of informal caregivers are important elements of good dementia care.

(4) Improvements in dementia care will depend on better coordination and communication between health-care, social-care, and other relevant sectors (eg, welfare benefits and housing).

(5) Programmes for case management and coordination need to be developed by different care providers to help people with dementia and their carers to access the services they need, when they need them.

(6) Local, regional, and national strategies are needed to recruit, educate, train, and retain staff skilled in dementia care.

(7) Action is needed to improve awareness of dementia among health-care and social-care staff, and across society more generally.

(8) Affordable long-term funding plans for dementia care that span health-care, social-care, housing, and other relevant sectors are needed.

Section 10. Ethical considerations

With expanding knowledge of the genetics (section 4) and biology (section 5) of AD, and innovation in the diagnostic and management options for patients (sections 6–9), new ethical issues require careful attention to ensure improved quality of life and wellbeing for this vulnerable group. These issues—which pertain to prevention, diagnosis, guidance in advanced-care decision making, treatment, and policy making—affect both research and care.

The rapidly growing number of people with AD and other dementias is leading to a substantial increase in expected health-care costs. The quest for sustainability in health care—in which health-care expenditures will need to be restricted—gives added urgency to the ethical and societal choices that have to be made for technical and psychosocial advances in dementia care. Here we focus on the ethical issues directly related to patients with pre-symptomatic AD, preclinical or prodromal AD, or AD dementia, their proxies, and the professionals delivering dementia care services (table 14). These issues are drawn mainly from the perspective of Beauchamp and Childress.[518] The principles they set out, which are internationally accepted as the framework for solving ethical dilemmas in health care, can be summarised as doing good (beneficence), not causing harm (non-maleficence), respecting patient autonomy, and striving for justice for all.

Linking these principles to the widely accepted paradigm of evidence-based medicine results in important messages for policy making. The first is that the introduction of new diagnostic tools should be assessed in terms of proven net benefit for patients, which extends beyond reaching sufficient added diagnostic value to realising the added value of being better informed and providing improvements in wellbeing. The second important message concerns shared decision making and efforts to maximise patient autonomy. Achieving maximum autonomy depends on a sound assessment of the patient's competency to consent, which should be a required skill for all physicians caring for patients at all stages of cognitive impairment. A diagnosis of dementia does not mean that a patient is incompetent, and patient involvement is desirable in all diagnostic and treatment decisions. The third key message is that management of end-of-life care and advance directives should be discussed at an early stage of the disease, irrespective of whether patients live in low-income, middle-income, or high-income countries. These ethical and public health questions could be a greater challenge in low-income countries, where the number of patients with AD is expected to grow most substantially.

Prevention and early diagnosis

As discussed in sections 2 and 3, evidence points to the potential of exercise, nutrition, and other lifestyle

	Patients	Proxies or caregivers	Professionals
Prevention	Are lifelong medication and lifestyle changes beneficial? Should recommendations be targeted to those at risk or extended to the population at large?	What are the effects of early risk assessment (eg, genetic, vascular, AD biomarkers) for dementia with respect to changes in work, family planning, behaviour of relatives, and insurance?	How long, extensive, and rigorous should prevention trials be? How can health-care providers be encouraged to advocate for appropriate changes (eg, lifestyle changes) to their patients?
Pre-dementia diagnosis	Is early biomarker or genetic testing beneficial? Should the whole family be tested genetically? Should a patient participate in prevention trials?	Should a person with a diagnosis of preclinical AD without symptoms be treated as a patient by his or her proxies? Should relatives also be tested for risk factors?	What is the added value of a pre-dementia diagnosis on the basis of biomarkers? How can shared decision making (between patients, family members, and clinicians) about the preferred diagnostic route be realised?
Diagnostic disclosure	What are the pros and cons of knowing *vs* not knowing the dementia diagnosis? Should truth telling be favoured over paternalistic protectiveness? Is earlier diagnosis beneficial?	Should relatives and other family members be made aware of the diagnosis, especially in the case of prodromal or preclinical AD?	How can advantages and disadvantages of a pre-dementia AD disclosure be balanced? How can stigma associated with an early diagnosis be minimised?
Management	Should a patient participate in drug trials? What should a patient continue to do independently and what should they not do (eg, driving)? How should a patient balance personal *vs* societal interests?	Should informed consent be given by proxy?	How should competency to consent be assessed?
End-of-life care	How and when should advance directives be realised? Should a patient have an advance directive, restricting use of health services? How active should a patient be in terms of end-of-life planning?	How can autonomy be maximised at home and after admission to an institution? When should active and supportive treatments be stopped? How can caregivers assist in good quality of dying?	How strictly should health-care professionals adhere to advance directives? When should active and supportive treatments be stopped? How can health-care professionals assist in good quality of dying?

