Lancet Neurology Commission Paper

on

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

INTRODUCTION

Dementia includes a range of neurological disorders characterized by memory loss and cognitive impairment. The most common early symptom is difficulties remembering recent events. With the development of the disease, symptoms occur such as disorientation, mood swings, confusion, more serious memory loss, behavioural changes, difficulties in speaking and swallowing, as well as walking. Alzheimer Disease (AD) is the most common form of dementia (50-70% of dementia cases). Increasing age is the most important risk factor for AD.

In 2012 and 2015, the World Health Organization (WHO) presented reports suggesting that Alzheimer Disease and other dementias (ADOD) should be regarded as a global public health priority [1,2]. Similar policy declarations have been presented by the European Union [3], as well as by some individual countries. These policy declarations acknowledge trends that sometimes are described in terms of an epidemic or a "time-bomb". In 2015, the number of people affected by dementia worldwide is estimated to be almost 47 million and the numbers are expected to reach 75 million by 2030 and 131 million by 2050, with the greatest increase in low and middle income countries. The main reason for the increase is the global aging trend, since dementias are associated with a high age-specific prevalence, i.e., increasing prevalence with higher age. The global economic costs of dementia were estimated to be more than 600 billion USD in 2010 [6] and 818 billion USD in 2015[5]. The direct costs in the medical and social care sectors, 487 billion USD, represent 0.65% of the aggregated global gross domestic products (GDP), which is an enormous economic impact of a single group of disorders, especially considering that 87% of the costs occur in high income countries. Care of people with dementia impacts several sectors in the society with the social care (long term care and home services) and informal care sectors constituting the greatest proportions – even greater than direct medical care [6]. In cost of illness studies, European cost estimates in 2010 ranged between 238,6 billion USD [6] and 105,6 billion € [7].

However, the economic and societal burden of ADOD corresponds to the aggregate burden of people with dementia and their next of kin. The progressive nature of dementia can influence the whole life situation for families over many years. So far, no cure or substantial symptom relieving treatment is available for ADOD. Thus, the impact of this terminal disease is already today enormous, and given the predictions for the future, ADOD represents an enormous challenge for any society, and particularly to the ageing European society.

Further knowledge is needed regarding the causes of ADOD. A more complete understanding of the disease mechanisms is required for new diagnostic and therapeutic strategies. There is also a need to establish new cell-based and animal models representing, as far as possible, major clinical components of the disease. For some studies, post mortem brain material will be most important, as animal models are unfortunately not always relevant.

The global burden of AD and its economic ramifications coupled with the very slow progress towards finding effective treatments, leads to a call for a significantly larger investment in treatment research for AD as well as a broad public health approach towards disease prevention. There is an opportunity and need to shift the treatment development paradigm towards ascertaining stronger proof of concept before launching very expensive phase 3 trials, to developing multimodal combination treatment approaches, and to precompetitive data sharing to accelerate learning and improving the likelihood of success.

Today, there exists a considerable heterogeneity in awareness among politicians, family members, health care professionals and related stakeholder groups about all different aspects of AD. New knowledge from research should be more quickly translated into practice and disseminated broadly. In all education programmes, health care professionals should be made aware of best available evidence-based care. Our public sector representatives and policy decision makers are ultimately responsible for assuring that clinical and basic research advances are effectively implemented into public health policy. Such an aim demands that our research agenda should be broad and engage a wide range of sectors. Policy decision makers in Europe must support universal access to better diagnosis, care planning, and to evidence-based treatment; at the same time, European countries should implement disease prevention programmes, and incent the undertaking of drug development and clinical trials.

Target reader

In this Lancet Neurology Commission Paper, we want to inform, guide and stimulate the public debate. We have assembled the leading health care professionals representing the areas of health economy, epidemiology, genetics, biologics, diagnoses, treatment, care and ethics. They have contributed with their experience, knowledge and viewpoints. One key focus of this article is to inform policy decision makers in Europe to provide a firm basis for making proper decisions regarding best care and future research strategies for AD.

KEY MESSAGES [Panel 1]

Areas of great importance when addressing the increasing problem with AD:

- **Demographic situation and societal costs**
  - Increasing prevalence of Alzheimer's disease will lead to an explosion in care costs which risks bankrupting care systems even in wealthy countries

- **Universal access to**
  - Diagnosis, treatment and care
  - Participation in Clinical Studies
  - Databases, biobanks and data from finished clinical trials for researchers

- **Prevention of age-related cognitive impairment and dementia**
  - Lifestyle intervention(s)

- **Strengthened research efforts to**
  - Elucidate origin and mechanisms, and to develop relevant animals models for AD
  - Achieve research breakthroughs in basic AD biology, identify patient subtypes with homogenous etiology and prognosis

- **Awareness**
  - Information to the public society, and need to change perceptions of the disease
  - Education of general practitioners, paramedics, caregivers

- **Ethical considerations** regarding
    - Diagnostic standards in the light of lacking disease modifying treatment
    - Risk of false positive diagnoses
    - Revealing genetic status of/to patients
    - End of life decisions

THE HEALTH ECONOMICS OF ALZHEIMER DISEASE

Summary

The societal costs of AD will increase dramatically as the global prevalence (ie total number of demented persons) of AD is projected to double about every 20 years through 2050. Even though recent studies have shown a somewhat decreased incidence, we still see an increased prevalence due to the demographic development with people living longer. As opposed to other chronic diseases where direct medical costs predominate, only about 16% of AD costs are direct – the majority of costs are indirect, including care and societal costs. New approaches to diagnose and treat AD should be evaluated in the context of new paradigms for cost-benefit analysis to maximize resource utilization and improve quality of life for AD patients.

Current status

The global economic burden of AD

AD has considerable economic impact for each person and family affected. A 2011 study based on a multinational (Spain, Sweden, United Kingdom and United States) sample of 1222 patients, estimated that societal costs amount to about 1,000 GBP per month (14,500 EUR per year) in patients with a high level of ADL autonomy living at home, but rises up to 5,000 GBP per month (72,500 EUR per year) in patients requiring residential care. [8] The global prevalence of AD has been projected to almost double every 20 years, from 35.6 million patients affected globally in 2010 to 65.7 million in 2030 and 115.4 million in 2050 [9]. The economic burden of AD is therefore expected to increase dramatically in coming decades. The 2010 World Alzheimer Report estimates the global costs of AD at 604 billion USD. In 2014 the direct cost of AD for payers in the United States alone is estimated to 214 billion USD (http://www.alz.org/downloads/facts_figures_2014.pdf). For comparison, the global direct cost (resources used for prevention and treatment) and indirect cost (resources lost due to morbidity or mortality, such as lost work productivity) due to cancer was estimated to 290 billion USD in 2010, while the cost of diabetes was estimated to 472 billion USD, and the cost for all cardiovascular disease (including cerebrovascular disease) was estimated to 863 billion USD [10].

For diabetes the direct costs amount to 80% of the global economic burden of the disease (almost 90% in high-income countries). Indirect costs constitute a minority of the costs of diabetes. This result stems from the availability of effective medical therapy, both to manage glucose controls and prevent complications, and to treat complications when they occur. By contrast, in AD, only 16% of costs were direct medical costs, while 41.7% were informal care costs and 42.3% social care costs. Thus the costs

of AD are mainly driven by resources spent to compensate for lost function, rather than resources used for treatment or prevention. The global market for acetylcholine esterase inhibitors, the mainstay of current pharmacological treatment of AD, was just over 4 billion USD in 2011, or less than 1% of the total costs of disease [11]. This illustrates the absence of effective therapy for AD, but also the opportunity for new treatment options to provide benefit by improving health outcome and shifting costs from indirect to direct costs.

The costs of diagnosing AD

Insufficient diagnostic services remain a major barrier to patients with dementia receiving access to appropriate care. Although disease-modifying treatments are currently not available, timely and correct dementia diagnosis is a prerequisite for accessing important support services (e.g. living arrangements) and symptomatic treatment.

It is estimated that only 20-50% of patients living with dementia have a documented diagnosis in primary care, while the figure is substantially lower in low - middle income countries [12]. Based on data from the Swedish Dementia Registry /SveDem), the average cost of diagnosing a case of AD in primary care has been estimated to 753 EUR, while the corresponding cost in specialist care was 1,298 EUR in 2010 [13].

Table 1 presents an example from Sweden of the costs involved in diagnosing a case with AD and a calculation of the cumulative costs as each new diagnostic procedure is added, starting in primary care and transitioning to specialist care.

It should be noted that even though the maximal diagnostic cost (assuming all available diagnostic procedures are performed) is over 5,000 EUR, which is high compared to the costs of diagnosing other common chronic disorders for which diagnostic biomarkers are available (e.g. diabetes), this cost would only be a small fraction of the lifetime costs of care incurred by an AD patient.

The costs for individuals with dementia remaining undiagnosed are largely borne by caregivers and by patients themselves. With the possible future availability of treatment, early identification of AD pathology becomes even more important. The cost-effectiveness of treatment will depend on the strategy for identifying patients eligible for that treatment.

Indirect and intangible costs of AD

Measuring the costs for informal care (care provided by family members and other non-professional caregivers) is associated with methodological issues, both for the estimation of the amount of time and how this time should be valued. Studies have indicated substantial willingness to pay among caregivers for reductions in the time required for caregiving tasks between 59 and 144 GBP per hour depending on the country of study [14].

In addition to the direct and indirect costs of AD, the burden of illness of AD also includes the “intangible” cost of reduced quality of life and mortality. In health economic evaluations, this is often quantified in terms of quality adjusted life-years (QALYs, see box).

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 (*e.g.*, with Alzheimer's disease) are assigned a weight (health utility), calculated based on preferences for the health state. A weight of 1 signifies perfect health, while a weight of zero means the health state is equivalent to death. Weights below zero are also theoretically possible, indicating a health state worse than death.

Disability Adjusted Life Years (DALYs) is a construct that like the QALY summarizes morbidity and mortality into a single index. The number of DALYs is calculated as

DALY=YLL+YLD

YLL (years of life lost) corresponds to the number of deaths multiplied by the standard life expectancy at the age at which death occurs. The formula for YLL (without including social preferences), is

YLL = N x L

where:

N = number of deaths L = standard life expectancy at age of death in years

To estimate the years of life with disability (YLD) for a particular disease over a certain time period, the 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 is the following (again, without applying social preferences):

YLD = I x DW X L

where:

I = number of incident cases DW = disability weight L = average duration of disease

Utility weights for disease states with AD have been calculated with the Health Utility Index (HUI) ranging from 0.69 in mild disease to 0.14 in terminal disease [11]. Using a different instrument, the EuroQoL EQ-5D, weights have been estimated ranging from 0.69 in mild dementia to 0.33 in severe dementia [15]. For comparison, population mean utility weights in the age group 65-74 years is 0.78 and the utility weight for legal blindness has been estimated to 0.26[16]. The DEMQoL instrument was, unlike the HUI and EQ-5D, specifically developed to measure quality of life in dementia, and a tariff linking responses on the DEMQoL to health utilities has been developed [17] . Most studies have relied on proxy assessments of the health status of AD patients. The agreement between patient and proxy ratings with the EQ-5D and DEMQoL have varied in different studies, however agreement is generally poorer in severe disease states. The quality of life of caregivers themselves may also be affected; studies have indicated an increased prevalence of depression in caregivers to patients with AD [359]. However, no direct link between caregiver health utilities and the severity dementia in the patient they care for was seen, using the EQ-5D [15]. More specific and sensitive instruments may be required to measure the potential disutility associated with caregiving.

WHO has estimated the disability weights for mild dementia: 0.082, moderate dementia: 0.346 and severe dementia: 0.438 (ref: WHO methods and data sources for global burden of disease estimates 2000-2011, (http://www.who.int/healthinfo/statistics/GlobalDALYmethods_2000_2011.pdf). On this scale, zero (0) equals no disability and one (1) equals complete disability. In 2012, AD and other dementias were estimated to cause 18 million DALYs globally. This is just 0.7% of all DALYs, however in European women aged 70+, AD causes 6% of DALYs '(WHO health statistics and information systems, estimates for 2000-2012, http://www.who.int/healthinfo/global_burden_disease/estimates/en/index2.html).

Assuming the QALYs lost would be equivalent to the number of DALYs, and valuing each QALY at 3 times the gross national product (GDP) per capita, the intangible cost of illness of AD and other dementias is 550 billion USD (**Table 2**). Thus the intangible cost of dementia might be almost as high as the total direct and indirect costs of care for AD. This is consistent with previous estimates indicating that intangible costs for non-communicable diseases may be close to the direct and indirect costs (according to World Economic Forum: the Global Economic Burden of Non-communicable Diseases, http://www3.weforum.org/docs/WEF_Harvard_HE_GlobalEconomicBurdenNonCommunicableDiseases_2011.pdf)

Current challenges and future goals

There is a strong imperative to attempt to reverse current course of increasing incidence and morbidity from AD by way of new treatment modalities and strategies for prevention and care. Projections of future burden of illness can underestimate the effects of introduction of new medical technology. In the case of AD, the main source of technological change over the foreseeable future is expected to come from the potential introduction of new treatments. Clinical trials are currently ongoing with several compounds with the objective of demonstrating a reduction in the decline of cognitive function and the progression of ADL disability, or the progression from preclinical states to AD dementia.

As new options for diagnosing and treating AD become available, these will undergo two stages of evaluations: the first by regulatory agencies to determine benefit/risk, and the second by Health Technology Assessment (HTA) agencies and payer organizations to determine value relative to 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 sufficient degree of certainty in order to make correct coverage decisions at the time these are introduced. If a new treatment receives regulatory approval but faces negative reimbursement decisions due to inadequate demonstration of value, uptake of the new treatment will be minimal and patients and caregivers will miss out on the potential treatment benefits.

A major issue in demonstrating the value of new treatments for AD is that the benefits of such treatments will largely fall outside of the health care sector, since most of the potentially preventable costs of dementia relate to long-term care and burden on informal caregivers. It is common that budgeting constraints prevent funds from flowing freely between “silos,” so that for instance savings due to reduced need for long-term care could be used to finance increasing costs for drug therapy. It is very likely that increasing availability of treatment options for AD will require increasing medical expenditures, at least in the short term. Reductions in the need for informal caregiving will benefit

caregivers but this does not appear on any budget and cannot easily offset treatment costs. Further, funding decisions sometimes adopt a short time horizon or apply discounting (by which the value of future costs and effects is decreased to reflect negative time preferences), which reduces the value of future costs and benefits. A new therapy with the potential of changing the long term course of Alzheimer's disease will likely require substantial upfront investments in diagnosis and drug costs, while the full benefits may take years or decades to realize.

The main value of therapies affecting the long-term course of disease will lie in shortening the time spent in the severe stages of dementia. However, this is not an outcome variable that is being studied in trials of new drugs. Rather, this 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 on disease progression rates, costs and health outcomes. Several epidemiological studies have followed patients with AD longitudinally from diagnosis until the end stages (Swedish National Study on Aging and Care (SNAC), EADC-ICTUS, *etc*). Much less data are available from the very early phases of AD, before the onset of dementia. As new therapies are being evaluated in preclinical states of dementia, new data sources are needed to model accurately the long-term benefits of these treatments.

The results from economic models are highly contingent on assumptions around 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[18]. If treatment improves survival but prolongs the time spent in with severe dementia, it might only bring 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 can be substantial. Thus, the goal of therapy is not merely to slow disease progression, but to minimize the time spent in a severe dementia condition and maximize the time with conserved cognitive resources, ADL independency and quality of life.

In addition, patients receiving new therapies will need to be followed in clinical practice, and data collected on resource use and health outcomes in order to gain further understanding of the value provided by new treatment options as they are being implemented in practice. Few countries have infrastructure to follow patients prospectively (e.g., the Swedish National Dementia Registry [18]). The data collected may not immediately be relevant for other countries due to important international differences in dementia care organization and delivery; observational studies collecting data across several countries is an important addition; one example is the ICTUS study, organized through the European Alzheimer's Disease Consortium (EADC).

RECOMMENDATIONS

- Economic evaluations of new methods for diagnosing and treating AD should include all elements of costs, and adopt a broad measure of outcome that captures full societal benefits of treatment.

- Accurate, reliable and timely diagnosis is a requisite for providing cost-effective care with currently available therapies and of key importance for realizing the potential value of novel

disease modifying therapies. The cost-effectiveness of new therapies will be uncertain at the time they are introduced, since there is limited experience of long-term benefits while up-front treatment costs can be substantial.

- Follow-up with routine data collection in clinical practice on resource utilization and patient-relevant outcomes will facilitate the evaluation of treatment benefits and cost-effectiveness in clinical practice.

ALZHEIMER'S DISEASE AND DEMENTIA IN THE POPULATION: EPIDEMIOLOGICAL ASPECTS

Summary

Additional epidemiologic surveillance is required to provide a complete picture of the epidemiology of dementia in Europe and worldwide. AD accounts for up to 70% of all dementia cases in most studies, but more information about stage, clinical progression and risk factors is needed. Temporal and geographic studies should be extended. AD is an age related disease developing over time, but it is not an inevitable consequence of aging – up to 50% of people reaching age 90 are free of dementia. More work is needed to understand why.

As stated in the introduction, dementia is a disabling syndrome characterized by progressive deterioration in multiple cognitive domains that is severe enough to interfere with daily functioning, including social and professional functioning [19]. Thus, dementia has an enormous impact on daily life of patients, their families, as well as on the society.

The burden of AD or dementia, which is projected to surge in the coming decades, poses a serious threat to the sustainable development of economy and social welfare system of the European society, along with continuous increases in the ageing population. Epidemiological studies generate knowledge concerning occurrence (e.g., prevalence and incidence), distribution (e.g., demographic, geographic, and temporal variations), determinants (e.g., genetic and non-genetic risk or protective factors), health economics (e.g., costs of health care and cost-effectiveness of treatment and intervention), and intervention strategies (e.g., therapeutic and preventive intervention) of AD and dementia. In the European Union (EU) countries there is a rather good knowledge about the number of people with dementia, but there are less data on the prevalence of dementia in the Eastern European countries **(Figure 1)**. Such knowledge is critical for policy decision makers to cope with the challenges of the devastating disorder because it will help design and develop care and social welfare system, and appropriately relocate the limited resources for care of people with the disease.

In the past decade, the work of the 10/66 Dementia Research Group has helped to better understand the epidemiology of dementia in middle- and low-income countries such as Brazil, India, and China [20-22]. The age-standardized prevalence of dementia for people aged 60 years or over is 5%-7% in most regions of the world. Recent systematic reviews and meta-analyses provide more precise global and regional estimates of dementia prevalence [3,23,4,24]. These analyses also demonstrate rather similar

patterns of age-specific prevalence of AD and dementia among worldwide regions, although substantial variations are evident among oldest old groups [4,24,25,26] (**Figure 2**).

Given the diversity in social service system and economic development across Europe, there is a strong need for epidemiological studies on dementia and AD in Eastern and Middle European countries to complete the picture [27,28]. In addition, higher prevalence and incidence of dementia and AD in women than in men, especially among the oldest old, have been reported in numerous studies in Europe and Asia, although finding of the gender difference has been less consistent in studies from North America [29].

Although AD diagnosed by current clinical criteria contributes to 60-70% of all dementia cases, autopsy-verified studies have suggested that mixed dementia owing to cerebral mixed vascular and neurodegenerative pathology accounts for the large majority of all dementia cases. In addition, early-onset AD that occurs before 65 years of age accounts for up to 5% of all AD cases. Early-onset familial AD is a rare form of AD caused by mutations in presenilin (PSEN)-1, PSEN-2, and amyloid precursor protein (APP) genes [30]. Non-familial (sporadic) early-onset AD often has no reliable family history, and may have a later onset of AD than familial early-onset AD [31]. Late-onset sporadic AD is the most common form of AD, accounting for about 90% of all AD cases. Late-onset AD is a multifactorial disorder that involves multiple biological mechanisms in which genetic susceptibility (e.g., APOE ε4 gene), environmental factors (e.g., psychosocial, lifestyle, and biological factors), and their interaction over the lifespan contribute to the pathological processes and clinical expression of the disease.