Important questions for patients, proxies, and professionals. AD=Alzheimer's disease.

Table 14: **Ethical questions in dementia care**

changes to reduce the risk of AD.[519] Moreover, long-lasting drug trials such as the DIAN study have started to focus on prevention in people at high risk of AD. Several ethical issues need to be considered in the testing and implementation of prevention strategies for AD, including those related to genetic testing, which we addressed in section 4.

In clinical trials, vascular and lifestyle-related risk factors cannot be left untreated in placebo groups because there is already strong evidence that treatment of vascular risk factors and healthy lifestyle are beneficial for the prevention of cardiovascular disease and other health outcomes. In people who do not carry a mutation for autosomal dominant familial AD, dementia risk is the result of interactions between genetic and environmental factors (eg, effects of environmental risk factors are more pronounced in carriers of the *APOE* ε4 allele). Thus, the need for genetic counselling or genetics-tailored guidance as part of dementia risk assessment in trials, and later in clinical practice, needs to be considered.

Another ethical issue is deciding when sufficient evidence exists to start recommending specific prevention strategies, or to start informing and educating the general public about modifiable risk factors. Many potential risk factors cluster in groups with lower socioeconomic status (eg, low education, smoking, obesity, and suboptimum treatment of cardiovascular risk factors), and socioeconomic differences are increasing in many countries. Thus, how these risk groups can be captured by prevention programmes is an important challenge for the future. Importantly, efforts are needed to avoid blaming people with dementia (albeit inadvertently) for having had an unhealthy lifestyle, and to prevent false promises about the benefits of preventive interventions from being reported, especially in the popular media. Results from epidemiological studies are applicable at a population level, but translating them to the individual level is not simple because not all characteristics of an individual can be captured by the average characteristics of a group.

At present, the diagnosis of AD in clinical care is usually made at the dementia stage (section 6). In research studies, however, AD pathology is increasingly detected with the use of biomarkers well before dementia is clinically diagnosed, and even before symptoms of serious cognitive decline occur,[520] in line with the proposed NIA–AA[325–327] and IWG[328–330] research diagnostic criteria. These criteria cannot be used outside the realm of scientific research at present. Apart from the absence of knowledge about the predictive value of these criteria for the development of clinically overt dementia in an average outpatient population, insufficient evidence exists that early (prodromal) or preclinical diagnosis can improve patients' health and wellbeing.[521,522]

But the shift to pre-dementia diagnoses in clinical research, and the prospect of identifying at-risk individuals who might benefit from preventive interventions in the future, raise several important ethical questions. For example, should we inform people that they might be at a high risk of developing dementia when no effective treatment is available? To answer this difficult question, individual benefits need to be weighed against possible disadvantages. Once there is sufficient certainty about a diagnosis of prodromal AD, early disclosure can pave the way for timely psychosocial interventions that can ameliorate symptoms of dementia at more advanced stages, which might be more effective when started early. Early disclosure might also reduce the burden on carers by helping them to adapt to the cognitive and behavioural changes that occur during the natural course of dementia.[523] Moreover, knowledge about the risk of dementia can empower patients and carers to make important decisions about future treatment, care, and life in general (section 9).[524,525] However, the decision to enter a diagnostic process might be stressful and provoke anxiety, and could be harmful if it raises false expectations of a potential cure.[526] Pre-symptomatic diagnosis might also lead to early stigmatisation, and social and emotional isolation, and have important practical consequences for daily life (eg, implications for obtaining insurance or maintaining a driving licence).[526]

Few empirical data exist on the benefits of early (prodromal) or preclinical diagnosis, and benefits are likely to vary from person to person. People differ in how they cope with perceived cognitive decline, and in their needs and preferences for an early diagnosis. GPs' experience is that many patients do not want an additional diagnostic assessment when they present themselves with cognitive disorders in primary care.[525] Memory clinics and Alzheimer's centres are visited by a select group of people, most of whom are highly motivated to receive an early diagnosis and are willing to undergo all diagnostics available.[527] Clinicians need to explain clearly which tests add value to the diagnostic process, and which are obtained merely for scientific research. The external validity of results from studies in these selected populations is limited by referral bias. This bias might result in professionals implicitly assuming that this proactive approach represents the preference of all patients with memory complaints, thereby overlooking those who prefer a more conservative approach.