As mentioned above, the costs of care for patients with dementia largely depend on disease severity[32]; patients with mild dementia have very different medical and social needs than those in more severe stages. However, prevalence data of dementia according to severity or stage are scarce. [33,34]

Living with dementia

Numerous population-based studies have suggested that people aged 65 years or above survive an average of three to nine years after a diagnosis of dementia, while some live as long as 20 years [35-43]. Clinical deterioration of people with dementia, and with AD in particular, is progressive, although the rate of decline in mental and physical function may vary. According to the WHO, in general, people with dementia can be expected to be in the mild or early stage of dementia (e.g., forgetful, some difficulty with language, and mood changes) for the first year or two, in the moderate or middle stage (e.g., very forgetful, increasing difficulty with speech, and need help with self-care activities) for the second to fourth or fifth years, and in the severe or late stage (e.g., serious memory disturbances and nearly total dependence and inactivity) for the fifth and more years [23]. Data from the Kungsholmen Project of community-dwellers aged 75+ years in central Stockholm suggest that people with incident dementia spend approximately a few months in the very mild dementia stage, two years in the mild phase, one to two years in the moderate, and one year in the severe stage [44]. Women with dementia live longer than men, owing to a longer survival in the severe stage [44,45]. It has been estimated that more than 50% of dementia cases reach the severe stage within three years. A population-based study of prevalent dementia cases showed an increase in the proportion of severe dementia from 19% at baseline to 48% after three years, and to 78% after seven years [46]. By contrast, a population-based prospective Cache County study of dementia progression found that a significant proportion (40-50%) of patients with incident AD deteriorate slowly in cognitive and functional ability (e.g., 1-point decline per year on MMSE score and clinical dementia rating sum of boxes) [47]. In spite of numerous studies

[46,48-51], the effect of cognitive decline on specific tasks of self-care activities of daily living (ADL) (e.g., eating, dressing, and toileting) or instrumental ADL (e.g., shopping, cooking, and basic housework) is still not completely clarified, owing largely to relatively short periods of follow-up for most studies [52-54]. Furthermore, the knowledge concerning the effect of potential compensatory factors (*e.g.*, social engagement, cognitive training, and mentally-stimulating activity) is still very limited.

In many countries, the health care policy aims at avoiding or postponing admission of patients with dementia to nursing homes and institutions; informal care (*e.g.*, home care provided by families and friends) as compared to formal care (*e.g.*, care provided at nursing homes or institutions) tends to be less costly for the social security system[55], although this may be not true when the costs are assessed from the society perspective [56]. In addition to the health and social care policies, the proportion of people with dementia living at home varies depending on several factors, mainly linked to characteristics of patients (*e.g.*, severity of cognitive and functional disability) and caregivers (*e.g.*, perceived burden and coping strategies), and cultural aspects.

Worldwide, the majority of people with AD or dementia are cared for at home, usually by a spouse or a daughter. The proportion of people with dementia living at home is higher in low and middle income countries than in high income countries, and in rural rather than urban areas. In high income countries, the estimated proportion of people with dementia living at home is around 66%, compared to approximately 94% in low- and middle-income countries [57]. A longitudinal study from Australia found that several baseline clinical features of dementia predicted a shorter time period until institutionalization, such as lower cognitive and functional ability, more neuropsychiatric symptoms, and use of antipsychotic medications [58]. Moreover, greater deterioration in these factors within the first three months after baseline also predicted faster time until institutionalization, which indicates that rate of disease progression is an important factor.

Dying with dementia

Several follow-up studies have consistently shown that dementia shortens life-expectancy, depending on age of dementia onset, gender, and dementia subtypes [45]. 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 the age of 90 years, around 60% of people died with dementia or severe cognitive impairment [59,60]. Finally, not only does dementia shorten life expectancy but a subtle decrement in global cognitive function, even in the absence of clinically recognized impairment, is strongly associated with shorter survival [61].

It has been estimated that the potential years of life lost (YLL) due to dementia in subjects over age 75 varies from three to five years[44,45]. A Swedish study of people aged 75+ suggested that the impact of dementia on lifespan (YLL, 3.41) is similar to that of cardiovascular disease (CVD) (YLL, 3.58), but is lower than cancer (YLL, 4.40) (**Figure 3**)[44]. The mortality in people with dementia or CVD is two times higher than the mortality in subjects without those disorders, whereas people with a diagnosis of cancer have a three times higher mortality risk compared with people without cancer [44]. Further, the estimated years lived with or lost due to one of those disorders is most dependent on the age at diagnosis, being higher among the younger old people (75-84 years of age) than in the oldest old group (85 years and above). This is supported by a recent study showing that the mortality risk for AD was higher for younger old ages than for oldest old people (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 been improved in the last 2-3 decades, owing to increasing awareness of the disease by health professionals and the public. The contribution of dementia to mortality is difficult to assess based solely on death certificates because dementia is rarely considered as an immediate or an underlying cause of death in death certificates [63]. Indeed, older people often experience different chronic and acute illnesses that may be related to the dementia process [64] but may be the 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 ages 75+, and that in the US, AD may contribute to close to as many deaths as heart disease or cancer [62]. Similarly, the US nationwide study estimated that among individuals aged 65 years or older, deaths with AD comprised 32% of all deaths in 2010, with the proportion being projected to reach 43% by 2050 [65]. According to the 2013 Alzheimer's Association report, AD was the sixth leading cause of death across all ages, and the fifth leading cause of death for people aged 65+ years in the USA [66]. In UK, the rank of the age-standardized YLL for AD increased from the 24th in 1990 to the 10th in 2010 [67]. When death with dementia is examined, the proportion of deaths attributable to dementia reached approximately one-third in persons aged 85+ years [68].

Temporal and geographical variations

Studying the secular trends and geographic variations of dementia occurrence and their determinants is crucial for policy development in a world facing a rapid increase in absolute number and proportion of older adults in the population. Thus, there has been increasing interest in investigating the time trend of dementia occurrence (*e.g.*, incidence and prevalence) (**Table 3**), as well as possible geographic differences of dementia distribution in the past few years. Although findings from various regions across the world have not been consistent, 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 [69,70]. Identifying temporal and geographical variations in prevalence and incidence of dementia may help identify modifiable risk or protective factors for the dementing disorders.

North America. In North America, a decline in prevalence of dementia and cognitive impairment has been reported in a few studies from the US [71-73], and another study suggested a stable age-adjusted prevalence of dementia and AD in African American people aged 70+ from 1992 to 2001 [74]. In addition, several population-based studies from the US have also shown a decline (2-3% per annum) in incidence of dementia and AD from the 1990s through the 2000s [75,76].

Europe. In Europe, two population-based surveys in Sweden showed a relatively stable prevalence of dementia over the last 2-3 decades [68,77]. The repeated cross-sectional surveys conducted in 1988 and 1994 in Spain suggested a stable prevalence of dementia in women but a decreased prevalence in men [78]. Finally, the large-scale study from the MRC CFAS provided evidence that a cohort effect might exist in the age specific prevalence of dementia among the 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 [79]. However, the MRC CFAS found no evidence of variations in incidence or prevalence of dementia among five regions in England and Wales. A systematic review did reveal evidence of geographical variations in the prevalence or incidence of dementia and, specifically, a higher risk of AD in rural as opposed to

urban areas [25]. Studies from the Netherlands, Sweden, and England also are suggestive of a trend of declining incidence of dementia in the communities [68,79,80].

Asia-Pacific region. In mainland China, the prevalence of dementia and AD increased steadily across all age groups of people aged 55 years and older from the 1990s to 2010 [81], although the trends might be partly due to the methodological variations over different time periods (*e.g*., diagnostic criteria, range of age, and sampling methods) [82]. The number of people with dementia was estimated to increase by 63.5% from 2000 to 2010 in China, compared to an average 46.5% increase worldwide during almost the same time period [4,24], largely owing to a faster pace of population ageing in China than the worldwide trend. The rural and urban difference in prevalence of dementia and AD is supported by a large scale study from China [83], suggesting that early experience or exposure to rural living (*e.g*., low education and SES) may contribute to the association between rurality and an increased risk of late-life dementia and AD. In Hong Kong, China, the systematic review revealed that the prevalence of clinically diagnosed dementia among community-dwelling people aged 70 and above increased from 4.5% in 1995 to 9.3% in 2005-2006 [84]. In Japan, the population-based Hisayama Study 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 [85]. After all the methodological variations were carefully evaluated, the increasing trend in the prevalence of dementia in Japan was confirmed by a systematic review [86]. This suggests that earlier estimates of dementia burden and long-term trend in the world, especially in the Asia-Pacific region, are likely to be underestimated [87].

Given the numerous factors that can affect estimates of the occurrence of dementia, it is not a surprise that temporal trends of dementia may vary within and among countries. For instance, the upward trend in prevalence of dementia from the 1990s to 2010 in China is consistent with the time trends of prevalence of stroke and ischemic heart disease and related lifestyle and metabolic risk factors (*e.g.*, smoking, physical inactivity, obesity and overweight, hypertension, and diabetes) over the similar periods, [88] together with a faster 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 (*e.g.*, smoking cessation and physical activity), improved management of cardiovascular risk factors (*e.g.*, hypertension and high cholesterol), and a reduced risk of stroke and heart disease have had a great effect in reducing the risk of dementia and AD, possibly by reducing number of brain lesions, thus preventing and delaying the onset of dementia in the general community [79,89]. In support of this notion, the Rotterdam study has provided evidence that the suggested decline in dementia incidence over time might be due to less brain atrophy and less cerebral small-vessel disease [80].

The new evidence for the temporal trend of 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 stayed constant. Even for regions such as Europe with evidence of declining prevalence or incidence, future burden of dementia is still likely to increase because the ageing population in Europe will continue to increase.

Dementia is not an unavoidable consequence of ageing

Not all nonagenarians, nor even centenarians develop AD or dementia [90,91], which implies that some people are able to reach very advanced ages while escaping severe mental deterioration. Neuropathologically, the population-based 90+ Autopsy Study of people aged 90 and older in USA found that nearly half of people with dementia did not have sufficient neuropathology in their brain to explain their cognitive symptoms [92]. On the contrary, intermediate or high Alzheimer pathology was present in about one-third of very old people without dementia or cognitive impairment [93]. Furthermore, the association between pathological hallmarks of AD (*e.g.*, neurofibrillary tangles and neuritic plaques) and clinical syndrome of dementia was less strong in oldest old persons than in younger old persons [18,94]. These findings imply that by providing brain reserve and cognitive reserve, certain compensatory factors (*e.g.*, high education, social engagement, and maintenance of cardiovascular health) may play a part in allowing people to tolerate a significant amount of Alzheimer pathology until very old without manifesting obvious dementia syndrome, even in carriers of the susceptibility genes such as APOE ε4 allele [95].

Risk and protective factors

Dementia, including AD, is a multifactorial disorder that is determined by the interplay of genetic susceptibility and environmental factors over the lifespan (**Table 4**). Older age is the strongest risk factor for dementia, and patients developing dementia before age 65 owing to gene mutations account for only a very small proportion of all cases (~5%). The majority of dementia and AD cases are at least partly contributable to cardiovascular risk factors (e.g., hypertension, diabetes, and obesity) and psychosocial factors (e.g., education, social engagements, and leisure activities), which represent the major modifiable factors that can be targeted for interventions. The qualitative and quantitative effects of most of these factors on AD and dementia have been evaluated in numerous systematic reviews and meta-analyses. [96,97]

(1) *Lifestyle-related cardiovascular risk factors*; Smoking is associated with a 50-80% increased risk of dementia; even second-hand smoking could increase risk of dementia. Diabetes in middle age or later in life increases risk of not only vascular dementia but also AD by about 50%. On the contrary, light-to-moderate alcohol consumption has been associated with a 30-40% reduced risk for dementia. Likewise, regular physical activity, even low-intensity activity such as walking, may reduce dementia risk by approximately 40%. Of note, systematic reviews from the life-course perspective have revealed age-dependent associations of dementia and AD with major cardiometabolic risk factors, such as hypertension, high cholesterol, and obesity or overweight, such that having these factors in young adulthood or middle age (e.g., age <65), but not necessarily in late life (e.g., age ≥75), is associated with an increasing risk of dementia and AD; low levels of these metabolic factors in later life may represent part of the prodromal dementia. These findings have significant implications for public health because it indicates the optimal time windows (e.g., young or middle ages) for intervention targeting these factors in order to be effective in delaying the onset of dementia. More importantly, population-based studies have also shown that concurrently having multiple cardiovascular risk factors (e.g., smoking, hypertension, diabetes, and hypercholesterolemia) at middle age or several years prior to dementia onset incrementally increases the risk for dementia and AD [98]. Risk indices at middle age or later life

for predicting risk of dementia have been developed and validated, with the accuracy ranging between 70% to 80%, in which unhealthy lifestyle and cardiometabolic risk factors constitute major part of the indices [99-103]. This implies that intervention targeting multidomains is likely to be more effective in delaying dementia onset.

(2) *Psychosocial factors*; High educational achievements in early life have been consistently associated with a reduced risk of late-life dementia and AD in numerous studies[104] . Cognitive activity or mentally-stimulating activity (e.g., reading, doing crossword puzzles, and playing games), which may be related to early life education, also has shown protective effect against dementia. Rich social network and social engagement are associated with a decreased risk of dementia. Finally, the temporal relationship between depression and dementia in older people remains debatable, but evidence from long-term follow-up studies has emerged that depression may act as a risk factor for dementia and AD[105,106].

Potential pathological mechanisms

In the last decade, population-based neuroimaging and neuropathological studies have significantly contributed to the understanding of pathophysiological mechanisms of cardiovascular risk factors and psychosocial factors in AD and dementia. Evidence from the multidisciplinary research supports the vascular mechanisms and reserve hypothesis to be involved in the development and clinical manifestations of dementia and AD. This has significant implications for preventing or postponing onset of dementia because the two pathways can be targeted for intervention.

Vascular mechanisms. It is well known that major cardiovascular risk factors (*e.g.*, hypertension and diabetes) cause cerebrovascular lesions. Recent research also provides evidence that these factors may contribute to global and regional brain atrophic lesions and neurodegenerative pathologies[107-109]. Biologically, cerebral atherosclerosis and neurodegeneration may share common mechanisms, such as oxidative stress, inflammation, and toxic beta-amyloid peptide (Aβ) deposition. Intracranial atherosclerosis could also induce cerebral hypoperfusion and trigger accelerated deposition of Aβ, which in turn contributes to cognitive deterioration and dementia[110]. Furthermore, cerebral macro- and microvascular and neurodegenerative pathologies may represent coinciding processes in ageing that converge to cause additive brain damage, and thus to promote clinical manifestation of dementia syndrome[111-114]. This is supported by numerous neuroimaging and neuropathological studies, which show that the majority of clinically diagnosed dementia and AD cases among older persons living in the community are due to mixed vascular and degenerative pathologies in the brain [115-117].

Reserve hypothesis. Psychosocial factors, such as social network, social engagement, and cognitive activities may postpone the onset of the dementia syndrome by increasing cognitive reserve capacity, such that older people with higher cognitive reserve need more pathology in the brain than those with lower reserve to express symptoms of AD and dementia. Neuropathological studies have shown that education, cognitively-stimulating activity, and social networks modify the association of neurodegenerative pathologies to cognitive function, such that cognitive function remains higher in subjects with a heavier burden of global neuropathology if they also have high education or rich social networks [118-120]. These studies illustrate that psychosocial factors, such as high education, mentally-stimulating activity, and rich social networks, could compensate for the deleterious effects of cerebrovascular and Alzheimer pathologies on cognitive performance in ageing.

Public health implications

A 2010 NIH state-of-the-science review concluded that firm conclusions cannot be drawn about the association of any modifiable risk factor with cognitive decline or AD [121]. Indeed, extant studies have been hampered by methodological issues, such as self-reported measurements of exposures, inconsistent control of relevant confounders (e.g., depression), and variations in diagnostic procedure and criteria of dementia and AD [122,123]. However, a different scenario would have emerged if the evidence was evaluated from a life-course perspective (i.e., early life, middle age, and later in life) [97]. For instance, a systematic review of epidemiological studies on seven modifiable risk factors (*e.g.*, low education, smoking, diabetes, midlife hypertension, midlife obesity, depression, and physical inactivity) suggested that a 10% reduction in exposure to these risk factors could potentially prevent up to 1.1 million AD cases worldwide [96]. Therefore, the life-course approach should be kept in mind when designing any intervention programmes [124]. It has been suggested that some intervention measures (*e.g*., pharmacologic control of hypertension), if implemented in middle-aged or young-old adults, may be effective in reducing the incidence of dementia[125]. Thus, although age remains the major driving force for dementia development [126], current evidence tends to support the notion that interventions targeting multiple modifiable risk factors, if implemented earlier in life, may be more promising in reducing the risk or in postponing the onset of dementia [29] , and several intervention studies to assess effect on disease onset are ongoing in Europe [127]. It has been estimated that delaying the onset of dementia by five years would halve prevalence of dementia and substantially decrease the number of dementia cases in the community; delaying the onset of dementia by even two years also would have significant public health, economic and societal benefits [128]

Traumatic brain injury and dementia

A systematic review found no convincing evidence supporting an increased risk of AD or dementia following mild traumatic brain injuries[129]. However, several epidemiological studies have suggested that a history of head trauma or traumatic brain injury (mTBI) is associated with an increased risk of dementia and results in an earlier age at onset compared to those without a head trauma [130-133]. Indeed, autopsy studies have reported significant amyloid β (Aβ) deposition in up to 30% of persons who die acutely following a brain injury [134,135]. In line with greater brain Aβ deposition, studies also suggest that brain interstitial fluid levels of the aggregation-prone 42 amino acid long Aβ form, Aβ42, and the axonal injury marker tau are higher immediately after severe TBI [136-138]. A history of head trauma is associated with greater Aβ deposition in patients with MCI [139] and recent data suggest that an important cause of dementia in individuals with a lifestyle associated with increased risk of repetitive mTBI (or concussion; the terms are used interchangeably) is chronic traumatic encephalopathy (CTE), a neuropathologically defined condition previously only described in professional boxers [140]. It is now clear that athletes engaged in contact sports such as boxing, American football and ice hockey constitute a new group at risk for dementia. The molecular mechanisms seem to involve diffuse axonal injury and Aβ and tau deposition due to repetitive acceleration-deceleration and rotational forces on the brain tissue[140]. The magnitude of this potential epidemic is currently unknown but worrying data on smaller hippocampus volume in American football players, CTE pathology in ice hockey players, American footballers and military personnel, and biomarker changes indicating brain injury following subconcussive head blows in amateur boxing are accumulating [141-143].

RECOMMENDATIONS

Epidemiology provides powerful tools to illustrate the burden and geographic variations of dementia and AD in the society, to understand the natural history as well as risk and protective factors for dementia, to identify the populations at an elevated risk for dementia, to monitor the time trends in occurrence of dementia, to evaluate the new therapeutic approaches for dementia, and to assess the different strategies for intervention against dementia. Indeed, significant progresses have been made in many of these epidemiological aspects of dementia and AD in the last 2-3 decades. However, we are still far away from developing a cure or efficacious pharmacotherapy for AD and dementia, from providing the cost-effective medical and social care for numerous patients affected by dementia, and from implementing successful intervention strategies against dementia. From epidemiological perspective, implementing the following recommendations is critical to meet the future challenge of dementia and AD owing to the increasing ageing population:

- There is a need in Europe to establish the *harmonized international database* for existing population-based longitudinal studies on ageing and dementia. This will provide powerful resources for further understanding the burden (*e.g.*, economic and societal costs), temporal trends (*e.g.*, prevalence, incidence, and mortality), nature history (*e.g.*, genetic and clinical markers for early detection), and etiopathogenetic hypotheses (*e.g.*, psychosocial stress, traumatic brain injury, nutrition, and frailty) for AD and dementia [28,150].
- There is still limited knowledge regarding certain critical aspects of the *impact of dementia at the individual and societal levels,* such as prevalence stratified by severity, factors linked to progression in cognitive and functional disability, and factors linked to institutionalization.
- *Multidisciplinary research projects* that integrate epidemiological approaches with genetic, neurobiological, neuroimaging, and clinicopathological techniques are critically needed to better understand the pathophysiological processes of ageing and dementia. Such knowledge will facilitate the development of new therapeutic approaches for dementia in the clinical settings and intervention strategies against dementia in the communities.
- *Life-course approaches* should be applied to epidemiological studies of AD and dementia. These approaches are particularly relevant with regard to understanding the ethology, nature history, and intervention strategies for multifactorial chronic diseases, such as dementia.
- *Long-term studies with harmonized methodology* will help better understand the *temporal trends* and the possible *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.
- 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* [151,152].

Glossary of Terms Epidemiology

10/66 Dementia Research Group: A collective of researchers carrying out population-based research into dementia, non-communicable diseases, and ageing in low- and middle-income countries. 10/66, as part of Alzheimer's Disease International, refers to the two-thirds (66%) of people with dementia living in low- and middle-income countries, where 10% or less of population-based research that has been carried out.

Brain reserve: 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 neurons is able to tolerate more pathology before it reaches the critical threshold for clinical symptoms to appear.

Cerebral small vessel disease (SVD): The term describes a range of neuroimaging, pathological, and associated clinical features. Signs of SVD on conventional MRI include small subcortical infarcts, white matter hyperintensities, lacunes, prominent perivascular spaces, and cerebral microbleeds [153].

Cognitive reserve[154]: Cognitive reserve refers to the brain's ability to adequately perform cognitive tasks despite neuropathological damage in the brain. Cognitive reserve represents either an enhanced ability to recruit alternative brain networks or a more efficient utilization of brain networks in general. Common measures of cognitive reserve include such as high education, leisure activities, mentally-stimulating activity, and rich social network.

Confounder: A confounder refers to a factor that is related to both an exposure of interest and outcome (e.g., a disease). The factor (confounder) may explain all or part of the association between the exposure and the outcome.

Early-onset dementia/Alzheimer's disease: A term refers to dementia/Alzheimer cases diagnosed before the age of 65 years.

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 may affect risk of chronic diseases and health outcomes in later life. It aims to identify the underlying biological, behavioural, and psychosocial processes that operate across the lifespan.

Population attributable risk (PAR): A proportion of cases that would not occur in a population if the factor were completely eliminated from the population. The PAR (%) in a general 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: $PAR=P_e (RR_e-1)/[1 + P_e (RR_e-1)]$. It is also called population attributable fraction.

Years of life lost (YLL): An estimate of the average years a person would have lived if the person had not died prematurely. It is an alternative to death or mortality rates, but gives more weight to deaths that occur among younger people. YLL can be estimated from the number of deaths multiplied by a standard life expectancy at the age at which death occurs.

PREVENTION OF COGNITIVE IMPAIRMENT AND DEMENTIA

Summary

Alzheimer's disease patology is complex but epidemiological studies have given us knowledge on protective factors and modifiable risk factors. Promoting cerebrovascular health and certain life-style changes affect the risk profile for AD. A significant challenge is to design dementia prevention programs based on firm evidence from well-designed and ethically-sound clinical studies. Modifying cardiovascular risk factors, including control of hypertension, diabetes and obesity, and increasing physical activity have been shown to reduce also the risk for AD, but more large-scale collaboration and multinational intervention trials are needed.

Finding effective preventive strategies is essential for a sustainable society in an aging world. Both the WHO (http://www.who.int/mental_health/publications/dementia_report_2012/en/) and the G8 Dementia Summit (https://www.gov.uk/government/publications/g8-dementia-summit-agreements/g8-dementia-summit-declaration) have described dementia as a public health priority and prevention has been identified as one of the key elements in addressing dementia epidemic, in a similar way as it is for other major non-communicable disorders such as cardiovascular disease. It is estimated that one third of AD cases worldwide might be attributable to seven modifiable risk factors (low education, midlife hypertension, midlife obesity, diabetes, physical inactivity, smoking, depression), and a reduction in the prevalence of those risk factors by 10-20% per decade would reduce worldwide AD prevalence by 8-15% in 2050 (between 8.8-16.2 million cases[155]). Even just the possibility to delay the clinical expression of dementia would have a significant impact on its prevalence. In fact, it has been estimated that postponing the onset of dementia by five years would decrease the number of cases in total by up to 50% during 50 years. This delay would have a major impact on societies. [156,157]

Observational studies in the general population starting already in early adulthood are necessary to monitor the distribution of risk and protective factors in different age groups and in different generations over long periods of time. Very few such studies are currently available, and data from the 1960s and 1970s may not be entirely applicable today because of the changes in society, lifestyle, pharmacological treatments, and risk factors levels. [158] For instance, in the last few decades there has been a widespread and substantial increase in prevalence of obesity and diabetes mellitus, which are main risk factors for dementia and AD[159] (http://www.idf.org/sites/default/files/EN_6E_Atlas_Full_0.pdf (2013). Knowledge about risk factors 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. Also, randomized controlled trials (RCTs) targeting such risk factors will be crucial to understand if reduction or removal of these factors can substantially decrease dementia incidence.

Evidence from observational studies and clinical trials

During the last 10-15 years, long term observational studies have linked various modifiable risk and protective factors to an increased risk of dementia and AD **(Table 4).** Vascular risk factors at midlife (e.g., high blood pressure, cholesterol, obesity, and diabetes) have been linked with an increased risk of dementia and AD later in life. On the other hand, lifestyle-related factors including physical, mental

and social activities and healthy diet may reduce the risk. Psychosocial factors (e.g., depression, loneliness, stress) have also been indicated as possible risk factors. There are complex gene-environmental interactions and some of the environmental factors may have more pronounced effect among the genetically susceptible persons (APOE4 carriers, the most important genetic risk factor for AD).

While observational studies have provided information about potential modifiable risk and protective factors, large randomized controlled studies (RCTs) are needed to verify that interventions targeting those factors can efficiently postpone or prevent cognitive impairment and dementia, and to test which interventions are most effective in preventing or delaying onset of dementia in different at-risk groups.

Positive results from observational studies have not automatically become successful prevention strategies in RCTs. For instance, this has been the case for the hormone replacement therapy (HRT) and non-steroidal anti-inflammatory drugs (NSAIDs). For both medications, encouraging data about preventive properties from observational studies were not confirmed in RCTs [160-162] An important reason is the problematic translation of observational data into intervention design. Trials based on the assumption that AD is a mono-dimensional condition (that is, mainly due to a single risk factor or cause) have consistently failed to identify effective prevention interventions. Additionally, a variety of compounds with different mechanisms of action (e.g., non-steroidal anti-inflammatory drugs, NSAIDs, HRT, statins, vitamins, ginkgo biloba extract) were tested in prevention RCTs that were often add-ons to trials with other primary outcome designs (e.g., cardiovascular or cerebrovascular events)[158]. Such methodological frameworks could have limited the possibility to detect an effect on cognition or dementia risk because of limited statistical power or too short duration of the study. To date, no studies have convincingly shown an effective single-drug approach to dementia prevention. Anti-hypertensive drugs represent the only exception, with some evidence for a protective effect against dementia [163]. In addition, single lifestyle-related interventions (physical activity, cognitive training) have only shown modest or short term positive results [164].

Prevention RCTs have pointed out several key issues that must be taken into account[165]. Effective interventions depend on proper timing. Starting at the preclinical states of AD, before the onset of dementia, may lead to better effects than starting when dementia is already established, and some interventions may have critical time windows (e.g., beneficial effects only at midlife or at the pre-symptomatic phase). Preventive measures need to be adjusted to their intended target groups, and larger trials (e.g., several thousand participants instead of hundreds) with longer-term (years instead of months) interventions are needed to show any effects in relatively healthy, younger (around 60 years) individuals. The very definition of 'effects' is important, and measuring performance in cognitive tests, which can capture subtle decline and entire continuum of cognitive functioning, may be a more sensitive outcome than just conversion to dementia. In multifactorial conditions, single-agent interventions may not be enough and targeting several risk factors and disease mechanisms simultaneously may be needed for optimal preventive effects.

Some risk or protective factors for dementia and AD have been investigated. The amount and quality of available evidence for such factors varies quite a lot. Opinions are also divided about what constitutes sufficient evidence for formulating specific prevention recommendations. RCTs are usually considered to provide the best evidence that an intervention has clinically meaningful effects. However,

conducting traditional RCTs is not always possible. Vascular risk factors cannot be left untreated in the placebo group because of ethical reasons (there is already lots of evidence that treating vascular risk factors protects against CVD), and strict double-blinding may not be possible with lifestyle-related interventions. Vascular risk factors (e.g., high blood pressure, high cholesterol, and obesity) at midlife have been linked with an increased risk of dementia and AD 20 to 30 years later in long term population-based observational studies [166]. However, it is not feasible to conduct 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 enough evidence for prevention. No RCTs have been needed for non-smoking guidelines and recommendations, since this would have been unethical.

As mentioned in the Epidemiology section, recent epidemiological studies in several countries (e.g., US, the Netherlands, Sweden, UK) suggest that the incidence or age-specific prevalence of dementia has declined in the past 20 years [68,79,80]. These findings suggest that dementia risk may be modifiable. Possible explanations for the declining dementia incidence include favourable changes in some vascular risk factors (better and wider use of medications 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. **Table 5** summarizes the major trials conducted/ongoing in Europe. This approach includes interventions targeting several risk factors simultaneously in individuals who are at increased risk of dementia. Other new approaches are for example selecting at-risk group for the FINGER study (clinicaltrials.gov NCT01041989; https://clinicaltrials.gov/ct2/show/NCT01041989?term=Finnish+FINGER&rank=2) according to the CAIDE Dementia Risk Score, the first tool for estimating long term risk of dementia based on risk factors present at midlife (**Table 6**). The risk score has been later validated in a large multi-ethnic population in the US [167]. The risk score can help to identify individuals who may benefit from intensive lifestyle consultations and pharmacological interventions (e.g., target interventions for those most at risk). It can also be used as an educational and motivational tool and to distribute easily understandable information about risk factors to 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 indicate that it is possible to improve lifestyle factors in older adults at risk of dementia, and such changes can significantly enhance cognitive performance and reduce the risk for cognitive decline[168]. Extended follow-up of FINGER study participant is currently ongoing to detect differences in dementia and AD incidence.

Another new approach is utilization of technology in dementia prevention. For example, in the HATICE trial (ISRCTN register, ISRCTN48151589, http://www.controlled-trials.com/ISRCTN48151589/HATICE), an internet-based platform has been developed aiming to motivate and support lifestyle changes and improve management of cardiovascular factors. The platform is interactive with readily available nurse/coach support and will test if making prevention more easily accessible for elderly persons in community can reduce CVD risk factors and dementia. Finally, between the ongoing multi-domain

prevention RCTs in Europe, a data-sharing platform facilitating in-depth joint analyses and collaborations between research groups in different countries has been established. This allows analyses concerning different target groups and interventions. Differences in health care systems across Europe can also be taken into account, which is crucial for planning future multinational dementia prevention studies and programmes.

Increased collaboration between research groups, among governments, public, and private institutions is required to create infrastructure for dementia/AD prevention research and to facilitate implementation of the results. Actually, some international large-scale initiatives have already been established aiming to increase collaboration, e.g., EU Joint Programme for Neurodegenerative Disorders (EU-JPND), Innovatives Medicine Initiative (IMI), G8 Dementia Summit, OECD mapping for big data in Alzheimer research. A common theme of these initiatives is to increase coordinate investments and collaborations between participating countries, by bringing together academic experts, private sectors (the pharmaceutical and other industries) and policy decision makers, and by building on existing infrastructures. 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 (i.e. general population, clinical settings).

Prevention trials in populations at high risk of dementia

The shift of focus from advanced dementia to earlier, preclinical stages of AD has also brought prevention and treatment trials much closer than before, meaning that these trials now target very similar groups of people in the preclinical stages of AD. In fact, potential disease-modifying strategies (e.g., anti-amyloid drugs) previously tested only in patients with dementia due to AD, are now being tested in selected populations of asymptomatic individuals who are at-risk of AD, because of an established biomarker burden or a specific genetic profile [169]. There are three ongoing RCTs testing safety and efficacy of anti-amyloid drugs as preventive measures in subjects with pre symptomatic (or preclinical) AD. The Alzheimer's Prevention Initiative (API) and the Dominantly Inherited Alzheimer's Network (DIAN) studies enrol subjects who carry genetic mutations for dominantly inherited AD: mutations in the APP, presenilin-1 (PSEN1), and presenilin-2 (PSEN2) genes can cause early-onset familial AD that accounts for no more than 5 percent of all cases. Data from the DIAN study have shown that different phenotypic changes can be detected several years before the onset of cognitive symptoms in individual with autosomal dominant AD: it has been shown that CSF levels of Aβ42 decline 25 years before expected symptom onset, and brain deposition of Aβ can be detected 15 years before [170] The DIAN study is an international study involving 210 individuals from North America, Australia and Europe *(*NCT01760005, *http://www.dianexr.org/)*, while the API RCT (NCT01998841) focuses on the world largest early-onset AD kindred in Antioquia, Columbia. Of about 5000 individuals in this kindred, approximately 1500 carry a mutation in the PSEN1 gene (E280A) causing early onset AD (mean age of onset: 45 years)[171]. Finally, the Anti-Amyloid Treatment of Asymptomatic Alzheimer's (A4) RTC (NCT02008357, http://a4study.org/), aims to prevent sporadic AD and evaluate the effect of an anti-amyloid compound in older adults with evidence of brain amyloid accumulation at neuroimaging evaluation. The A4 study includes also an ethics arm examining the psychological impact of disclosing information to individuals about their risk of developing AD[172].

While Europe has been at the forefront of initiatives promoting lifestyle-based interventions for dementia prevention, North America has led the start of RCTs testing anti-AD medications in preclinical AD. However, studies on both pharmacological and non-pharmacological interventions for prevention of cognitive decline and dementia are being started in several regions of the world. In Europe, the recent launch of the European Prevention of Alzheimer's Dementia Consortium (EPAD, www.ep-ad.org), within the Innovative Medicines Initiative, is expected to create readiness cohorts and novel framework for RCT testing numerous disease-modifying drugs in preclinical stages of AD.

Assessing health economics of dementia prevention

Evaluating the benefits of dementia prevention or delaying onset from an economic perspective is a complex endeavour. AD has a long 'silent' phase before the first symptoms appear, and it can also take time for milder symptoms to develop into full-blown dementia. Compared to late stages of the cognitive disorders, in the early stages there is less need for health care services use and costs are lower. Intervention methodology may also be misleading, for example a very broad intervention in younger individuals around 40-50y with no symptoms will result in a very low occurrence of dementia even if no prevention activities are taking place. This is because dementia incidence is very strongly age related and dementia is rare at midlife. Some prevention activities, such as targeting vascular and lifestyle factors, can be embedded in an implicit way in daily life and in medical care settings, making it difficult to separately estimate their costs. Public health prevention trials outside the medical care system are easier to assess than trials embedded in the medical care system since they tend to demand some kind of separate infrastructure with associated programme costs.

Approaches such as economic simulations may be useful for estimating cost-effectiveness. One example of an economic simulation is a study where the cost-effectiveness of a potential dementia prevention programme using the CAIDE Dementia Risk Score and a Markov model adapted to Swedish conditions was evaluated [173]. The prevention programme consisted of two main components, a healthy lifestyle promotion programme and pharmacological treatment of cardiovascular risk factors. Figures of costs (intervention costs, costs of care for people with and without dementia), utilities (health utilities expressed as quality adjusted life years, QALYs), and mortality according to age group were obtained from literature or databases. The multi-domain preventive intervention was less costly and had better dementia-related outcomes compared with 'usual care,' supporting cost-effectiveness. This is a promising outlook for future research on preventive interventions in dementia. To evaluate the cost effectiveness of prevention programmes, it is important to have a multifactorial approach with a 'filter' for selecting at-risk participants, and to have sufficient statistical power in terms of sample size and intervention duration.

Ethical aspects of prevention

Prevention strategies need to consider several ethical issues. In clinical trials, vascular and lifestyle-related risk factors cannot be left untreated in placebo groups because there is already strong evidence that treating vascular risk factors and healthy lifestyle are beneficial for CVD prevention and other health outcomes. Dementia risk is the result of interactions between genetic and environmental factors (e.g., effects of environmental risk factors are more pronounced among ApoE4 carriers). The potential need for genetic counselling or 'genetic-tailored' guidance as part of dementia risk

assessment in trials, and later in clinical practice, will have to be considered. Another ethical aspect is deciding when the evidence is sufficient to start recommending specific prevention strategies, or to start informing and educating the general public about modifiable risk factors. Many risk factors cluster in groups with lower socioeconomic status (e.g., lower education, smoking, obesity, suboptimal treatment of CVD 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.

Most importantly, blaming persons with dementia for presumably having had an 'unhealthy lifestyle', as well as false promises for preventive intervention effects in popular media must be avoided. Results from epidemiological studies are applicable at population level, but translating them to individual level is not simple because not all characteristics of an individual can be captured by average characteristics of a group.

RECOMMENDATIONS

Compared to cardiovascular prevention, dementia/AD prevention is a rather young field and much work is still needed. However, prevention or delaying onset of dementia/AD seems to be possible since many known risk factors are modifiable or amenable to management. There is already enough evidence to justify some immediate actions in dementia prevention [174] including for example public health policies encouraging middle-aged people to stop smoking; treat high blood pressure; avoid becoming obese and diabetic; increase physical activity, and improve education level. At the same time, knowledge about modifiable risk factor for dementia/AD needs to be refined and validation of the observational studies with large intervention studies is needed.

- Many modifiable risk factors such as high blood pressure, obesity, physical inactivity and unhealthy diet are shared among dementia/AD and other major late-life chronic conditions like heart disease and stroke. Public health efforts promoting healthier lifestyles in midlife have the potential to improve generally health status in advanced age.

- Population surveillance of risk factors in different age groups and countries is urgently needed to better estimate the effects of preventive interventions on future dementia and AD prevalence. This can help planning of public health policy.

- Observational studies need to start early in midlife and have a long duration in order to identify windows of opportunity for effective interventions. Building on existing infrastructures and cohorts developed for other chronic diseases will allow optimizing the use of resources.

- Effective dementia/AD prevention needs tailored intervention strategies for appropriate target groups (different ages and contexts). Also, health care system differences between countries need to be considered for developing preventive strategies that can be easily translated and implemented internationally.

- Given the multi-factorial etiology of dementia/AD, multi-domain interventions with simultaneous management of various risk factors based on lifestyle changes and pharmacological treatment may be needed for optimal preventive effects.

- Scientific collaborations among research groups in Europe require the development of appropriate infrastructures to facilitate more effective use of existing data, and rapid recruitment of participants in multinational intervention trials. Increased collaboration among governments, public, and private institutions is required to facilitate AD/dementia prevention research.