Gauthier[526] and Pepersack[528] propose a framework for diagnostic disclosure to reduce practice variation and improve average quality of care, which they divide into three phases. In the phase before disclosure, key objectives include determining whether the patient and his or her family members wish to know the diagnosis, identifying the coping style of the patient (defined as the ability to develop adaptive strategies in the face of emotional distress) and the psychological profile of the patient and his or her entourage (ie, carers or companions), and establishing the time and place where the disclosure will take place and the words that will be used to convey the diagnosis and related information.

Important elements for the disclosure phase include establishing what the patient and his or her family know about AD, using terms such as "Alzheimer's disease" or "memory complaints" instead of "senile dementia", and avoiding use of words such as "incurable". The diagnosis should be directed first and foremost to the patient, with the proviso that, should the disease be in its initial stages, the patient's family should not be informed of the diagnosis without the patient's consent. Objectives for the phase after the disclosure include ensuring that the information presented is understood by the patient and his or her family members, providing contact information for psycho-education programmes, and scheduling a follow-up meeting.

For the whole process of early, preclinical diagnosis and disclosure with the use of new techniques (eg, imaging and CSF biomarkers), doctor and patient together need to balance the potential benefits and costs before starting the diagnostic process. Before the specialty can reach this point in routine clinical care, new research frameworks for the evaluation of diagnostic tests should be applied, in which the value of a test is measured not only by its diagnostic accuracy, but also by how it affects patients' health and wellbeing.[529] In patient care, a tailor-made approach with shared decision making is the best way to meet the expectations of the patient and his or her family to prevent disappointment about the outcome of a diagnostic work-up and subsequent treatment. This tailored approach is not yet standard clinical practice, and great inter-doctor variability is present. Awareness of the patient's needs and expectations is a necessary precondition for shared decision making, and appropriate use of decision aids such as evidence-based outcome tables support this shared decision making with patient and family.[530] Cultural differences in weighing the principles of doing good, not causing harm, respecting autonomy, and giving all people equal opportunities for good dementia care might lead to different outcomes in shared decision making across countries.[531]

As long as evidence for a net benefit of preclinical diagnosis is lacking, efforts could be made to develop guidance for optimum decision making around pre-dementia (prodromal) diagnoses, taking into account the point of view of all involved (patient, proxies, clinicians, and other professionals). As early diagnosis is introduced into general practice, data should be gathered to understand the effects on quality of care, quality of life, and cost-effectiveness.

Competency to consent

Clinical assessment of competency to consent needs further consideration as more complex decisions have to be made about early diagnostic testing, treatments that are potentially harmful, and genetic testing, which also affects family members. Patients' competency to consent needs to be addressed when considering options for clinical management and in recruitment for research, but methods used in these different settings will have to meet different criteria. We focus on the assessment of competency to consent in research, as new ethical questions will be encountered first in experimental contexts. Adequate informed consent is the cornerstone of shared decision making, and because it is now well accepted that a diagnosis of dementia does not mean that a person is, by definition, incompetent to consent, methods are needed to assess capacity to consent on an individual basis. Classically, the following abilities are deemed to be necessary for a judgment of competency: first, ability to receive and understand information; second, ability to process information; third, ability to appreciate the situation and its consequences; fourth, ability to weigh benefits, risk, and alternatives; and fifth, ability to make and communicate a decision.

Several instruments are available for the assessment of competency based on the specific research question that motivated the assessment of capacity to consent, such as the Aid to Capacity Evaluation[532] and the MacArthur Competence Assessment Tool (MacCAT).[533,534] Other instruments are based on vignettes that provide a hypothetical description of a research situation, including elements that are generally thought to be crucial in decision making for dementia treatment, such as whether or not injections should be given or serious adverse events have taken place. Variation in the instruments available to assess competency to consent shows the substantial variation in routine practice in assessments for informed consent. On the one hand, a judgment can be made on capacity to consent in general; on the other, judgment of ability can be made for a specific situation.