GENETIC RISK OF DEMENTIA: Individual susceptibility

Summary

The heritability of AD is estimated to be greater than 60%. Several specific gene mutations cause, or contribute to, early-onset (before age 60) AD, but only about 2% of AD cases fall into this category. Gene variants that increase the susceptibility for AD have also been identified and large-scale genome-wide association studies are ongoing. Well-organized biobanks and large collaborative groups that share data are essential to advance the understanding of the genetic underpinning of AD pathology and risk factors. There is hope that an understanding of inherited early-onset AD might provide insights for therapies directed at sporadic, age-related dementias.

The epidemiological evidence summarized earlier helps to understand the relationships between lifestyle factors, such as physical activity or smoking, and medical conditions, such as hypertension, at midlife and the risk for developing dementia several decades later. The evidence from genetic studies of AD, reviewed in this section, explains how genetic variability, present in our DNA from conception, contributes to the development of AD later in life. Genetic epidemiology attempts to study how our genetic make-up lends resistance or vulnerability to environmental exposures, such as life style and medical illnesses. The impact of individual genetic susceptibility in the occurrence of AD is substantial, considering that the heritability for AD is usually estimated to be greater than 60% [175].

The very first genetic determinant of AD discovered in 1991 was a mutation located in the amyloid beta (Aβ) precursor protein gene (*APP*) associated with a familial form of early onset (before 65 years of age) AD [176]. Indeed, approximately 2% of all AD cases are hereditary explaining about half of the early onset AD cases, in which the occurrence of the disease is explained by mutations in one gene with a major effect. Most of these monogenic hereditary forms follow a *Mendelian autosomal dominant transmission*, affecting at least one individual in each generation. For the other 98% of AD sporadic cases, with an age at onset after 65 years of age, very often, clinicians identify a family history of dementia without any specific mode of transmission. However, due to the late age at onset of the disease, the precise estimation of this family history is difficult because of both parent survival and diagnostic assessment limitations.

Genetics plays a major role in our current understanding of AD and will play an important role in the general prevention and care of the disease in the future. For example, genetic tests can be used to

identify and classify individuals with various level of risk of disease, ranging from low to high, before symptoms have appeared, so called predictive pre-symptomatic genetic testing, and for early diagnosis in preclinical states of dementia. A detailed understanding of the level of AD incidence associated with genetic susceptibility will be important in future when efficient treatment has been developed because genetic testing may thus be used to identify and treat at risk individuals before symptoms of cognitive dysfunction have developed. Genetic discoveries also offer new clues to what pathological processes (gene functions) are involved in the development of the disease and thus potential treatment approaches can be developed to intervene in these processes.

Already genetic testing procedures require special ethical considerations since genetic information on one family member gives information about other family members indirectly, especially since there is no treatment available for Alzheimer disease. Thus, for instance, genetic testing in AD hereditary forms should be performed in the context of clinical genetic counselling with strict guidelines for communicating genetic information in the context of a lack of treatment.

The progress of AD genomics: the pivotal role of international collaboration and data sharing

Since the discovery of the mutations in *APP*, the first gene associated with familial AD in 1991, a second major milestone was achieved with the discovery of the first susceptibility gene in sporadic AD, the ε4 allele of the apolipoprotein E gene (*APOE*) in 1993[177,178]. In contrast to *APP* mutations, the *polymorphism* of the *APOE* ε4 allele is frequent in the population, with a *co-dominant 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, with a high *attributable fraction* in the population (between 20 and 40%)[179]. Two other genes were identified in 1995, Presenilin 1 (*PSEN1*)[180] on chromosome 14 and Presenilin 2 (*PSEN2*)[181] on chromosome 1 in familial forms of AD, explaining, together with the *APP* mutations, almost half of these familial forms. Between 1995 and 2009, more than 500 potential new susceptibility genes were reported, but none of them could be consistently replicated and confirmed [182]. We had to wait for the first achievement of the Human Genome Project [183] and the incredible development of nano-genome-sequencing technologies in biological sciences [184] to stimulate the deciphering of the genetic susceptibility of AD. That is, the natural genetic variation in the human population consisting of single nucleotide polymorphisms (SNPs) has been mapped across all chromosomes such that it is possible to define the unique position (locus) of individual SNPs with respect to the rest of the genome.

Indeed, the genome wide association study (GWAS) approach that was developed thanks to these new technical developments has allowed for the identification of a large part of the genetic susceptibility of human diseases. Based on high throughput genomics technologies, GWAS can characterize 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 may lead to the discovery of numerous false positive associations. Thus, the AD geneticists had to use very stringent P-value thresholds ($<5 \cdot 10^{-8}$) and to replicate systematically their discoveries in additional follow-up studies [185]. Consequently, they had to enlarge the size of their samples from hundreds to thousands of cases and controls to increase their statistical power, improving chances to detect frequent polymorphisms with small individual effects on the disease risk. The only way to collect very large samples of cases and controls was to create large collaborative consortia sharing their clinical data, biobanks and genotypes. In 2009, two such consortia,

the European Alzheimer's Disease Initiative (EADI) [186] and the Genetic and Environmental Risk in AD (GERAD) [187] discovered three new AD susceptibility loci; in 2010, another consortium, the Cohort for Heart and Ageing Research in Genomic Epidemiology (CHARGE) [188] in collaboration with the two previous ones, published two new loci among which one was confirmed; in 2011, another consortium, the Alzheimer Disease Genetic Consortium (ADGC) [189] published, back-to-back with a paper from the three other consortia [190], five new loci. Thus the total number of susceptibility locus associated with late-onset AD was 10 including APOE. These four consortia decided to work together and to give birth to the largest and most efficient genomics collaboration in AD ever done, the International Genomics Alzheimer's Project (IGAP) [44,191] that recently discovered 11 new loci clearly confirmed and 13 new potential ones. Finally, using different approaches, four other genes were identified. In 2015 the total number of confirmed genetic effects is 26, with 14 that still need to be validated, located in 39 different loci (**Table 7**), a significant portion of which have unknown function.

Effects and frequencies of genetic variants

Based on the level of association of the genetic variant with the disease risk (weak or strong) and on the frequency of this genetic variant in the general population it is possible to classify the AD associated loci into different groups of genetic influence on AD (**Table 8**). Generally, causal mutations are rare and deterministic meaning that they contribute only to a minor fraction of the total number of patients with AD (rare mutations) but these mutations have a strong impact on the individual (very strong association), being sufficient to cause the disease and are thus classified separately as "disease genes". In contrast, susceptibility genetic variations are usually more common in the population (Single nucleotide polymorphisms with a minor allele frequency, MAF >10%) and thus an association may have a large impact on the total burden of disease in the population but relatively small impact on the individual risk. Susceptibility loci may have a "high impact" or "low impact" depending on how strong the association to AD is (OR ≥ or < 2).

Disease genes were identified using segregation studies in familial forms of AD with a disease inheritance supporting the involvement of a single gene mutation as the etiology of the disease. Most high impact susceptibility loci have been identified through hypothesis driven candidate gene approaches, targeting one or a few specific genes based on their biological function or on systematic sequencing approaches associated with functional studies. Finally, the low impact susceptibility loci have been identified in GWAS. GWAS approaches are based on the association of SNPs to a disease with no *a priori* hypotheses. These SNPs are usually markers distributed evenly all over the genome in order to build the most extensive coverage. Some of the SNPs mark regions of the genome where only one gene is present that may be considered as the functional one, while other SNPs are located in regions containing several genes with no simple way to identify the responsible one. Thus, in the absence of any functional or experimental information, GWAS results refer in general to susceptibility loci mostly without any known functional implications to the disease etiology because of their non-hypothesis-driven approach.

The first two groups of genes in the first column of **Table 8** are the disease genes and the high impact susceptibility loci discovered in familial forms of autosomal dominant AD with Mendelian inheritance. These diseases are early-onset monogenic forms of AD caused by deterministic mutations in genes

which are at the origin of the amyloid cascade hypothesis: *APP, PSEN1 and PSEN2* [192]. However, these three genes are only found in half of the families with autosomal dominant early-onset AD, suggesting that other major genes still remain to be discovered. For instance, systematic exome sequencing in these autosomal dominant early-onset familial forms has led to the discovery of non-sense and missense mutations in *SORL1*, not detected in large control samples. Following *in silico* analyses, these mutations in the gene that encodes the Sortilin-related receptor LR11/SorLA, a protein involved in the control of the amyloid β peptide production, are likely to have a pathogenic effect [193]. This reinforces the implication of the amyloid cascade hypothesis in the early onset forms. Moreover, common polymorphisms of *SORL1* are also associated with sporadic AD.

Concerning sporadic AD with an older age at onset, the very first and only gene to be consistently associated was *APOE*, which constitutes the third group of disease loci with high frequency in the population and a high impact on disease risk. *APOE* was already known to be associated with high levels of LDL-cholesterol and myocardial infarction risk [194,195]. In AD, the risk effect of the *APOE ε4* allele was discovered in 1993 thanks to candidate gene approaches [177,178]. Then more in depth analyses demonstrated that another allele of this gene, the *APOE* ε2 allele, was conversely a protective factor reducing the risk for AD [196]. The strong association between the *APOE* ε4 allele and AD was largely confirmed in all populations. In recent studies, lifetime risks for AD, without reference to the *APOE* genotype, at the age of 85 was 11% in males and 14% in females. This lifetime risk was 50% for *APOE* ε4 homozygous men and 60% for homozygous women, while for heterozygous *APOE* ε3ε4 carriers the lifetime risks were 23% and 30% respectively for men and women. These estimations are consistent with a semi-dominant inheritance of a moderately penetrant gene, similar to the effect of *BRCA1* mutations and risk for breast cancer and other major-effect genes with incomplete penetrance in Mendelian diseases [197]. Despite this major susceptibility impact on AD, the role of *APOE* on the AD pathophysiology remains heavily discussed.

In 2009, built on the experience of the genomics of other complex diseases, and on the development of the GWAS, three new loci were reported by two major consortia [186,187], constituting a fourth group of susceptibility loci with high frequency and low impact. These loci were centred within three genes: *CLU, CR1 and PICALM*. The SNPs identified in these loci were frequent (more than 20% *MAF*) and associated with 20% of the risk variation being either protective (the minor allele is more common in the control group compared with AD thereby associated with a lower risk for AD) or deleterious (the minor allele is more common in AD compared with the control group and is thereby associated to increased AD risk). Following a similar approach, the *BIN1* locus was identified in a new GWAS and replicated [188]. Finally, the four research consortia had identified nine AD loci and, as mentioned above, decided to come together in a global collaboration called IGAP, sharing their data to increase significantly the statistical power of these genetic studies. The combined sample population of 25 580 AD cases and 48 466 controls in IGAP lead to the discovery and confirmation of 11 new AD loci and to the proposition of 13 new potential loci [44]. All these loci in this fourth "low impact" group still need to be explored to understand their role in the pathophysiological process of AD i.e. through which biological disturbances the genetic variants contribute to the development of AD. Some of the associated loci point to a specific gene, while others cover larger regions with numerous possible candidates. Thus, future research must focus on the identification of the specific genetic variants that are responsible for the increased risk of AD and subsequent functional studies will unravel their biological relevance in the pathophysiology of AD [198].

Thanks to the development of the next generation sequencing (NGS) technologies it is now possible to sequence the exomes of a given genome, allowing to characterize all the mutations present in the coding regions of patients, and comparing their presence or absence in controls. This sequencing approach was successfully used to discover two new AD genes with low frequency mutations (<1%) with high effects, almost as high as the one observed for heterozygous *APOE* ε4 allele carriers, outlining a fifth group of susceptibility genes. The first gene was *TREM2*, previously associated with a rare disease, the Nasu–Hakola disease presenting with bone cysts and early-onset dementia [199]. While sequencing *TREM2* in a series of AD cases and controls, several low frequency mutations could be identified and associated with an increased risk of sporadic AD, increasing the risk more than 4 times [200]. *TREM2* was simultaneously discovered in an Icelandic population and similarly extended to sporadic AD risk in other populations [201]. Recently, a second gene was added to this fifth group, the *PLD3* gene [202]. A non-synonymous coding mutation was discovered in a whole exome sequencing study of 14 large late-onset AD families with AD in four or more individuals. The mutation segregated with AD in two independent families and doubled the risk for AD in a large case-control multicentre study. Unfortunately, this observation could not be replicated[203]Functional experiments suggested that *TREM2* is related to the immune pathway , a pathway previously implicated in AD pathogenesis. Similarly, while searching for rare variants in the *APP* gene with a significant effect on AD risk, Icelandic researchers found a coding mutation (A673T) that potentially protects against AD and cognitive decline in the elderly population [204].

Early-onset and late-onset AD genes

About 200 different mutations have been identified in early-onset AD cases. These mutations are usually inherited from an affected parent in autosomal dominant fashion suggesting that new, *de novo*, mutations are rare and the penetrance is generally high, reaching almost a 100% life time risk. There have also been two reports on recessive *APP* mutations in rare cases [205,206]. Thus, by screening for mutations in *APP*, *PSEN1* and *PSEN2* in individuals affected by AD who belong to families with a dominant inheritance of the disease, it is possible to identify the causal mutation in almost half of the 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, it becomes possible to use genetic testing to predict the risk for relatives who are still asymptomatic, a procedure known as presymptomatic genetic testing. In research, there is a major opportunity to increase our understanding of AD by studying the natural history of the disease in such at-risk subjects who are asymptomatic mutation carriers. Indeed, several studies in sporadic forms of early onset AD have demonstrated that the pathophysiological process that underlie AD begins several years before definite clinical symptoms appear: in a prospective study of subjects aged over 65 and followed-up more than 15 years, the first decline in cognitive performances, using, for example, measures of semantic memory, appeared 12 years before the dementia diagnosis [207]. So being able to identify individuals, very early and with limited comorbidities who later will develop AD may help our advancement in tracing the natural history of the disease. Thus, the study of at risk individuals from families with early onset AD caused by mutations in *APP*, *PSEN1* or *PSEN2* may serve to understand also the sporadic disease process [208]. Several research groups have studied the natural history of early onset AD through prospective examinations of healthy, asymptomatic mutation carriers and their healthy non-mutation carrier siblings. These autosomal dominant AD cases have pathophysiological changes decades before any cognitive symptoms exists

[209,210]. For instance, concentrations of Aβ42 in the CSF decline 25 years before expected symptom onset; Aβ deposition, as measured by positron-emission tomography (PET) is detected fifteen years before, as are increased concentrations of tau protein in the CSF and increase in brain atrophy. Given the low frequencies of these familial AD forms, a collaborative effort of international AD centres has been launched, the Dominantly Inherited Alzheimer Network (DIAN) [211].

As indicated in **Table 7**, GWAS has led to the identification of several susceptibility loci in addition to *APOE* whose relative contribution to the total load of AD in the population is relatively high compared with the population attributable fraction of risk associated with the rare early onset AD genes. However, the use of this susceptibility information in any genetic testing at the individual level remains very limited. Thus, there is a consensus agreement not to offer *APOE* genetic testing, the gene with highest attributable fraction in the population, as a predictive test.

Finally, other unknown genetic susceptibilities may result from interactions with environmental factors and other genes and from mechanisms for which we still do not have the tools to uncover. These other potential mechanisms of action include *epigenetic modifications* of DNA and DNA-binding proteins such as cystein-methylation and histone acetylation as well as *somatic mutations* in the target tissue (*i.e.*, nerve cells) [212]. There are still not sufficient data on these mechanisms to know if they are at play and future research must be engaged in such hypotheses. In order to decipher these underlying complex genetic mechanisms, there is a need for increased access to high quality databases of detailed electronic health records and biobanks to be able to correlate efficiently genotype to phenotype and estimate interactions.

From gene discovery to clinical application

Much work remains to elucidate disease mechanisms in AD. However, the amount of data already accumulated from genomics prompts thinking about the consequences that this information may already have for translational research and clinical practice. Indeed, we can outline three major consequences in the medium term: risk prediction, clinical trial enrichment and precision medicine.

The most obvious application of genomics in clinical practice resides in using genetic testing to support early and presymptomatic diagnosis. However, the questionable clinical utility associated with presymptomatic genetic testing for sporadic AD as long as there are no proven pharmacological interventions which can stop or delay the disease also raises ethical concerns. Thus in the current circumstances of lack of specific treatments or lifestyle changes with robust proven efficacy, the major use of genomics in AD is to increase the scientific knowledge and to help improve translational and clinical research.

However, in cases with a strong family history of early onset AD, clinical genetic testing may be requested by patients themselves. In case such requests are put forward, these should be better handled in a clinical genetics setting with access to physicians allowing a medical, social and psychological continuous support rather than by direct-to-consumer genetic testing companies with limited medical follow-up and support.

Before any type of genetic test can be administered, each individual to be tested must have had the opportunity to be fully informed about the consequences of these tests: information about the disease itself, *a priori* risk of inheritance and consequences of these genetic tests for other family members.

Performing a diagnostic genetic test on a patient diagnosed with AD often has as much consequences for the rest of the family as for the patient himself or herself, such as being implicitly able to deduce the risk of the other members as a result of Mendelian (mostly autosomal dominant) transmission.

Although rare, identification of a causal mutation in a patient with AD may result in requests for presymptomatic genetic testing in other members of her family. If so, this genetic testing should only be performed in the context of genetic counselling provided by teams with experience in the neurodegenerative disease field. This request can come from family members with autosomal dominant AD, individuals with a family history compatible with a 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 individuals with an isolated case in a sporadic context.

When genetic testing is requested by a symptomatic individual, this patient should be accompanied by a family member or any declared representative. If the individual is presymptomatic, a protocol based on the International Huntington Association and World Federation of Neurology Research Group on Huntington's Chorea Guidelines is recommended [213]. This testing has several limitations. In autosomal AD, the search for the causative gene in a family will be performed among the three known ones: *APP*, *PSEN1* and *PSEN2*. However, half of the families do not present any mutations in these three genes. Furthermore, due to the heterogeneity of dementia etiology, misdiagnosis of AD in the family must be considered. In particular, the most common genetic cause for familial frontotemporal lobe dementia, an expansion of the hexanucleotide repeat in C9orf72, has been identified in families misdiagnosed with AD [214]. Thus, in families with a clear autosomal dominant inheritance pattern, the possibility of other causative genes should be considered, allowing an extension of the number of target genes if mutation screening has been requested. A neuropathological examination in the family will also help to define the clinical diagnosis [215]. Finally, in families who request genetic testing but lack mutations in the known genes, it may be valuable to store the DNA for future mutation screening in novel genes. Beside these three causative genes, the other gene that could be tested is the strongest susceptibility gene for AD, *APOE*. However, despite a relatively high attributable fraction of the *APOE* ε4 allele in population (around 20%) and a high lifetime risk in homozygous carriers, the ε4 allele is neither necessary nor sufficient to cause AD. Using *APOE* genotyping for predicting AD risk is not recommended because of its low sensitivity and specificity to diagnose AD, the lack of preventive options, and the difficulty of estimation of an absolute individual risk.

As outlined in **Table 9**, 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 BIN1* (**Table 7**) in late onset AD. Indeed, for deterministic mutations, the outcome is binary, either the mutation is present and the disease will unequivocally develop at some point in future, or the mutation is absent and the early onset form of AD will not develop. In contrast, the presence of a risk allele for a susceptibility risk gene will result in a life time risk probability score for developing the disease in future and cannot be used to estimate a binary outcome as for deterministic genes [216]. In most situations, this multigenic risk confers only a genetic susceptibility that will be modulated in a favourable or unfavourable way by gene-gene and gene-environment interactions.

Ethical concerns of genetic testing

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

Some ethical concerns have been addressed in clinical trials that examined the impact of *APOE* genetic susceptibility testing on asymptomatic individuals, The Risk Evaluation and Education for Alzheimer's Disease (REVEAL) Studies [217]. Results of REVEAL trials demonstrate that disclosure of *APOE* genetic results by trained professionals using appropriate educational approaches does not generally result in short term adverse psychological effects. REVEAL studies were not fully representative of a typical clinical setting. The individuals recruited were a preselected (having a parent with AD), volunteering highly educated group, generally female, receiving a free of charge testing whose results were not included in their medical record. However, these studies provide insight into what we have to expect from the various all-in-one personal genomic services delivering scores of health conditions which usually includes results on AD susceptibility genes. Finally, early identification of presymptomatic individuals might have major psychological effects for the individual and other consequences [218,219] both for the individual and for his/her family members, who might be indirectly informed of their own risk. [220,221]

The way forward in genetics

Genetics and genomic discoveries are a major entry point in AD research by offering new research leads through non-hypothesis driven approaches. Already in 1991, the discovery of a causative mutation in early onset autosomal dominant AD gave support to the amyloid cascade hypothesis. Less than 20 years later, the intense development of genomics allows expansion of the research landscape thanks to a non-hypothesis driven approach based on whole genome screening. The 40 genes and susceptibility loci, confirmed or suspected, identified to date, offer insight into the high level of complexity hidden behind the brain pathology of amyloid plaques and neurofibrillary tangles in AD. However, the genetic discoveries must now be brought forward. We have entered a post-GWAS era that will need to integrate all the research tools that are available today in biological and computer sciences: bioinformatics, "omics" technologies, system biology, epigenetics, molecular and cellular studies, animal models, risk factor assessments and social and health care research (**Figure 4**). The future is transdisciplinary and will require well planned and target-oriented development of databases and biobanks which can harbour information from all areas of research and health care, including population based studies, clinical data, and experimental research results.

In 2012, the US launched a major sequencing programme in the context of their National Alzheimer Plan, aimed at sequencing 10 000 whole exomes and 600 whole genomes in selected AD patients and controls. Similar European initiatives have been launched in the context of research calls through the European Union Joint Programme on Neurodegenerative disease (EU-JPND). Following the example of the GWAS consortia, sequencing consortia are now arising that will share data. However, the dimension of the information collected will require big data handling infrastructures.

In parallel, the use of genomics in clinical research must be reinforced. Ready-to-use tools allowing rapid identification of genetic markers in patients attending memory clinics can be developed. These tools could be used to facilitate differential diagnoses in dementia and other neurodegenerative disorders. These tools would allow physicians and patients to be prepared and educated to the next revolution associated with *precision medicine*. In this context, and as long as we are not able to provide efficient treatment for AD (and even after), social and ethical research must be strongly supported to help our patients to cope with the concept of an increased AD lifetime risk, and to protect them from any negative consequences of early diagnoses developed in the context of clinical research, as a possible limitation of access to employment or insurances. To this end greater efforts must be made in the European health care systems to facilitate the understanding of the genetic underpinnings of neurodegenerative diseases. To achieve this, professionals need to be educated and families and patients should have universal access to qualified genetic counselling. In parallel to the progress in AD genetics and genomics, genetic research in other neurodegenerative dementias, such as frontotemporal dementia, faces similar challenges [222].

In conclusion, tackling AD is not anymore in the hands of any one researcher, one team or even one country. The first pilot JPND research was initiated during the French Presidency of the European Union 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. If we want to progress more rapidly, this global collaboration must be extended to even more countries as AD does not know any borders. In that context, the JPND initiative gathers today 28 different countries beyond the European traditional limits, including Canada and Israel (www.jpnd.eu). Moreover, this momentum should also support not only academic research but also private research as the Innovative Medicine Initiative (*www.imi.europa.eu*) has brilliantly done. The awareness of this need for global collaborative research is progressing as demonstrated by the last G8 summit that was dedicated to dementia, in London in 2013. The ultimate goal of all this mobilization is to lead to increased global collaboration and data sharing for the greatest benefit of our populations and economies.

RECOMMENDATIONS

Genetics plays a major role in our current understanding of AD and will play an important role in implementing prevention and care strategies in future.

To allow for optimal utilization of genetics in prevention of dementia, pre-symptomatic and early diagnoses, and present and future treatment approaches, we need to:

- Favour data sharing and large scale national/international collaborative studies
- Facilitate clinical and genetic interdisciplinary research to embrace the complex and heterogeneous nature of neurodegenerative diseases
- Develop guidelines for health professionals to support the use of new genetic tests including the clinical validity of clinical total genome and exome testing (Next Generation Sequencing)

- Develop a legal framework that regulates the use of personal predictive health information by third parties, protects the individual and the family, and facilitates research.

- Increase the societal awareness and knowledge of the use and limitations of genetic testing and its ethical concerns

- Provide genetic counselling by appropriately trained personnel in an adapted and professional psychological support system (similarly to the genetic counselling provided for Huntington disease)

- Develop systematic searches using GWAS and NGS data to identify the biological pathways and "causal variants" involved in the disease

- Systematically collect and store DNA and clinical data in clinical settings, as well as in clinical trials and prevention studies, for post-hoc research studies and patient stratification

- Explore the role of gene-gene interactions and gene-environment interaction in disease etiology and progression

- Engage in functional studies to unravel the molecular mechanisms of associated genetic variants and pathways in the post-GWAS era

Glossary of terms Genetics

Mendelian autosomal dominant transmission: a mode of inheritance of a genetic disease resulting from the presence of a disease mutation in one of the two alleles which is located on one of the 22 autosomes (chromosomes 1 to 22) and which is independent of gender of the parent from which the disease mutation was inherited as well as the gender of the offspring who has inherited the mutation. Thus diseases with Mendelian autosomal dominant transmission results in a risk of 1 in 2 or 50% in children and siblings to an affected mutation carrier.

Single Nucleotide Polymorphism: a genetic variation in the DNA code (sequence of nucleotide base pairs). Generally there are two alleles for each SNP.

Allele: a term to describe that there are alternative genetic variants a specific gene or locus.

Locus: (plural loci) a specific location or position in the genome or chromosome which could be considered as the specific coordinates for a geographical place in a map.

Co-dominant: meaning that there is an additive increased effect, on the phenotype, of the genetic variation with increasing number of alleles, i.e. two copies of the allele result in a more severe phenotype than one copy of the allele.

Attributable fraction of risk: the total number of cases that could be avoided if a risk factor (in this case a mutation) could be totally suppressed.

Minor allele frequency, MAF: the frequency of the less common (usually of two different alleles in a SNP) genetic variant (allele) in the population.

Epigenetic modifications: effects on the genetic make-up which does not include the DNA-code itself such as modifications of the DNA (methyl-groups added to the nucleotide cytosine) and modifications of proteins (e.g. acetylation) that bind to the DNA in order to make it more or less accessible for activation (transcription).

Somatic mutations: Acquired genetic variations that occur during cell division (mitosis) in the cells of the body and that are not transmitted to the next generation (because transgenerational transmission requires that the mutation has occurred/ is present in the gonadal cells).

Precision medicine: also called personalized medicine meaning that individualized choices of treatment and prevention can potentially be made based on the specific genetic background of the individual when the trait or disease is influenced by the genetic make-up. This concept can be extended to all type of –omics information (transcriptomics, proteomics etc)

ALZHEIMER'S DISEASE BIOLOGY

Summary

The brain pathology of AD is distinct. Amyloid plaques are made up of deposits of derivates of amyloid-β precursor protein (APP) and neurofibrillary tangles are due to the abnormal accumulation of another 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 levels in neurons. However, a better understanding of the basic biology of AD pathogenesis and how clinical dementia relates to the presence of amyloid plaques and tau tangles is urgently required so that prevention and therapy can be focused on the proper disease target.

In 1906, Alois Alzheimer described the major changes present in the brain of the first AD patient, Auguste D. In the last hundred years, we have gained considerable knowledge in understanding the genetical and environmental factors contributing to the disease. However, unfortunately we still do not know what triggers the pathology and which are the mechanisms by which the disease progresses.

One distinctive feature of AD brain pathology is the accumulation of small (around 0.1 mm) spherical structures called amyloid plaques. The plaques are composed of fibrils formed by a protein fragment called amyloid Aβ-peptide (Aβ), and are surrounded by dysfunctional neurons. There are different variants of Aβ, and it is one of the longest forms, called Aβ42, which is believed to be particularly toxic. The other major hallmark of the disease is the accumulation of another protein, called tau, inside the neurons, forming fibrillary tangles. Amyloid plaques and Tau pathology are present not only in AD, but in several neurodegenerative disorders, which suggest a central role for these proteins in neurodegenerative mechanisms. For example, Aβ is accumulated in cerebral amyloid angiopathy (CAA)[224] and tau in frontotemporal dementia (FTD) or Niemann Pick Disease[225].

In the 90s, studies of early onset familial AD (FAD) identified distinct mutations in some genes that cause the disease in some families: the amyloid-β precursor protein (APP) and the presenilin (PS) 1 and 2 genes. The proteins resulting from these 3 genes are involved in the production of Aβ, the majority, but not all, of these mutations cause an overproduction of Aβ peptides[226], [227]. These neuropathological and genetic observations led to the proposition of the "amyloid cascade hypothesis" whereby Aβ initiates a molecular cascade of toxic effects causing neurodegeneration and subsequently the clinical manifestations of dementia[192]. It is now believed that Aβ forms (1-42 or 1-43) are trigger factors for AD [228], although which conformational structure (fibrils [229], oligomers [230], soluble forms[231], or dimers [232]) of these peptides drives neurotoxicity is still debated.

The amyloid hypothesis has dominated the debate about the etiology and pathogenesis of AD, as well as guided the efforts to find treatments. Thus, today there is a considerable understanding of the mechanisms by which these rare genetic mutations lead to excessive Aβ generation, but the precipitating factors that lead to Aβ accumulation in the much more common sporadic forms of AD (more than 95% of all cases) are still unknown, although they most probably result from a combination of environmental factors and risk genes. Moreover, Aβ plaques are ubiquitous to old-age (>70 years) individuals and around 30% of the healthy aged individuals have as much plaque load in their brains as in typical cases of AD (reviewed in [233]).

Following the "amyloid cascade hypothesis" a number of explanations have been proposed for the mechanistic link between Aβ and Tau pathology (**Figure 5**). However, the mechanistic relationship is not yet clear, as transgenic animals carrying FAD genes and expressing huge amounts of Aβ show no or little tangle pathology. Also, a major unmet scientific need in the AD field is to understand the biological function(s) of the protein precursor of Aβ, APP, and its metabolites, including Aβ, in the healthy individual. Thus, the potential risks of targeting Aβ production (in brain and in the periphery) are yet undetermined. The biological role of Aβ is largely unknown. Aβ has been shown to act as antioxidant[234], have anti-microbial activity [235], activate other signalling proteins[236-238] or modulate cholesterol transport [239]. As β-secretase (BACE1) and γ-secretase are the enzymatic proteins responsible for Aβ generation, efforts have been made to develop inhibitors of these proteins for clinical use in AD. However, increasing number of studies reveal their role in the metabolism of multiple substrates, which complicates efforts to achieve selectivity to inhibit only Aβ production. Moreover, some of these substrates are fundamental for normal cell biology. For example, BACE1 cleaves β subunits of voltage-gated sodium channels [240], and neuroregulins. These are crucial molecules for neuronal development and myelinization [241,242] processes also important in adult life, particularly for the reparation of neuronal damage.

Similarly, γ-secretase is a promiscuous enzyme that cleaves more than 90 protein substrates having different structures and localization, and regulates a wide variety of cellular events such as cell fate determination, adhesion, migration, neurite outgrowth, axon guidance or formation and maintenance of synapses [243]. Besides APP, the most studied γ-secretase substrate is Notch, a signaling molecule 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. 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 agents that will selectively inhibit γ-secretase cleavage of APP without affecting other substrates. These efforts received a boost by the recent discovery of modulators that control γ-secretase cleavage of specific substrates by binding and recruiting them to γ-secretase for processing [244], which are small molecules capable of reducing Aβ42 production without affecting the generation of functionally important γ-secretase products [244].

Inhibition of the enzymes producing Aβ, BACE1 and γ-secretase, has also consequences for the metabolism of the Aβ precursor, APP, affecting the production of other APP metabolites (*e.g.*, sAPP or the cytoplasmic tail, AICD). AICD has more than 20 interacting protein partners which regulate important signalling pathways and cell functions, such as transcription, apoptosis and cytoskeletal dynamics [245,246]. The biological function of APP is partially known, and roles have been described in cell migration [247], trafficking and signalling [248], neuronal calcium homeostasis, synaptic transmission and neuronal networking [249] and in neurotrophic mechanisms [250]. In consequence, targeting APP processing to reduce Aβ levels is not an easy task and might have a large number of biological consequences. This difficulty has been seen in clinical trials and, as discussed in the section of pharmacological interventions, to now all the numerous clinical trials with agents targeting Aβ production have failed to reach their primary clinical endpoints and in some cases caused serious side effects.

An alternative to reducing Aβ levels is to increase Aβ clearance from the brain. Since the absence of Aβ does not lead to any loss of physiological function in mice [251], the elimination of this peptide could be a safe approach for AD treatment, but it remains to be seen if clearance of this peptide has some benefits or slows down the progression of AD. With this aim, some immunotherapy approaches have been tried in AD patients, as discussed previously, with disappointing results.

Consequently, the question of if Aβ (production or clearance) is a good target for AD treatment is still unknown, and improved efforts are needed in basic research to understand the limitations and the real possibilities of this approach.

The other distinguishing feature of AD, formation of tau tangles in brain neurons, has historically been a secondary player to explain the disease pathology, despite its direct correlation with neuronal death and disease progression. In contrast to the APP gene, mutations in tau do not cause AD, but they do cause familial frontotemporal dementia [252]. In contrast to Aβ, some biological functions of tau are well known. Tau regulates microtubules assembly, dynamics and spatial organization, and participates in the axonal transport of organelles, and vesicles in the cell [253]. The biological activity of tau is regulated by its degree of phosphorylation. Tau in neurofibrillary tangles is abnormally hyperphosphorylated [254]. Hyperphosphorylation of tau converts it from microtubule-stabilizing to microtubule-disrupting protein [255]. Accumulated data strongly suggest that neurodegeneration is most likely a consequence of the loss of 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 the neurons with corresponding impairments of neuronal cytoskeletal organization and of the transport of proteins and organelles along the cells. Since basic research has demonstrated that excessive tau phosphorylation is crucial to tau pathology, efforts have been done to develop inhibitors of the responsible molecules, called tau kinase inhibitors, as potential therapeutics. However, there are multiple kinases involved in generating hyperphosphorylated tau, raising the question of whether specific or multiple kinase inhibitors will be more effective [256]. Other anti-tau based strategies, such as tau anti-aggregants or tau immunotherapy are being tested. Then again, as for the Aβ-based approaches, the lack of good predictive animal models, good biomarkers for disease progression, and well defined target populations in clinical trials are strong difficulties for demonstrating their potential benefits against AD.

As for models based on brain accumulation of Aβ, many treatments have been successful to "cure" mice designed to accumulate hyperphosphorylated tau in their brains. Several tau kinase inhibitors, mainly glycogen synthase kinase 3β (GSK3β) inhibitors, or lithium, were successful in animal models [257]. However, despite previous encouraging positive effects, the GSK3 inhibitor tideglusib failed to meet primary cognitive endpoint in a 26-week Phase IIb trial for the treatment of over 300 mild-to-moderate AD patients [258].

Methylene blue (methylthioninium chloride), a drug identified in 1891, 15 years before the first description of AD by Alois Alzheimer, as a possible anti-malaria agent [259], has been recently proposed as potential drug for AD treatment. The mechanism of action of this compound is unknown, but it has been speculated that it could inhibit Tau aggregation [260]. Phase II clinical trial data suggested slowed decline. However, methylene blue colors the urine and eyes, which raises the question of how the study was blindly performed. A new version of methylene blue is now heading towards Phase III testing in patients with frontotemporal dementia.

As an alternative to kinase inhibition, activation of phosphatases has also been proposed as a strategy for reducing tau phosphorylation. Protein phosphatase 2A (PP2A), the main brain phosphatase involved in tau phosphorylation, have received special attention. Treatment of tau transgenic mice with the PP2A activator sodium selenate reduced tau hyperphosphorylation and tangle formation, as well as improved memory and prevented neurodegeneration [261]. However, a problem is that PP2A acts in a broad number of molecules and the activation of this enzyme to specifically reduce tau phosphorylation is not an easy task. In other words, treating with non-specific enough activators of PP2A could result in multiple unwanted side-effects.

Several other anti-tau treatments were effective in preventing and intervening in the progress of tau hyperphosphorylation in animal models, improving neuronal function or cognition, for example microtubule-stabilizing agents as davunetide [262]. Disappointingly, a 12 week placebo-controlled study of intranasal davunetide failed to detect statistically significant benefits in 144 subjects with amnestic mild cognitive impairment [263].

Increasing efforts are being made to design an effective vaccine against tau pathology. Few studies regarding passive immunization (transfer ready-made antibodies against at target protein to enhance its clearance) against tau protein are currently available [264]. Also, several studies suggest that active immunization (induction of immunity after exposure to an antigen; the recipient develop antibodies that may be stored permanently) may be effective against tau in animal models [258]. Very recently, the

first in-man active anti-tau immunization studies started (AADvac1; http://clinicaltrials.gov/ct2/show/NCT01850238).

Similarly to the Aβ -based approaches, a number of key questions remain still to be answered in the Tau-based immunotherapeutic approaches. Still, we do not know which is the exact species to be targeted (aggregation states, fragments, subtypes), or the mechanism of action by which antibodies clear target molecules. We will see in the coming years if current anti-tau immunotherapeutic approaches are effective or if they will be "lost in translation," as has seemed to be the case with previous strategies.

The reasons for the lack of successful translation from preclinical to clinical studies in treating AD are unknown. It is possible that the use of simple animal models reflecting a single aspect of AD is not enough to mimic the disease, and thus, to develop new treatments. Some limitations of the current animal models for AD are discussed below.

Animal models for AD

Transgenic animal models (animals genetically modified by genetic engineering techniques to mimick some aspect of the disease) are very important tools in tackling the molecular basis of neurodegenerative disorders and in understanding the mechanisms of disease progression. Many organisms, including mouse, zebra fish, worms, and fruit flies, have been used to model AD. The vast majority 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, the drugs that have made it to human clinical trials have so far failed. Moreover, in some instances the failure was not only in reaching the primary objectives, but also due to serious adverse effects in the tested patients. Thus, it could be concluded that animal models are highly informative for molecular processing of Aβ and tau, but may not reflect the pathophysiology of sporadic AD in humans. Despite some efforts to generate disease-relevant experimental animal models [265,266] this issue remains as a critical need area for defeating AD. We should bear in mind that there are some inherent problems with transgenic mice: the gene is inserted at unknown locations in the genome and other genes could be disrupted, non-natural promoters are used and the expression is un-naturally high. Recently, a knock-in mouse has been developed were the endogenous mice APP gene has been substituted for a human version carrying a FAD mutation. The major advantage of these mice with respect to the previous models is that they show ageing dependent amyloid pathology, neuroinflammation, synaptic alterations and memory impairment, all in a more AD-like manner. However, they do not develop tau pathology and, although promising models for future studies on amyloidosis, still are limited models for AD [267] .