Assessment of general decision-making capacity is still often used in clinical practice, although the mental functions needed for competency differ substantially depending on the complexity of the question at stake. Generally, helping the individual to understand specific research information as fully as possible, and checking whether or not they have understood the information (eg, by some standardised questions)—the basis of the MacCAT instrument—are prerequisites for a valid assessment of informed consent. Information should be compatible with the cognitive, visual, and hearing capacities of all patients, including the elderly, and sufficient time should be provided for the information process.

If an individual is judged unable to provide independently informed consent on a specific issue, proxy consent (eg, of a family member) or double consent (of patient and proxy) are good alternatives. However, provision of simplified information for the patient, and asking for verbal consent or assent, are always relevant. Patients' behaviour should be closely monitored, and in those who demonstrate objection or signs of refusal, any planned procedures should at least be reconsidered. Ultimately, application of the best competency-assessment instrument—which means asking the right

questions to check for competency on specific issues—should be combined with knowledge of the patient's personal hopes, beliefs, and history. Combination of these elements will give physicians and researchers the best chance of arriving at an ethically justified answer on any diagnostic or management questions raised, while maximising the patient's autonomy.

A range of complex issues in genetic testing were introduced in section 4. Participation in research projects can have a major effect not only on the participants themselves, but also on relatives' self-assessment of their health at present and their health prospects for the future.[535] At present, relatives do not have a role in the standard individualised informed-consent procedure for patients with dementia in most European countries. However, the question arises as to whether relatives' consent should be required, especially when diagnostic information disclosed as part of a study pertains to the dementia risk of research participants and their family members.[536] In the case of clinical genetic diagnostics in the research setting, an investigation of all family members at risk and all patients involved is generally preferred to provide an overview of the familial risk status and the different phenotypes present. Familial investigations of this type should directly involve the family in genetic testing, for which each family member has to give informed consent. If family members do not consent but participating patients do, data collection will be incomplete.

Properly addressing informed consent in people with AD is a routinely required but complex undertaking both in research and in clinical practice, and the optimum approach to informed consent should therefore be an obligatory part of the training for all physicians working with patients with AD. It is the first essential step towards shared decision making, which patients and professionals should try to establish in the face of dementia care dilemmas at each important stage during the disease trajectory.

End-of-life care

When AD or a dementia syndrome due to other causes is the main health problem at the end of life, increasingly complex dementia-specific treatment decisions have to be made in current practice. The increased level of autonomy that most patients and families strive for, together with increased societal awareness of dementia, will probably result in an important increase in ethical, political, and societal dilemmas around end-of-life care for patients with dementia. Patients, family members, and caregivers increasingly play an active part in the weighing of benefits and disadvantages of diagnostic and treatment proposals at the end of life. For physicians, it is increasingly relevant to personalise end-of-life care to do good, cause no harm, and safeguard autonomy as far as possible. Here, we focus on the decision-making process in the use of advance directives, because these directives could substantially improve the quality of end-of-life care, and are supported by reasonably strong evidence (see appendix for a systematic review of this topic). For the delicate debate on euthanasia and end-of-life care, we refer the reader to other papers.[537,538]

In advanced-care planning for patients with AD, a key example of what is often debated as appropriate-versus-unnecessary care is the delivery of artificial nutrition and hydration. Decisions on this question are among the most challenging of the various decisions that confront family members and physicians with regard to the medical care of patients with advanced AD.[526,539] Family members frequently state that non-initiation of such measures would amount to allowing their relative to "starve to death", leaving them with no choice but the placement of a feeding tube. However, the use of feeding tubes has not been shown to prevent or delay death, or to improve functional status, quality of life, or life expectancy, whereas it can cause dysphagia, aspiration pneumonia, and malnutrition.[540] Despite the existing evidence, many physicians still feel that such measures benefit patients with advanced AD.

Although completion of advance directives at an early stage of the disease is desirable, in the event that advance directives have not been drafted or are incomplete, decision making can be guided by a consensus-based approach that incorporates the patient's preferences, as stated or determined by close family members and others who know the patient well, the wishes of family members, and the opinion of the attending physician.[541] In the event of an impasse in this process, clinical ethics consultants or local clinical ethics committees could provide counsel and assistance. However, in most European countries, these services are not available at present in routine dementia care. Finally, it is imperative that end-of-life decisions, whether guided by advance directives or a consensus-based approach, are based on the principles to minimise harm and to maximise the patient's comfort.