Since, the use of simple animal models reflecting a single aspect of AD has not been successful for developing potential new treatments, to create good animal models for AD is crucial to advance the understanding of the basic disease biology (reviewed in [268]). New research breakthroughs are needed for the development of new models, which optimally should reflect the heterogeneity of the disease. Another possibility is that in the majority of the AD cases, Aβ and tau pathologies are end points of other disease driving mechanisms. Thus, achieving a successful inhibition of Aβ and tau pathologies

might not necessarily mean finding a successful drug for AD. Considering the heterogeneity of AD, it is probable that a multi-target approach will be necessary.

Mechanisms of Alzheimer disease

Epidemiological evidence underlines the importance of vascular health and diabetes in the development of AD and hypertension and high blood cholesterol levels have been shown to enhance the risk for AD in many studies [269]. In addition, several other pathways have been identified that can contribute to disease development, such as head trauma-traumatic brain injury [270], ischemia and hypoxia [271], neuroinflammation [272], environmental toxin β-N-methylamino-L-alanine from cyanobacteria [273], and metabolic abnormalities involving decreased brain glucose uptake [274]. Although at present, using risk indicators only modestly enhances the reliability of predicting who will develop AD, their larger importance is that they identify pathways and processes leading to AD. In the recent years, large new genome wide association studies (GWAS) and systematic exome sequencing approaches have confirmed some of the previously known pathways and have also identified other novels. The new loci identified have however modest effects on AD risk (with odds ratios in the 1.1-2.0 range) [275]. These analyses continue with pooling of larger number of samples.

In broad terms, GWAS identified cholesterol metabolism, innate immune system, and endosomal vesicle recycling as important contributors to AD. Before these new genetic studies, a large amount of evidence suggested a pathogenic link between disruptions in cholesterol metabolism and AD. The strongest known genetic risk factor for sporadic AD is the presence of the E4 allele of the cholesterol carrier apolipoprotein E (APOE) [178]. Since the discovery of APOE4 as a major risk factor for AD, considerable efforts have been made in linking this molecule to Aβ metabolism, aggregation, and deposition. An increased plaque deposition has been observed in APOE4 individuals and in animal models of brain amyloidosis (accumulation of Aβ in brain tissue) [276]. APOE4 can potentiate Aβ toxicity *in vitro* [277,278] and in animal models [279]. It has also been suggested that carriers of the APOE4 allele might be less efficient in mediating Aβ clearance [280]. On the other hand, the contribution of APOE4 to tau pathology remains poorly understood. A reduced capacity for neuronal delivery of cholesterol of APOE4 allele carriers is believed to have consequences for the development of new synapsis (connections between neurons) and for repair mechanisms. Indeed, the brain is the major cholesterol containing organ in the body [281] and an efficient cholesterol metabolism is the brain is crucial for recovering damaged membranes. Also, neuronal axons are surrounded by cholesterol rich myelin, which both protects the axons and facilitates neurotransmission. Thus, an impaired cholesterol synthesis, delivery or metabolism is likely to contribute directly to disease progression [281]. This notion is supported by GWAS, where genes related to cholesterol synthesis, transport, uptake or metabolism were found to be linked to AD (*e.g.*, ABCA7, ABCA1, CLU, CYP46A1) [275]. However, new efforts are necessary to understand the underlying mechanisms by which APOE4 other cholesterol-related molecules contribute to AD pahtology. Also, if experimental manipulation of brain cholesterol metabolism has therapeutic potential for AD needs to be clarified.

Studies in the late 80s already indicated the role of the innate immune system and the complement cascade (a part of the immune system that helps the ability of antibodies and phagocytic cells to clear toxins or pathogens from an organism) in relation to AD pathogenesis [282]. The brain has its own innate immune system, which can maintain a low grade, systemic inflammatory reaction. Presumably, the innate immune system of brain, as in other tissues, has a protective and defensive role. But it is also

probable that a chronic inflammatory process may damage the neuronal cells. AD brains show activated immune system cells (microglia/macrophages), as well as a large variety of proteins resulting of inflammatory reactions. Proteins of the classical complement cascade may also be of particular importance, since studies have shown that they are largely expressed in the cortical pyramidal neurons which are severely affected in AD [283]. Whether complement-producing neurons are particularly vulnerable to immune system attack remains unknown. Inflammation has been recently proposed as an early pathogenic event in the disease [284]. Lately, GWAS studies have clearly shown that variability in the innate immunity confers risk for AD [186,187]. The isoform S of the complement receptor type 1 (CR1) has been associated with AD [189] and it has been hypothesized that is likely associated with increased complement activation [285]. Indeed, the complement cascade is known to be activated by A β [286] . This would activate phagocytic mechanisms remove the A β deposits. If this process fails, a persisting complement activation would cause excessive inflammation that could damage the neurons. Another AD/inflammation associated gene uncovered by exome sequencing is TREM2 [201]. TREM2 has being shown to suppress inflammatory response in microglial cells [287]. Thus, it has been speculated that TREM2 could participate in the regulation of phagocytic processes to remove amyloid. Consequently, a lack of function of TREM2 could also result in chronic inflammation, and amyloid accumulation. Interestingly a very recent report has identified apoE as a ligand for TREM2 [288] , the biological consequences of this association and its relation with AD pathology remain to be defined.

Despite the solid links between inflammatory and immune components to 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.

The recent GWAS studies have also revealed endosomal vesicle recycling as one of the pathways of importance for AD pathogenesis [186,187]. Endosomes are a dynamic vesicular network that provides an environment for material to be sorted before it being degraded. Some material from endosomes is recycled to the plasma membrane of cells and SORL1, PICALM and BIN1 are all likely to be relevant molecules in this category. Very little is known about the functional implications of this discovery. However, it is worth mentioning that some on the metabolism of APP occurs in the endosomal pathway [289], and it seems plausible that impairment of vesicle recycling would have detrimental consequences for important cellular systems such as secretory or autophagy pathways for secretion or degradation. In other words, impairments in the machineries to secrete or to degrade unwanted proteins could affect the survival of neurons.

Together, epidemiological and genetic studies of AD individuals have categorized insulin resistance, deficits in cholesterol transport, hypertension and neuroinflammation as mechanisms contributing to AD[275].

Another hypothesis has proposed that AD is a prion-like pathology. According to this model, Aβ or Tau, misfolded or aggregated, are produced in one cell, secreted to the extracellular space, and entered gain into neighboring connected cells, where they trigger further Aβ or Tau aggregates. Thus, Aβ and Tau inclusions begin in specific regions of the brain and are spread to other areas (for review, see[291,292]. Intracerebral or intraperitoneal injections of Aβ or extracts from AD brains were shown to induce amyloidosis in the brain of *in vivo* models [291,292]More recently, Jaunmuktane et al [293]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. Indeed, further research is necessary to clarify the mechanisms and possible risks deriving from transmissible Aβ or tau.

However, it is unclear whether they are upstream or downstream of the amyloid and tau pathways. There is a consensus that Aβ aggregation and accumulation is the cause of FAD. However, this view is not consensual for the majority of AD cases (without genetic mutations) Indeed Aβ is also important in the pathology, but may not be the cause of AD in non-genetic cases. The existence of variant pathways to AD is probably reflecting the heterogeneous etiology of the disease. To discern which overlapping, intersecting or synergic mechanisms in these pathways induce brain Aβ and Tau pathology remains as an important challenge for the future. The identification of patient subtypes with homogenous etiology and prognosis will result in more accurate, personalized, treatments. Intensifying innovative basic research will also result in the identification of novel biomarkers for subtyping AD, which will open possibilities for precise medicinal interventions (**Figure 5**).

Future goals and vision

Despite the efforts in the past three decades, we still need to elucidate the causal mechanisms of AD. Also, the assumption that the molecular mechanisms mediating the genetically determined forms of the disease are identical to those resulting in late-onset AD needs to be demonstrated. Ongoing non-European Initiatives like the Alzheimer's Prevention Initiative (API) and Dominantly Inherited Alzheimer Network (DIAN) studies[211] will determine, in the near future, if clearing Aβ from the brain will be effective to treat FAD. API is an international public-private consortium established to conduct research in a 5,000 member family (the world's largest in which a gene for FAD has been identified) in Antioquia, Colombia. DIAN, is an international initiative funded by the National Institute on Aging (NIA) tracking participants from families in whom an Alzheimer's-causing mutation has been identified. A possibility is that targeting Aβ will be only successful for the autosomal dominant types of the disease, where increased Aβ production occurs from birth. For the majority of AD cases, where amyloid accumulation is likely a late event resulting from other metabolic disruptions, the strategy will probably not be so simple. We have considerable information on different pathways contributing to the disease. To discern the causative forces and the overlapping mechanisms among them, is one of the priorities for the future. To determine how these mechanisms result in Aβ accumulation and tau hyperphosphorylation will be fundamental to understand the disease.

The identification of patient subtypes, with homogenous etiology and prognosis, will result in more accurate treatments in the future. It is likely that different subtypes, resulting from different causative pathways, should be treated differently. Intensifying innovative basic research will also result in the identification of novel biomarkers for subtyping AD, which will open possibilities for precise medicinal interventions.

RECOMMENDATIONS

Epidemiological and genetic studies have successfully uncovered risk factors and molecules for AD. Now, it is essential to understand the molecular mechanisms behind those factors. It is likely that preventive strategies will be successful in delaying a few years the onset of the disease. However, in an increasing aging population, the need to find a cure or an effective therapy for AD remains imperative. For that, there is need of ambitious programmes in basic research. Without new breakthroughs in understanding AD pathogenesis, the development of a cure seems unachievable.

- To implement large-scale programmes to support of basic research in AD
- To intensify the identification of novel, "out-of-the-box," disease modifying strategies.
- To increase efforts in understanding disease mechanisms with emphasis in systems biology, vascular research, neuroplasticity and inflammation.
- To develop relevant animal models for AD. Optimally, these models should reflect the heterogeneity of the disease.

ALZHEIMER DISEASE DIAGNOSIS AND CLINICAL ASSESSMENTS INCLUDING BIOMARKERS

Summary

The diagnosis of AD and other dementias is complex, requiring cognitive and functional assessment, sometimes with serial evaluations, and exclusion of other morbidities causing dementia. New robust and affordable tools are required for AD diagnosis. The use of AD biomarkers, from blood or cerebrospinal fluid (CSF) and brain imaging such as MRI or PET scanning, are not yet widespread, except in the setting of clinical trials in specialist clinics. Better approaches are needed for both subjective cognitive testing and objective diagnostic criteria for AD.

What effect does an AD diagnosis have in patients and their families? The consequences of the diagnosis of AD for patients and families are complex. Given the background that AD is one of the most feared diseases, the disclosure of a dementia diagnosis can result in severe mental distress and there is evidence for an increased risk of suicide after the diagnosis has been made [294]. However, there is also evidence that the adequate disclosure of AD can relief symptoms of anxiety in patients, because it clarifies a frightening loss of cognitive capacities [295]. At more advance stage of AD, self- reflection is often impaired and the meaning of the dementia diagnosis is not understood fully by the patient, which prevents severe mental distress. For caregivers, the disclosure of an AD diagnosis is also stressful and associated with fears and grief, but can also trigger seeking and receiving help and coping with the situation. Overall, the process of providing information on diagnostic procedures and meaning of outcomes, applying and interpreting diagnostics, disclosing the diagnosis and providing counselling on prognosis and treatment options is very complex and individualized procedure, which is becoming

even more complex with earlier diagnosis and the increasing availability of new biomarkers and treatment options. This constantly increases the demands on the skills of the physicians and requires increased specialist knowledge. If provided in an individualized and highly competent fashion the diagnostic process of Alzheimer's disease can be helpful for patients and caregivers. If applied with insufficiently or inadequate, it can be devastating and harmful.

What health services and professionals are usually involved in such diagnosis? There are a wide variety of involved services and professionals in different European countries depending on the health care system and the reimbursement structure. In many countries, for example Germany, a large proportion of patients with AD is only seen by the General Practitioners (GP), where often the diagnosis is not firmly established. Other patients are referred to neurologists or psychiatrists in private practice. Only a very small proportion of patients is diagnosed in specialized centers, such as memory clinics, which are usually linked to large hospitals and universities. There is no specific reimbursement structure for guideline based dementia diagnosis. In Germany, there is currently also no defined pathway of care or diagnosis for dementia. In the UK, policies to increase recognition of dementia have introduced limited screening into hospitals for acute admissions and into some dementia practices. Such introduction of policy without prior trial evidence has been controversial and, some would argue, has led to further delays in access to diagnostics services because of the large volume of referrals.

Why is diagnosis relevant? A diagnosis of the dementia syndrome and clinical diagnosis of AD is usually the basis for the pharmacological and non-pharmacological treatment and can be a route to access for support for the person with dementia and their loved ones. In younger people the differential diagnosis of different causes of dementia will be important for treatment decisions and estimation of individual prognosis. In older people in whom most dementia is mixed this is arguably less helpful. Rarely are fully reversible causes detected but most guidelines do highlight those that should be ruled out, such as hypothyroidism.

Current status

Increased awareness has led to dementia being the top disease in terms of what individuals most fear. This was not necessarily the intention of the awareness campaigns, but may be a consequence. In the absence of improvements in quality of life and treatments for people with dementia, there might be few incentives for family doctors to pursue a diagnosis of dementia**.**

The main challenge for clinical assessment of patients with AD today is the transfer of concepts and methods, which were mainly developed for advanced dementia, to the early stages of the disease. The focus on early stages, however, is crucial, because future treatment, still to be developed, will most likely have to be initiated at those stages to be effective. This transition can be achieved by understanding AD as a slowly progressive disorder of cognition starting gradually before full dementia is reached. The main aim of the assessments tools for symptoms of AD is identifying and mapping individual components of cognitive decline (e.g. memory, attention, language) from the earliest disease stage to progressive impairment of function and relate them to biomarkers as indicators of AD pathology.

The identification of very early disease symptoms, of effects of treatment on these symptoms, and of predictors of treatment outcomes at the very mild symptomatic stage are urgent priorities. Related to

this is a conceptualization of the very early stage of AD as a disorder with distressing impairment of memory, which affects individual's well-being even in the absence of severe impairment in daily functioning**.**

AD as a neuropathological process is a slowly evolving condition in the brain with a quite long preclinical period without symptoms, followed by a prodromal phase with very mild symptoms and finally the dementia phase. Currently the clinical diagnosis of AD in clinical care and in the majority of clinical trials is made at the stage, where dementia is reached. Overlapping but slightly different criteria set for AD dementia are provided by the clinical classification system ICD-10, which is being used in Europe and by the US diagnostic manual DSM V, as well as by IWG-2, NINCDS-ADRDA and NIA-AA research criteria. These criteria list features to make the clinical diagnosis of typical AD, such as the slowly and progressive onset and course and memory deficit as the initial presentation. They also acknowledge atypical presentation such as the language variant (logopenic aphasia), the visuo-spatial variant (posterior cortical atrophy) and the variant with executive dysfunction (frontal variant). The reliability of criteria has been established in the clinical settings (i.e. different physicians agreed reasonably well when applying the same set of criteria to the same patients) [296]. People with a clinical diagnosis of AD when followed to post mortem, however, do not always have Alzheimer type pathology, with around 20% suggested to be misclassified during life in one report [297]. Also, there are many older people who fulfil neuropathological criteria for Alzheimer's disease, but who are not demented when they die, creating a continuing and largely unaddressed conundrum for the field of AD and its early detection.

The two major conceptual changes in recent years have been the introduction of biomarkers in combination with the clinical syndrome definitions in new research criteria [298-301] and the introduction of criteria for pre-dementia stages of AD, which can be diagnosed based on mild symptoms plus biomarkers or even in the absence of symptoms based on biomarkers alone [298-302]. These two recent approaches are currently applied in research including validation studies and in clinical trials on dementia and dementia prevention. They are not used in clinical practice yet.

Clinical assessments of AD patients need to lead to the detailed description of symptoms, to better understand the natural history of the disease in individual patients, including those with atypical variants of AD. This knowledge would be helpful for evaluating the variation in disease courses, as well as for assessment of efficacy of interventions, stratification in clinical trials, and prediction of cognitive and functional decline.

The standard instruments in clinical care and clinical trials today include comprehensive and detailed cognitive test batteries, rating scales of functional impairment, informant-based questionnaires on instrumental and basic activities of daily living (IADL and ADL), on neuropsychiatric symptoms, on quality of life, on disease related burden and others. The majority of tools 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 relatively 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 (i.e. coming to the same result, when applied several times in the same person).

Required improvements

Cognitive assessment

There are three main challenges with regard to improved assessment of cognition. First, it is common today in clinical practice and clinical trials to describe the cognitive performance of patients with a single global score (e.g. the commonly used Mini-Mental-State Examination Test (MMSE) expresses the level of cognitive performance with a single number ranging from 0-30; the standard scale for cognitive testing in clinical trials, the Alzheimer's Disease Assessment Scale, cognitive part -ADAS cog- expresses cognitive function by a single number between 0 and 70). This approach needs to be extended by measuring individual components of cognition (e.g. memory, attention, language) to increase understanding of how these individual components are affected over time by the disease and how they individually respond to treatment. Also, this would aid in describing different clinical subtypes of AD.

The second main challenge is detection of earliest symptoms and symptomatic changes below the detection threshold of currently used tests. Several studies have described decline in different cognitive domains at the preclinical stage of AD in individuals at risk [302]. Measures of this change, however, have not been standardized and are not applied on a large scale across studies. Also, they are not tested in all the different patient groups to which they might be applied to in the future (i.e. patients of GP, patients of memory clinics). New tests therefore need to incorporate techniques, which allow reliable detection of very subtle early changes in AD.

Subjective cognitive decline (SCD), defined by the experience of worsening of cognitive abilities, is often reported by elderly people [303] . SCD is associated with increased risk of progression to dementia in population studies, (e.g. [304,305]). Some studies have shown that it adds predictive information with regard to the risk of future dementia in an individual, which is of a similar magnitude as impairment in performance on a memory test (e.g. [306]). There is an increasing number of studies reporting that subjects with SCD show evidence for AD pathology by biomarkers, such a Aß42 reduction and Tau increase in the CSF [307] or AD typical changes in brain imaging (e.g. [308,309]) more often than subjects without SCD. Recently, it has been shown that subjects with SCD and evidence for AD pathology measured by cerebrospinal fluid (CSF) markers are at increased risk to develop dementia[310]. According to a recent international consensus publication [303], future research should develop improved and standardized assessments of SCD, and should investigate the relationship with objective decline in cognition as well as with psychiatric conditions such as depression and anxiety [311].

The third challenge of cognitive testing is improved robustness against intra--and inter-individual variance and rater- /rating-related confounds. Intra-individual variance refers to the fact that in some tests the performance of one individual is subject to day-to-day changes, for example related to different levels of alertness and concentration, and subject to learning effects, when the test is repeated (repetition effect). Problematic inter-individual variance can occur for example in the case of a verbal recall test, which aims at testing memory, in which individuals with greater language abilities may have an advantage over subjects with poorer language abilities. The rater- or rating related confounds describes the observation that patients score differently on a test depending on how it is administered with regard to task instructions, but also with regard to behaviour of the person who is giving the test (the rater). In particular, at the early disease stage (the late asymptomatic at risk stage and the very early AD stage) [302], 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, there is a strong need to develop tests with less variation. These tests require very standardized task instructions to reduce the rater-related confounds and should minimize components which increase the inter-individual variance (e.g. being independent of language skills). The intra-individual variance may be reduced by applying test without repetition effects.

Functional assessment

Current ADL scales have low sensitivity for early functional changes in the course AD. However, effects of early cognitive impairment already affect IADL at the pre-dementia stage of AD and IADL impairment actually predicts decline to dementia [306]. At present, some diagnostic criteria acknowledge the presence of mild IADL impairment and define the cut-point to dementia by a level of impairment which interferes with independency. Mild IADL impairment already reflects disease burden for individuals. Thus, it is important to improve assessment of IADL and to measure effects of early interventions on IADL to establish evidence that a particular intervention have a relevant and meaningful effect for the patient. Current scales for IADL impairment in very early AD rely largely on observations reported by the informant. Innovation in IADL assessment therefore also includes direct measures of the time needed and number of errors in a patient, while performing IADL activities [312,313].