Several international surveys show that most older people consider it relevant and desirable to have information on the health-related scenarios that can be expected in the course of the disease.[542,543] Advance directives are already widespread and routinely documented as part of hospital and nursing-home admissions. However, most elderly people in the community still do not have an advance directive, even though the benefits in this population—eg, having more control over future hospital care—will probably be the greatest. In older adults, a support service guided by primary-care professionals can lead to a substantial increase in the number of advance directives realised[544]—approaching almost full coverage of older adults in specific regions of the USA, Canada, and Australia with a 10 year tradition of advance-directive support in primary care.[545]

Advance care planning can have a large impact on the care supplied and on the wellbeing and quality of life of

patients and their carers.[546] For example, the Physician Orders for Life-Sustaining Treatment (POLST) form—which emphasises patients' wishes about the care they receive and is now a legally recognised approach to end-of-life planning in several states in the USA—has a substantial effect on the care provided to older patients, even though advance directives do not always result in care that reflects patients' preferences.[547,548] As hospital admission is usually stressful and acute or semi-acute, such advance care planning should ideally be implemented proactively in primary care. However, GP support in initiating and completing advance directives is not yet provided routinely as part of primary care in Europe; national support services that educate professionals (appendix) and supply them with evidence-based materials such as information leaflets and clear advance-directive forms might help to remove some of the barriers to the use of advance directives.

In the Netherlands, 5–10% of all elderly people in general practice currently have some form of advance directive or advance care planning.[548] In older people with advanced dementia and chronic obstructive pulmonary disease or another terminal illness, the number of directives rises to 10–40%.[549] However, in other European countries and beyond, the figures are probably much lower. In summary, the use of advance directives and advance care planning could be much improved as a crucial step towards better end-of-life management and palliative care in AD. An increase in the use of such directives could improve the quality of care, and reduce the use of limited health-care resources in realising the most appropriate care for patients with dementia.[550,551]

Summary and recommendations

Ethical considerations are important in dementia risk assessment, treatment, and routine care. The inherent loss of autonomy and competency that coincides with the clinical progression of AD and other dementias is a complicating factor. Ethical considerations can also raise important challenges for the design of clinical trials, especially in large clinical therapeutic trials in which regulatory organisations must work hand-in-hand with academic and industry partners. Bearing in mind the widely accepted framework for solving ethical dilemmas in health care—doing good (beneficence), not causing harm (non-maleficence), respecting patient autonomy, and striving for justice for all—and the need to link these principles to the paradigm of evidence-based medicine, we make the following recommendations.

For more on the **Horizon 2020 programme** see https://ec.europa.eu/programmes/horizon2020/

(1) For early diagnostic procedures in people at very early symptomatic stages, with cognitive complaints or cognitive decline, new research frameworks for the evaluation of diagnostic tests should be applied in which the overall benefits and disadvantages of a new diagnostic test are assessed from both the biomedical and the patients' perspective.

(2) Diagnostic disclosure at all stages of AD should always be based on an accurate diagnosis, and should be well structured, evidence based, and guided by quality indicators and teaching programmes.

(3) Assessment of competency to consent cannot be based on a diagnosis, staging, or neuropsychological testing alone, but requires an individual assessment that is specific for the decision to be made and undertaken with the aim of maximising patients' autonomy.

(4) End-of-life care in dementia can be improved substantially by advance care planning, which can improve wellbeing and quality of life in the latest stages of dementia. The use of advance directives should be discussed and supported as a routine part of primary care.

(5) Increased international collaboration both in research and in dementia care services will demand harmonised ethical standards and will push questions of informed consent and end-of-life decision making to a national or international (EU) level.

G8 targets: towards an international dementia data-sharing network

One of the main targets agreed at the G8 dementia summit is for researchers to work together and share data from their studies, including sharing initiatives for so-called big data (ie, the analysis of large datasets, mostly acquired by online tracking of a large population's behavioural patterns).[552] However, many obstacles need to be overcome in sharing research and clinical data for dementia research. For example, data sharing demands the safeguarding of relevant privacy and legal issues, the regulation of valid and trustworthy re-analyses, ethical conduct and transparency of conflicts of interest by sponsors, and a guarantee of high-quality research practice for the people who participate in trials and other research. Still, in view of the enormous challenges in the dementia health-care domain, data sharing is the only way to make progress and deliver the promises made by the G8 to our ageing societies.[553] Smart use of big data might answer the challenge recognised by the futurist John Naisbitt: "we are drowning in information, but starved for knowledge".[554]

The promotion of data sharing in the European call for research proposals through the Horizon 2020 programme should be applauded.[555] However, the EU is steering in the direction of effectively hindering secondary data use by requiring the approval of participants, with increasingly strict privacy legislation that makes no exception for research use.[556] With regard to dementia research, some points demand specific attention.

Challenges

The first challenge is to establish an international database for longitudinal studies on ageing and dementia, in which the harmonisation of data collection

across all research domains to be covered by the database is sufficiently addressed. As genetic, molecular, imaging, epidemiological, observational, and trial data are all important, this is a huge undertaking. Adequate, standardised description of the data and the characteristics of the setting in which these data are collected (ie, metadata) is crucial but not straightforward.[555]

The second challenge is to safeguard proper informed consent for this broad and gradually extending data application in people who might already have considerable problems with informed consent for the trial in which they participate. Participants' contributions to scientific progress should be facilitated, and they should have a right to innovation[556]—ie, all patients should be able to profit from scientific progress, and be allowed to contribute to research efforts if they want to or be sufficiently protected if they do not.

The third challenge is to organise the quality control and management of such an endeavour.[557,558] Interests of participating subjects, researchers, pharmaceutical and other companies, universities, research institutes, the general public, and society should be balanced, with transparency about the interests of all parties involved. This overall quality control is a prerequisite for high-quality, reliable research on big data to have the expected impact and value. Interests in the proprietorship of databases and the competitive demand to increase published output might hinder data sharing, and should be tackled with a smart and transparent management structure. The fourth challenge is to make the technical process of sharing data both feasible and safe, for research databases and clinical records.

The way forward

Despite these challenges, the effort is very much worthwhile and should be supported by the G8 and other countries. Data sharing has the potential to trigger changes to public health strategies, to support and improve the preventive strategies that already show promise,[93] and to allow breakthroughs in other research areas. These advantages are increasingly recognised throughout scientific communities, prompting 17 major European funders of public health research, coordinated by the Wellcome Trust, to draft a joint statement supporting public data repositories.[557] Importantly, the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort study has shown that large-scale data sharing is possible and, if done to the highest possible research standards with careful pre-planning, can be highly successful.[559]

Lessons have been learned from the Dutch National Care for the Elderly Programme in the Older Persons and Informal Caregivers Survey Minimum DataSet (TOPICS-MDS) initiative, a national data-sharing project that encompasses 64 research studies in elderly care.[560] To comply with data protection legislation, external users will be able to access a fully anonymised database only.[561] To circumvent issues related to publication rights and to prevent uses of the data for which they are unsuitable, selected members of the research consortium will assess all applications for secondary use for scientific feasibility and overlap with studies that are already planned or in progress. Rather than erecting barriers to secondary use, this brief assessment aims to improve secondary use because the goal is to identify potential synergies with studies that are already underway to connect applicants with researchers focusing on the topic, and to optimise the methodology of a proposed study to the possibilities offered by TOPICS-MDS. To further protect the interests of external users, to guarantee the involvement of patient representatives, and to improve the societal relevance of requests, a societal board has been established, which acts as a safeguard against preferential release of data and evaluates the societal relevance of proposals.

International data sharing in dementia research is challenging, but recent examples show that it is possible. However, the development of overarching research databases takes time, money, effort, and expertise. The establishment of an international dementia research network would help to support the exchange of best practices and experiences, and to produce international consensus guidelines on the subject. As the G8 countries underlined the importance of data sharing in dementia, a commitment to support financially and organise such a unique international dementia data-sharing network sets the framework for the ambitious goal of finding a cure within 15 years.