Closely associated with IADL assessment is the approach of individualized outcomes of treatment This refers to defining specific IADL (e.g. using a telephone) which are individually identified with a patients as a goal of treatment (goal attainment), as opposed to applying an identical IADL scale to all patients [314]. This approach is appealing as it directly reflects individual patient-related benefit (i.e. the most relevant areas of impairment for an individual are defined as opposed to assessing in everybody whether for example cooking still works, including those, who never cook). It also mirrors clinical practice, where the patients discuss and work on individual goals with the treating physician.

Standardization of the goal attainment approach for clinical trials, however, is challenging.

Quality of life assessment

Evidence of effects of treatment on quality of life of patients is increasingly required by decision makers on reimbursement in some countries (e.g. in Germany) as a measure of patient-related benefit of an intervention. Reliability and validity of most currently used scales for the assessment of Quality of Life in AD are very limited [315]. Recently developed instruments of refined disease-specific Quality of Life assessment in AD, including early disease stages, are being validated and will be increasingly integrated in observational studies and clinical trials [316,317].

Post-mortem diagnosis: the need for an increase in autopsy rates

Despite biomarker discoveries in the clinical diagnostics of AD and other neurodegenerative dementias, there is still a need for neuropathological confirmation for a definitive diagnosis which requires a postmortem examination, to confirm the presence of extracellular deposition of Aβ peptides and

intraneuronal aggregates of neurofibrillary tangles in brain tissue **(Figure 6)** (National Institute on Aging (NIA)/Reagan Institute of the Alzheimer Association (AA) Consensus Recommendations for the Post-mortem Diagnosis of AD or NIA–Reagan Criteria[318]). Unfortunately, in many European countries and the US, the number of autopsies has decreased by at least half since the 1970's, which can potentially mask diagnostic errors. Such diagnostic errors will reduce power in research studies and may thus hamper the progress. The reduced autopsy rates will lead to less reliable records of cause of death and this is of even greater concern in the aged population with chronic conditions where the individuals will have multiple morbidities and the cause of death might be uncertain. The low autopsy rate for neurodegenerative diseases is particularly alarming since the reported cause of death for dementia in Sweden for example has quadrupled since 1987. Furthermore, in a study on 176 consecutive neuropathological examinations of clinically diagnosed patients with dementia, the clinical and pathological dementia diagnoses were in agreement in only 49% (86) of cases [215].

The global decline in autopsy rates underpins the need for collaborative and specific efforts to facilitate neuropathological examinations in patients, particularly if included in clinical research studies or clinical trials. Indeed, advances in neuropathological characterization of neurodegenerative diseases suggest that there is a complex interplay of several pathologies underlying the clinical presentation of our most common dementias including AD, [319] which has resulted in new guidelines [320,321]. Equally important, there is a 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 post-mortem. Studies on autopsy rates for other conditions suggest that the rate of autopsy is correlated to how effectively physicians recommend it [322].

Thus one strategy to increase the autopsy rates is to train physicians and health care professional in understanding and communicating the value of a neuropathological confirmation of the diagnosis as well as the value for researchers to have access to human post mortem tissue for basic research. Another strategy is to build and facilitate national and transnational brain biobanking infrastructures which would ensure that the tissue is collected using standardized and harmonized protocols such as the Brain Net Europe (BNE) Initiative.

The use of biomarkers in Alzheimer's disease diagnosis

Biomarkers allowing accurate, early and differential diagnosis are being developed and are currently in a transitional state between research and clinical practice. Widespread application is being delayed by a number of methodological, economic and political factors. Particularly, their practical usefulness is questioned at a time when interventions are lacking to significantly delay the progression of neurodegeneration. The major methodological factor is related to standardization issues. For CSF biomarkers, we need certified reference materials and methods and automated assays to allow for uniform measurements and decision limits irrespective of what laboratory performs the measurements. Similarly, standardization is an important topic in neuroimaging. The economic and political factors relate to costs for sample acquisition and analysis and how the biomarker results influence the clinical management of the patient. Validated diagnostic algorithms are currently lacking but several have been suggested, most recently in the IWG-2 research diagnostic criteria report [302]

(**Table 10)**. Another initiative, the NIA-AA criteria has been developed in parallel [323]and a comparison between these criteria and the IWG criteria is shown in **table 11**.

Current status

We have seen a quite dramatic development of several diagnostic biomarkers that can be used to detect AD neuropathology even in individuals at preclinical stages of dementia. Biomarkers can be classified into diagnostic markers and progression markers. Diagnostic biomarkers are pathological markers, reflecting *in vivo* pathology. They can be used to detect changes even at asymptomatic stage and may not correlate with clinical severity. PET imaging of amyloid plaques in brain and measurement of Aβ42 and P-tau in CSF are examples of diagnostic markers **(Figure 7, 8)**. A progression marker may have poor disease specificity and may not be present in the early stage of the disease, but will reflect clinical severity. PET imaging of cerebral glucose metabolism, CSF T-tau and brain atrophy measured by MRI both can be considered as markers for disease progression (9) **(Figure 9).**

Brain volume and structure can be investigated by computerized tomography (CT) and magnetic resonance imaging (MRI) imaging. The size of certain brain regions as the temporal lobe (hippocampal) are used to evaluate brain atrophy [324]. In order to study the functional activity of the brain, imaging techniques as positron emission tomography (PET) are used to measure the cerebral brain glucose metabolism and cerebral blood flow, which both correlates with cognitive function [325]. Molecular PET imaging also allows detection of AD pathology manifested as amyloid plaque deposition [325]. Several PET tracers are under development for imaging tau deposition in AD and non-AD dementia disorders [326]. CSF can easily be obtained by lumbar puncture which is a well-established and safe procedure in clinical neurology (Peskind ER et al., Alzheimer Dis Assoc Disord. 2005 Oct-Dec;19(4):220-5). A CSF test result showing increased levels of CSF T-tau and P-tau levels, and decreased levels of Aβ42 [327] indicates AD-like neurodegeneration in conjunction with Aβ pathology.

Amyloid imaging and CSF biomarkers thus allow early detection of AD, and most importantly, discrimination of patients with mild cognitive impairment (MCI) that have underlying AD pathology and therefore a high risk to progress to AD dementia (prodromal AD) [328,329] (**Figure 10**). Three amyloid PET tracers florbetapir (Amyvid™), florbetaben (Neurozec™), flutemetamol (Vizamyl™) have during 2012-2014 been approved by US Food and Drug Administration (FDA) and European Medicines Agency (EMA) for use in clinical assessment of memory disorders to exclude AD (Lerner AJ Neurology 2013:81:1108-1109, 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 the CSF biomarkers [330,331] and a fully automated assay of CSF Aβ42 with very low inter-laboratory coefficients of variation (1-4%) was just described While structural imaging is well established in clinical assessment of memory impairment, the use of CSF and PET imaging biomarkers for tau and Aβ pathology are starting to become incorporated into clinical routine in memory assessment at specialist clinics in many countries in Europe. However, an important question in many countries is the reimbursement from health assurance.

The use of these biomarkers in longitudinal studies of cognitively normal individuals at risk has shown that the pathophysiological process of AD begins a decade or more before the appearance of symptoms. A prospective cohort study in healthy controls, AD and MCI patients indicated that the Aß deposition is slow and that it takes around 20 years to reach onset of clinical symptoms[332]. Meta-

analyses show correlation between amyloid positivity and clinical diagnosis, age and APOE genotype [333,334]. A patient with clinical symptoms of mild AD is already at a stage of the disease with profound losses of neurons in specific brain regions, such as the entorhinal cortex [335]. Thus, it is not surprising that it is extremely difficult to reverse or slow down the symptomatic decline at this disease stage. It is likely that disease-modifying approaches will work best in clinical trials aimed at preventing the progression of the clinical syndrome in individuals with very mild or no clinical symptoms of AD yet, but with a genetic predisposition or positive CSF or radiological AD biomarkers, *i.e.*, with prodromal or preclinical AD according to the IWG-2 lexicon [302]. As explained above, some trials are already underway [336]. In these studies, AD biomarkers will be evaluated both before and after initiation of treatment to ascertain that 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. This would facilitate the evaluation of the overall results of the trials and also help in the design of new trials. Specifically, biomarkers would allow for addressing if the results of a negative trial could be explained by a lack of drug effects on the intended target or if the intended target changed in the expected direction but without resulting in clinical benefit. Similarly, clinical benefit in a positive trial would be a considerably stronger finding if it was backed by expected biomarker changes.

Many AD biomarkers are at present not standardized enough to be applied in clinical routine, but standardization initiatives are ongoing[337-339]. It should also be acknowledged that Europe is not homogeneous technology-wise in regards to neuroimaging scanners, laboratory equipment and personnel with the necessary expertise; the diagnosis of neurodegenerative diseases in memory clinics is at present made mostly on clinical grounds with brain imaging (CT or MRI) and clinical chemistry tests (CSF tau and Aβ) excluding other potential causes of the cognitive decline, such as depression, normal pressure hydrocephalus or cerebrovascular changes. Recently proposed diagnostic algorithms incorporating AD biomarkers [340,341] are presently being adapted to clinical realities around Europe, for example in the EU-JPND BIOMARKAPD project, which is a pan-European network of memory clinics and laboratories engaged in the uniform implementation and standardisation of diagnostic algorithms in the evaluation of patients seeking medical advice because of cognitive symptoms.. The diagnostic use of biomarkers will be dramatically boosted by the availability of treatments proven to be effective in pre-dementia disease stages, where biomarker evidence of AD pathology will be essential to allow for accurate diagnosis making.

Proteomic studies on plasma biomarkers have so far been disappointing, with only a few replicated positive results[342]. A recent study on lipid profiles in plasma gave promising results [343], indicating that it may be possible to discriminate AD from cognitively healthy older adults by the use of a blood test. However, the number of cases was limited and independent replication of the results is necessary before any conclusion on the usefulness of such a test can be made. It is possible that a novel approach, such as the analysis of the profile of the different sugars (i.e., glycans attached to proteins) in CSF or plasma could be helpful. Interestingly, defects in glycosylation of proteins involved in the pathogenesis of AD, such as for example tau, have been reported in AD [344]. Ideally, patients should be stratified on biomarker grounds, e.g., by amyloid and tau PET imaging or by the use of CSF Aβ and tau markers, as to whether they have Aβ- or tau-predominant AD. This stratification will most likely be facilitated when methods for imaging of tau deposition in brain by PET are available, as well as for additional processes such as neuroinflammation or cerebrovascular dysfunction, detected by MRI, PET or CSF markers. The aim will be to personalize the selection of drugs to individual patients on objective grounds. If current

secondary prevention trials with anti-amyloid therapies are successful, patients may be selected for treatment during the preclinical stages of AD based on biomarker detection [336]. Such therapies should be initiated at specialist clinics until more information on the clinical use of such therapies has been obtained. From a safety and cost perspective view, it will also be important to exclude individuals from certain treatments; for example an amyloid-negative patient should not be treated with an anti-amyloid drug. Finally, novel generic markers of neurodegeneration that may be relevant to a broad range of neurodegenerative conditions would be helpful to evaluate the effects of disease-modifying treatments intended to slow down neurodegeneration, e.g., markers of synaptic dysfunction. Novel ultrasensitive measurement techniques have just opened up the possibility to measure such biomarkers in serum and plasma [345]

What needs to be done

At a time when an effective treatment is lacking, an accurate appraisal of the societal values and utilities associated to knowing the diagnosis seems key for decision makers to allocate public funds to relatively expensive diagnostic procedures, but there are virtually no studies addressing this aspect so far. Biomarkers can help diagnosis at the preclinical stage of AD and more accurate differential diagnosis at the mild to moderate dementia stages [340,341,346] and some biomarkers are quickly gaining routine use in memory clinics. Still, guidelines for routine use of biomarkers for diagnosis are lacking, which may lead to uncontrolled and poor, non cost-effective use; overuse could lead to the identification of AD-related pathological changes with uncertain importance for the symptoms the patient presents; underuse could lead to that we misdiagnose AD as depression or other non-degenerative brain disorders. Data are also scanty on the added diagnostic value of individual biomarkers, the optimally cost-effective sequence of biomarker assessment, and the role of key variables on patient characteristics such as age, co-morbidities and social factors (e.g., education level)[347]. It is essential to develop and standardize biomarkers into practical and affordable tools for clinical use to prepare for the next generation of preventive and disease modifying AD drugs.

RECOMMENDATIONS

In summary, the diagnostic biomarkers field is under rapid development. The robustness and predictive value of biomarkers are under investigation and novel biomarkers are being actively sought.

- Currently available biomarkers need to be further developed into standardized and affordable tools that can be used in clinical routine to select patients for appropriate care and treatments as they become available.

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

- There is a need to develop tools to measure cognitive characteristics of prodromal AD. The tools should be informed by cognitive neuroscience, should be sensitive to minor impairment

and changes, and should be robust in application and informative in the populations for whom they are intended.

PHARMACOLOGICAL TREATMENT AND PRIORITIES TO ACHIEVE NEW EFFECTIVE TREATMENTS

Summary

An effective therapy for AD is perhaps the greatest unmet need facing modern medicine. To develop effective and affordable AD therapies will require an organized and concerted effort among governmental agencies, academic researchers and industry. Several drug candidates are currently in clinical trials, and a few drugs are approved for symptomatic treatment of dementia, but the overall success rate for AD drug development has been poor. New paradigms are required to incorporate advances in early diagnosis, genetic factors and epidemiology into the design of clinical trials for new drug candidates. Major longterm financial commitment will be required.

In this section, we review the few available drug treatments for Alzheimer's disease (AD) and summarise the symptoms that cannot be currently treated pharmacologically. We then describe drugs in development, and discuss the major challenges in developing effective pharmacological treatment. Finally, we provide a set of recommendations for policy decision makers.

Pharmacological treatments for Alzheimer's disease

The increasing number of people with AD is leading to markedly more use of pharmacological treatment 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 [348]. Although drug costs are a small proportion of the total societal cost of dementia (the major cost proportion is within the municipal sector for long term care (about 80%), mainly for long term care), it constitutes a significant proportion of health care costs for people with dementia and in Sweden, the dementia drug cost proportion as proportion of the costs of dementia care in the health sector has increased from 23% in 2000 to 39% in 2012. This trend indicates that the incentives to provide treatment may be different from a health care budget viewpoint than from a societal viewpoint, since the economic impact of dementia drug costs in the health sector costs of dementia is so large. Moreover, the drift in diagnostic boundaries of AD toward earlier diagnosis may lead to greater use of marketed drugs even in the absence of efficacy evidence for pre-dementia cognitive impairment.

Marketed drugs

Approved drugs for marketing in Europe are the acetylcholinesterase inhibitors and memantine. They are indicated for either mild to severe AD or moderately severe to severe AD, respectively. These marketed drugs are approved for the dementia of AD. In addition, rivastigmine is approved for Parkinson's disease (PD) dementia. No drugs are approved for mild cognitive impairment MCI, prodromal AD, preclinical AD, or for at-risk conditions or prevention. But still in the US the drugs are provided.

As all are available as generics, the price has dropped considerably, for example for donepezil: in Sweden by 98%, in UK by 97%, and in Germany by 84%, similar to previous price drops of for example enalapril, simvastatin and citalopram. However prescription *rates* have not necessarily increased although total prescriptions have due to the increasing number of people with AD is leading to markedly more use of pharmacological treatment perhaps because information campaigns from the 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 lack of evidence, as higher doses of proprietary drugs have not been shown to be more effective than the lower recommended doses.

Effectiveness of marketed drugs

The evidence we present comes from clinical and effectiveness studies of marketed drugs for the treatment of Alzheimer's disease, and does not address other conditions, such as cognitive impairment due to mixed AD, LBD, older old.

Although AD influences many functional domains, the main focus and primary outcome in most AD trials has been on cognition. Other potential meaningful outcomes, such as global measures of functionality, activities of daily living (ADL) and behaviour are in most studies secondary outcomes, and are more relevant in advanced dementia stages than in early phases of the disease. Studies in mild AD cases should include outcomes focusing on memory functions, while in later stages of the disease effects on ADL, psychiatric and behavioral disturbances are more clinically relevant.

Efficacy based on cognitive tests and daily activities inventory can be reliably assessed in clinical trials of drugs for AD. The effects for the marketed cholinesterase inhibitors, however, have been statistically small and engendered controversy on just how effective, and cost-effective, they are. The few RCTs (randomised control trials) where data on resource use and costs have been collected have not shown any significant cost savings or cost effectiveness for the brand-name drugs[349]. However, these clinical trials have not been designed for economic evaluations and the duration of these trials have been short (6 months to 1 year) in relation to the period where long term cost effectiveness is of interest. Thus, several simulation approaches have been applied, where inputs of effectiveness as well as data on mortality and costs can be applied on, for example, the expected period of survival[350]. The conclusion from such simulations (largely sponsored by drug companies) is that treatment is cost effective [349,351]. Notably, these models assume long term use of the drugs over several years even though most patients take them shorter term.

Outcomes from the trials cannot be easily generalised to clinical practice or to effectiveness. Study populations in randomized controlled trials are generally highly selected in terms of inclusion and exclusion criteria. Very old people (for example 85+), who constitute a great proportion of the population with AD, as well as persons with medical comorbidities (which are common in the oldest old) are underrepresented, making generalisations to the clinical practice of dementia care from the trials problematic. Duration of treatment in clinical trials is generally up to six months, with only a few trials extending beyond this period. In clinical trials, cholinesterase 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 when there is uncertainty about its effects[352]. There is very little unbiased information on long term use or safety. Rather there is a reliance on the medical records from research centres, research cohorts, and prescribing data.

For policy decision makers and stakeholders, long-term cost effectiveness may be of greater interest than efficacy in trials or clinical effectiveness *per se*. Since such long-term data will be unlikely available from clinical trials, other sources such as economic simulations as mentioned above, registry data or results from epidemiological studies may be of interest. From an evidence based viewpoint, these alternative sources have lower creditability than randomized clinical trials. Thus, there is no single design that can be used, and a synthesized approach where results from several sources are used may be a feasible way.

Furthermore, instead of focusing on single drugs, combined drug treatment (and combined also with various non-pharmacological treatments) in various settings are perhaps better approaches. It is the total effect of an intervention package rather than of single interventions that are of interest, as shown in the FINGER study [168]

Effectiveness of the drugs for disruptive behaviours

Randomized controlled trials evidence does not show donepezil or memantine to be effective for patients with significant behavioural disruption (i.e., agitation or aggression) [353,354]. In mild to moderate AD patients, measurable changes can be observed on behaviour rating scales but these are in patients without marked agitation, and significance of the small mean change is unclear[355].

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[356]. Antidepressants have not been demonstrated effective for depression, but in some case have shown limited efficacy as, for example, citopram for agitation in dementia[357]. Yet cardiovascular adverse effects and worsening cognition limit their use as well (FDA warning citalopram, http://www.fda.gov/Drugs/DrugSafety/ucm297391). Anticonvulsants should not be used. Newer drugs with different mechanisms of action might eventually be helpful.

It is also of importance to combine non-pharmacological and pharmacological treatment, where it is the total effect that is of interest, not the effect of a single treatment component *per se*[358].