Conclusion and future European perspectives

AD is the leading cause of dementia, and because the primary risk factor for AD is old age, the prevalence of the disease is increasing dramatically as life expectancy increases worldwide. The explosion in care costs and associated societal burdens of AD and other dementias threatens to become overwhelming, even in resource-rich countries. However, AD is not an inevitable consequence of ageing, and further work is needed to identify modifiable risk factors and protective factors—including a range of lifestyle factors—that could form the basis of effective, feasible preventive interventions. Although no cure for AD exists and no therapeutic option is available to delay the inevitable progression of the disease, an emphasis on early detection and integrated, team-oriented, evidence-based care—with a focus on the physical, psychosocial, and existential health needs of the patient and support for informal caregivers—has the potential to improve the quality of life of patients and their families.

For more on the **ADNI study** see http://www.adni-info.org/

The pharmaceutical industry and government-sponsored research programmes, in partnership with multinational academic consortiums, have advanced several promising therapeutic leads but, overall, progress in the development of effective treatments for AD has so far been disappointing. Nonetheless, basic biomedical

For more on the **TOPICS-MDS initiative** see http://topics-mds.eu/

science has provided important insights into the genetics and biology of AD, and knowledge about the causes and pathological mechanisms of the disease could ultimately lead to the identification of new, valid therapeutic targets and the development of a cure.

AD research with human participants is extremely complex and expensive, partly because of the limitations of study design (eg, non-optimum outcome instruments), the absence of accessible biomarkers at early stages of the disease, and ethical considerations. Moreover, drug-development programmes now pose an unacceptably high financial risk to investors. But in the absence of a cure for AD and in view of the increasing financial and societal burden of dementia, policy makers and governments have a powerful incentive to provide more resources to develop therapeutics. Even minor advances to delay progression or ameliorate symptoms might have substantial financial and societal benefits. At present, several factors in Europe constitute bottlenecks to progress in basic, translational, and clinical AD research:

(1) Investment, funding, and human resources: in Europe, investment in AD research is low compared with that in the rest of the world and for other diseases.

(2) Fragmentation and poor coordination of research efforts: in Europe, research policy is set by the European Commission and by the 28 member states at a national level, whereas cooperation and collaboration are needed.

(3) Knowledge application: Europe must support innovation and introduce new methods and processes for promoting the application of research results in clinical practice.

(4) Research infrastructure: European research infrastructures should be strengthened—eg, with standardised imaging capacities, CSF analyses, biobanks, and databases to achieve more reliable data.

(5) Improvements are needed to help researchers build careers in Europe, with full freedom of movement within the EU.

Although much more basic biomedical research will be required to understand the biology of dementia, there is a clear need to develop and implement new approaches for pharmaceutical research and development to target AD and other dementias. In the context of current knowledge and available resources, no individual pharmaceutical company (or even an alliance of companies) is likely to be able to develop an effective therapy. Large clinical trials of drug candidates will continue to be extremely expensive and complex to plan and administer, and no clear strategy exists to mitigate risk when an emphasis on shareholder return predominates. Therefore, we advocate the formation of public–private partnerships in which large consortiums of pharmaceutical companies and public governmental agencies can deploy capital resources and share risk.

An alliance of EU health research agencies, in partnership with the pharmaceutical industry, will be able to assemble the required expertise and provide the capital necessary to initiate and advance large-scale programmes of drug discovery and development. Essentially all major clinical-trial initiatives in progress that target early-onset or familial dementia syndromes are USA led, with at least partial NIH support. A complementary European strategy could be extremely productive—perhaps to target sporadic cases in which the onset of symptoms occurs at older average ages. Such a strategy might be most effective with several therapeutic approaches tried in parallel, rather than the typical approach of successive linear trials with long individual timelines.

At the same time, a public health perspective should be systematised and viewed as a core principle in efforts to defeat AD and other dementias, rather than playing second fiddle to the search for a magic-bullet therapy. Would controlling known risk factors decrease the incidence or severity of AD? Do elderly people with normal cognition and mental function harbour protective factors such as antibodies against amyloid protofibrils? These types of questions can be addressed only through complex epidemiological studies, perhaps in combination with diagnostic testing in the setting of sophisticated public health networks. The infrastructure for such studies might already exist within the EU, and should be exploited to provide solid data that might lead to new approaches to mitigate disease or provide new targets for therapy.

In an environment of increased pressure to reduce public spending, options should be debated in an open forum with a well informed public constituency so that long-term strategic support can be assured. The funding of translational research, drug discovery, and patient-oriented clinical trials will need to extend beyond the time horizon of any individual political campaign, and the public should understand that long-term commitment is necessary. It is likely that treatment of dementia syndromes will become multidimensional, with combinations of treatments for a specific diagnosis, or several treatment options that depend on a particular molecular or genetic diagnosis. As an example, cancer treatment is now often patient-specific and cancer is no longer thought of as a single entity, but rather as a complex multifactorial constellation of disease, often with acute and chronic phases. Oncology centres have evolved to become clinical research enterprises where gene sequencing can be part of routine care. The future of dementia treatment might be similar, and will require systematic public investment to focus scientific biomedical resources, while not depleting basic clinical care and support. Dementia syndromes are insidious, progressive, and chronic, and the importance of evidence-based care and support cannot be over emphasised. Even quite low-cost innovations and interventions could have a huge effect on the quality of life of patients and their families and caregivers.

The science of disease biomarkers in AD and related dementias is still in its infancy. The discovery of informative biomarkers should be a priority. New biomarkers and diagnostic strategies to detect synaptic loss and apoptotic cell death in the central nervous system are urgently needed. The search for biomarkers could take place in large cohorts of patients, even independently of therapeutic options. At present, in most countries, payment for expensive diagnostic services is linked to the potential for treatment. For example, a diagnostic PET scan might not be indicated because the results would not be used to direct therapy, but more widespread use of advanced diagnostics—especially in the setting of the collection of metadata, including blood, CSF, and genetic analyses plus advanced memory, cognitive, and behavioural testing—might lead to better understanding of the natural history of disease and the stratification of dementia syndromes for the purposes of effective therapeutic trials. Of course, the ethical concerns about clinical-trial design for diagnostic and therapeutic modalities are paramount when informed consent cannot be readily or reliably obtained from participants, at least at more advanced stages of disease.

In summary, the use of effective strategies to prevent or cure AD and other dementias will demand an urgent reassessment of traditional paradigms of health-care practice. Although basic biomedical research initiated by individual investigators can lead to breakthroughs and important discoveries, and the pharmaceutical industry has had an unparalleled series of successes over many decades, a disease threat as large and complex as AD in an ageing population cannot be left to the fortunes of unfocused research programmes on the one hand, or to the whims of corporate risk–return business analysis on the other. A public–private partnership on a multinational scale is needed, and the EU is well positioned—in view of its excellent health-care delivery system, basic single-payer model, outstanding research infrastructure, and strong pharmaceutical industry base—to take the world lead, in partnership with international organisations, to develop new approaches to prevent or cure AD and other dementias and to provide models of compassionate care for patients with dementia.

Contributors

BW chaired the *Lancet Neurology* Commission. Together with GJ, AC-M, and TPS, he oversaw the collation of sections and did the final general editing of the paper. BW, GJ, and AW wrote the introduction. The executive summary was written by TPS, BW, GJ, and AC-M. Lead author for section 1 was LJ; AW and MKn contributed to the organisation, writing, and editing of the section. Lead authors for section 2 were LF and CQ, who contributed equally to the work; SA, CBr, and JG participated in the development, writing, and editing of the section, and HZ wrote the subsection "Traumatic brain injury and dementia". Lead authors for section 3 were MKi and FM, who contributed equally to the work; SA, HF, LSS, and BW contributed to the writing and editing of the section, and AW wrote the subsection "Health economics of dementia prevention". Lead author for section 4 was CG; CG and PA contributed equally to the section. Lead author for section 5 was AC-M; TPS, KI, LOT, and FJ contributed to the section. Lead author for section 6 was FJ; PS, GW, CBr, and AC-M contributed to the section, and CG wrote the subsection "Post-mortem diagnosis of AD". AN was lead author of the subsection "Use of biomarkers in AD diagnosis", with contributions from HZ (CSF biomarkers), BD, RS, GBF, and LOT. Lead author for section 7 was LSS; AC-M, BW, HB, HF, and MKi contributed to the section, and FM compiled tables 11–13. Lead author for section 8 was CBa; MKi, HB, DE, and SG contributed to the section. Lead author for section 9 was AW; DE, LJ, JG, SG, GW, and MKn contributed to the section. Lead author for section 10 and the systematic review of advance directives (appendix) was MOR; HB and SG contributed equally to the section. The section "G8 targets: towards an international dementia data-sharing network" was written by MOR and RM, who contributed equally to the work. The concluding section was written by TPS, BW, GJ, and AC-M.

Declaration of interests

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