Inequalities in AD treatment in Europe

Reimbursement is crucial to the availability of many drugs. There are substantial inequalities in AD treatment in Europe despite the existence of common standardised diagnostic and treatment procedures. The proportions of people with AD who receive treatment with approved medications and treatment durations vary across Europe (**Table 12**) [359]and globally [360]. This can be partly explained 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 (**Table 13**). Some others also require a continuous evaluation of the treatment decision to be made by a specialist, see **table 13**. Reimbursement may not be made available to people with AD living alone or living in nursing homes. Other systems require specific examinations to be carried out prior to a reimbursement decision being made. Finally, there are considerable differences between European countries in the specified cognitive test scores that limit the initiation and discontinuation of treatment (www.alzheimer-europe.org).

As seen in **table 12**, the situation varies across Europe, although the drugs are both approved or reimbursed in most countries.

The centralisation of the market authorisation process at the level of the EMA has solved the problem of existing delays between the different European countries for marketing drugs for neurodegenerative disorders. However, the launch dates of products continue to vary across countries, as well as the timing for the integration of approved drugs in the reimbursement system. Thus, inequalities in the access to new drugs for AD still exist. The demand for AD social and medical care will continue to increase. Successful future medications need to be introduced such that access to them is fair and equitable, that they are priced fairly. Any effective treatment anticipated for patients with presymptomatic or prodromal AD will also increase the size of the market and the numbers should be estimated and provided for.

Long-term effective therapy for cognitive impairment is a major unmet need. A drug that provides even one to two years of stable function or quality of life will be useful and cost-effective [361] regardless of whether the underlying Alzheimer's pathology has been affected. Indeed, current clinical trials for drugs in development for mild Alzheimer's disease and prodromal AD are 18 to 24 months in duration in order to demonstrate longer term effects.

Discussions are ongoing between the European (EMA) and US (FDA) authorities to harmonise the rules for drug approvals, since drug trials for approval often are done separately in the US and in Europe.

Challenges and recommendations with marketed drugs

Considerations with regard to current treatment include the diagnosis of AD, patients who will be offered treatment, use of evidence-based prescribing standards, and patient-preference-based standards to assist in treatment decisions; reimbursements across health care systems that are fair to patients, valid, including decisions to start and stop; and more consistent access and reimbursement policy across Europe. Patient- and family-centred standards of pharmacological treatment have yet to be developed, the use of current medications needs to be linked to their ability to show better health outcomes including better function. One need is to continue to assess effectiveness, the circumstances under which the marketed drugs are most helpful, whether there are groups or individual patients who can be recognized and who may particularly benefit.

Drugs in late-stage development

AD is a complex disease and there are many drug targets under investigation. Current research emphasis is on amyloid-β pathways, tau, and small molecules. **Table 14** lists drugs and their mechanisms that are in late-stage clinical development, i.e., phase 2 or 3. The diagnostic targets for new drugs include mild to moderate AD, prodromal AD [302] (i.e., MCI due to AD, [298]), preclinical or presymptomatic AD, and treating at-risk populations (prevention).

Drugs directed toward amyloid-β – immunotherapy, β- and γ-secretase inhibitors

The most active research is taking place in the disruption of the amyloid pathway, as Aβ production or clearance are thought to be among the earliest pathological changes and to lead to neurodegeneration. These new drugs include vaccines and antibodies to Aβ, and β- and γ-secretase inhibitors, and

modulators. The first vaccine removed amyloid plaques, but caused brain toxicity and had no clinically significant benefit [362,363]

Current active trials for Aβ immunotherapies are taking place with monoclonal antibodies: solanezumab, gantenerumab, crenezumab, aducanumab, and with several Aβ vaccines, including CAD-106 and ACC-001 (http://www.alzforum.org/therapeutics)

γ-Secretase cleaves amyloid precursor protein (APP) intracellularly to produce Aβ fragments that are thought to be toxic and critical to the pathogenesis of AD; this enzyme was thought to be a valid therapeutic target. Unfortunately, clinical trials failed with an unexpected degree of toxicity and worsening cognition (avagacestat[364], semagacestat[365]). Reasons for the failures may have involved off target effects, the particular drugs used, and dosing[366].

β-secretase inhibits the β-site amyloid precursor protein cleaving enzyme 1 (BACE1), which cleaves APP extracellularly to produce β-amyloid peptides (Aβ). The development of BACE1 inhibitors is being avidly pursued and several have entered clinical trials (**Table 14**), including AZD3293 (AstraZeneca), LY3202626 (Lilly), R7129 (Roche), E2609 (Eisai), HPP854 (High Point); and others in preclinical stages. The most advanced is MK-8931 (Merck) which is in combination phase 2/3 trials for either mild to moderate AD or prodromal AD. In phase 1 it reduced CSF levels of total and soluble AB by up to 84% and 88%. The two latter phase trials will involve approximately 1800 participants each[367] treated over 18 to 24 months. Outcomes and marketing authorization (if successful) are expected in 2018.

Tau-targeting drugs

Downregulating tau-related toxicity may reduce the impact of beta-amyloid by reducing the pathological hyperphosphorylation of tau protein, and has been demonstrated in vitro for many drugs often by inhibiting GSK3b (glycogen kinase3) which may detach tau from neurotubules. Several companies have been developing tau-related approaches, Abbvie Bristol Myers Squibb, Lundbeck, Pfizer, Tau Rx (Singapore).

Merck (Alectos) has aimed at inhibiting O-linked N- acetylglucosamine (O-GlcNAc), which modifies cell signalling and is decreased in Alzheimer's brains, and related to increased tau hyperphosphorylation[368]. Antibodies can target the *MAPT* gene or tau protein (for example, AC Immune and Genentech and J&J programs(http://www.acimmune.com/content/img/pdf/FinancingD_20140109_final.pdf) ((http://www.alzforum.org/therapeutics/aci-35)(http://www.alzforum.org/news/conference-coverage/therapies-take-aim-tau). Axon Neuroscience is in a phase 1 study with active vaccination against tau[369,370]. Tau Rx, methylene blue, is based on the view that tau clearance in general must be achieved to modify disease progression. A formulation of methylene blue, LMTX [371-374], is being tested in a phase 3 AD trial and a phase 2 frontotemporal dementia trial, with 833 mild-to-moderate patients followed for 12 months, and 500 mild patients for 18 months, respectively. Outcomes of both trials are expected in 2016.

Alternative targets and therapeutic approaches

As the targets for AD are not validated and potentially many, there are alternative therapeutic approaches to Tau- and Aβ targeted drugs.

Recommendations to advance therapeutic development

In summary, since the advent of the acetyl cholinesterase inhibitors, drug development for AD has been disappointing. All drugs in phase 2 and 3 have failed. Pursuit of the amyloid cascade hypothesis has not so far been rewarding, and clinical research efforts are now being directed more broadly. AD drug development is moving towards earlier stages of the illness, with prodromal AD and preclinical AD RCTs. This raises questions about ethics, cost sustainability, costly diagnostics (biomarkers) and analyses, as well as longer durations of trial participation for people with AD and their families.

In future, if drugs are approved for AD treatment and marketed as disease modifying or as long-term treatments**,** the spectrum for diagnostic work-ups will likely shift from mild and prodromal AD to preclinical AD. This shift may have two implications, firstly regarding the validity of early-stage or preclinical diagnoses and secondly regarding 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 have to have very high levels of sensitivity and specificity (e.g. 95-99%) to be clinically useful. There will be challenges in terms of positive predictive values when the prevalence in the target population will be (for example 10% instead of 50%, as it may be on memory clinics today). The risk for false positive and false negative cases needs to be carefully considered [375]

There is a lack of predictive biomarkers. There is no evidence that a patient with mild memory impairment will evolve differently from one with worse impairment, or, for example, that one with a small hippocampus or low CSF Aβ levels will respond to treatment better than a patient with a larger volume or higher levels. The prognostic value of AD biomarkers such as aβ and tau is unclear in very advanced age, and 70% of dementia cases in the general population are people aged 75+.

As there are difficulties in estimating the long term cost effectiveness of currently available drugs, a shift to earlier stage diagnoses, such as to preclinical and prodromal AD, the duration for expected effects of treatment will be prolonged by many years. Furthermore, the resource use and costs during the predementia period are low, and conventional trials such as RCTs will not be useful for cost-effectiveness discussions. Other strategies, such as simulations or the use of registry data will probably be better options than conventional trials.

The ageing of populations is occurring worldwide, led by the demographic transition that has already happened in many European countries and 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 critical problem is the multifactorial nature of dementia in old individuals (concurrent vascular and different types of neurodegenerative lesions).

Physical comorbidity is also frequent in advanced age, generally accompanied by poly-pharmacotherapy, with not optimal use of drugs, and with anticholinergic and sedative effects being common in geriatric patients with AD[376,377]

These challenges highlight the importance of offering a comprehensive geriatric assessment (GSA) to every patient, defined as a multidisciplinary diagnostic and treatment process that could identify medical, psychosocial, and functional limitations of a frail elderly person in order to develop a coordinated care plan to maximize overall health with aging [378,379]. GSA can support both evaluation and management of people with dementia, improving pharmacological treatment decisions. Also, proper management of multimorbidity can have benefits on cognition.

Existing and future regulatory processes

The unique challenges in AD and other dementias have driven regulatory policy. Some relevant guidance documents from the EMA and FDA in the area of AD and other neurodegenerative diseases: EMA "Discussion paper on the clinical investigation of medicines for the treatment of Alzheimer's disease and other dementias"; EMA "Qualification opinion of a novel data driven model of disease progression and trial evaluation in mild and moderate Alzheimer's disease"; FDA "Guidance for Industry, Alzheimer's Disease: Developing Drugs for the Treatment of Early Stage Disease"; FDA "Guidance for Industry, Expedited Programs for Serious Conditions – Drugs and Biologics"; FDA "Guidance for Industry, Investigators, and Reviewers, Exploratory IND Studies".

Drug development

Our conceptual models for age-associated cognitive impairment, dementia syndrome, and AD need development, and consideration of their effects on drug development. The causes of AD remain to be elucidated; it is a complex disease; and there are formidable barriers to treatment research. The several AD- related clinical diagnoses, including AD (i.e, AD dementia, mild cognitive impairment due to AD, prodromal AD) result in biologically and clinically heterogeneous groups of patients. Patients will show various cognitive profiles, severity of early memory impairments, genotypes, and expressions of putative biomarkers. This heterogeneity makes drug discovery and development more complicated. Furthermore, similar efforts should be made on the range of age-associated cognitive impairment conditions and other neurodegenerative conditions beyond AD.

Diagnostic criteria can very much affect the numbers of affected people and who are treated in clinical trials. The lack of validated drug targets and too many targets lead to ethical challenges in clinical drug development. Many drug targets may be applicable to cognitive- or brain- aging as well, not just to AD. Thus far, drugs in development for AD have lacked of action on the brain target. That is, they may target and alter one aspect of disease or brain function but then adversely or unpredictably alter another aspect.

There is great difficulty relating mechanisms of drugs to clinical outcomes. One urgent need is the development of efficient clinical trials designs and outcomes. Clinical trials have been restricted in design. The designs and outcomes tend to be nearly identical from one program to the next, and are not necessarily relevant to the modelled action of the drugs. There is a need to develop targeted clinical trials designs to allow individualisation of treatment.

Another is the need to develop a clinical trials infrastructure. Delays and barriers to recruitment limit trials. Samples of convenience may not constitute valid trials samples for many purposes. For example, the median onset of dementias and AD is in the early 80s, who also have substantial concomitant illnesses, and neuropathology is usually mixed[380,381]. Clinical trials are done with much younger patients in their 70s with little concomitant illness or medications, and attempts are made to exclude other causes of cognitive impairment.

One important challenge is the need to identify the real benefit of anti-Alzheimer drugs for elderly patients, taking into account the mixed nature of the brain damage and neurodegeneration causing dementia and the impact of other illness, and poly-pharmacotherapy on cognition. Generalizability of clinical trials results is limited when conducted in young older people with no or little comorbidity, to

the general population. It is likely that substantial numbers of subgroups of the Alzheimer's population will not be helped by any particular treatment.

Major barriers to successful drug development are our *current translational models* and translating the way drugs work in the pre-clinical and animal models to humans. It is possible that newer approaches to prevention trials, stratified medicine, and smaller phase 2a trials to gain early signals of potential efficacy may be helpful.

The *failures of the trials and development programs* have led to many explanations, although, the most likely explanation for the lack of effective medications is that the drugs do not work. When truly effective drugs are tested, however, their effects will overcome the current inefficiencies in clinical development.

Major challenges in drug development

- The evidence generated so far is limited by the underlying assumptions and theories implicit in the generation of the data
- The decisions on the right drug development, for the relevant groups in society, should not be taken before setting the aims that might ultimately be achieved
- Very long clinical trials using "soft" or uncertain clinical and biological endpoints are obstacles to progress.
- Other factors that can affect the success of clinical trials are the heterogeneity of patient populations, the overlap of cognitive impairing conditions, and trial participant samples which are not typical of everyday clinical practice.
- In clinical research, the risk faced by participants is higher in early phases of trials than in late phases; – hence, concentration of risk and resources on early phase research is essential.
- The development of safe therapeutics that can be used for very early intervention to prevent dementia in at-risk people
- Optimisation of clinical outcomes assessments
- Make all clinical trials data publicly available
- Drug development as a collaborative rather than competitive effort

Prospects and goals for experimental treatments

Establishing validated drug targets requires greater understanding of the several neurodegenerative illnesses, other age-related cognitive impairment syndromes, cognitive impairment with other conditions, and the numerous processes leading to illness. Advances in basic and clinical science, better knowledge and selection of drug targets will drive future drug development.

Advances in clinical trials and development methods will be incremental and iterative. AD clinical development advances have evolved through the several failures and have improved prospects for identifying effective drugs. Predictions of an effective treatment in the near future can be based only on the current drugs in development, preclinical evidence and the interest of experts and investors.

The clinical development enterprise [MAKE THIS A PANEL]

- Drugs are needed to both prevent and treat the cognitive and functional symptoms of preclinical, prodromal and AD.
- Plans need to be developed to decide what drug development to support, and to identify the determinants of successful translation of drugs to AD treatment.
- Clinical development should be justified by prior knowledge that would help to determine the likelihood for success. More resources should be provided to early clinical development so that more potential treatments can be assessed. Resources should be directed to areas where there is evidence for efficacy.
- Detailed results and outcomes trials should be broadly available immediately after studies have concluded in a manner easily understandable by the general public. Protocols should be published.
- Preclinical drug research and early phase clinical trials need replication before continuing to later phases. Avoid enrolling at-risk and AD patients in trials that should not be performed. The emphasis on phase 3 without fulfilling 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 mega-wagers.
- Assess whether or not particular clinical research is worth pursuing. (For example, is an expected 1.5 point ADAS-cog effect after 2 years of treatment worthwhile? Might efforts be better spent elsewhere?) For example, the capital put into the recently failed bapineuzumab and solanezumab phase 3 programs could have funded perhaps 20 focused phase 2 development programs for a range of compounds with different mechanisms, the outcomes of which would have provided more information than the outcomes for just two drugs.
- There should be consideration for collaborative risk-sharing with governments and industry. Drugs or approaches with common mechanisms might be developed collaboratively rather than competitively.
- Failures of very large programmes may have devastating effects. There is a societal need to reduce redundant approaches and competition between similar approaches (See Lancet series on waste in clinical trials and drug development).

RECOMMENDATIONS

Improve the clinical development infrastructure:

- Increase collaboration between governments, public, and private institutions, Alzheimer's Associations and pharmaceutical industry to facilitate clinical research. There is substantial redundant research in AD drug development.
- Increase drug discovery, development and clinical trial research budgets. Establish international methodology, cohorts, and ethical and regulatory frameworks to facilitate trials. Clinical drug development and clinical trials should be coordinated internationally. Recognize and support the different approaches to drug development.
- Improve public, private, corporate funding such that decisions are based on evidence and scientific merit, rather than by advocacy, opinion and persuasion.
- Strengthen the patients' voice in risk-based approaches to the conduct of early first-in-human clinical trials where the pre-clinical evidence base is limited. Options should be discussed for

an earlier entry into clinical development allowing the collection of valuable pharmacokinetic and pharmacodynamic information from patients. This would help to refine adaptive clinical trials and enable early failure

- Involve more patients in research. Establish registries of elderly patients with and without cognitive impairment to facilitate recruitment into trials.
- Enable a more synchronised implementation of regulatory processes for clinical trial conduct into national laws[383,384]

NON PHARMACOLOGICAL INTERVENTIONS FOR THE TREATMENT OF PERSONS WITH DEMENTIA AND MILD COGNITIVE IMPAIRMENT

Summary

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 for AD patients and their families. Lifestyle changes, exercise and nutritional support might play a role at all phases of the disease, but more research is needed to guide the implementation of significant intervention programs.

Whilst considerable efforts have been made to improve understanding of the neurobiology of Alzheimer's disease and to identify and evaluate candidate disease modifying therapies, far less effort has been focussed on developing and implementing non-pharmacological interventions. This is a vital missed opportunity, as establishing effective non-pharmacological interventions for key indications is a much more tractable target and effort focussed in this area is likely lead to tangible benefits to help people live better with dementia within a much shorter time frame.

Current Status

Cognitive Training and Brain Training games involve teaching individuals strategies to improve cognition. Generally interventions follow one of two approaches, either strategies based on theoretical neuropsychological models of cognition and/or learning (eg errorless learning) or teaching skills to try and improve specific aspects of cognition (eg mneumonic strategies to improve new learning). These interventions can be delivered to individuals or in groups and can include computer based approaches. A meta-analysis of ten, mainly small, RCTs focussing on healthy older individuals (age ranged from 60-76 across the studies) indicated a small but significant benefit (effect size 0·15, 95% CI, .103 to .194), which was generally limited to the specific cognitive domain targeted by the training.[385] A common limitation in many of these studies is that the comparison has been "no treatment" and the absence of an active control treatment. In such circumstances where the comparison group does not receive any treatment, they will not benefit from the non-specific advantages associated with any intervention due to placebo and Hawthorne effects. The consequence is that this may exaggerate the comparative benefits of the intervention being investigated. The largest and most extensive study, the ACTIVE trial, followed more than 2500 cognitively healthy older adults

of 65 years of age or older (mean age 74) during five years at 6 US sites. Ten groups of participants received training focused on attention, memory or reasoning, as well as practice and teaching people specific mneumonic (organization, visualization, association) and reasoning (teaching strategies for finding the pattern in a letter or word series) strategies in to improve cognitive performance in the respective intervention groups. The study reported benefits in the cognitive domain that was the focus of the specific training package, with memory training improving memory and attention training improving attention. Only reasoning training had the added benefit of more general improvements in memory and attention as well as reasoning, and conferred additional benefit on IADL-.[386].

Findings from studies investigating benefits of cognitive training in people with memory impairment or dementia are more conflicting. In the ACTIVE study, training in memory conferred no benefit to the sub-group of individuals with memory impairment (based on a threshold of a 1·5 standard deviation below normative values on the Rey Auditory Verbal Learning Test). Eleven RCTs, mainly with less than 50 participants, have evaluated cognitive training in RCT designs in people with AD. Out of eight studies evaluated for general cognitive outcomes (MMSE or ADAS COG), three showed significant benefits. Of note however, neither of the trials considered to be high quality by the reviewers reported a significant advantage of cognitive training. A number of studies did report benefits in at least one specific aspect of cognition, but without any consistency in cognitive domains across studies. The authors did not undertake a meta-analysis because of the huge variability between studies, so the effect size and overall statistical significance has not been elucidated. The authors concluded that there was sufficient evidence of benefit for cognitive training to merit further larger intervention studies[387].

Based upon current evidence, cognitive training does appear to have value in healthy old people, but further work is needed to examine cost-effectiveness. There is also a suggestion of benefit in some initial studies of cognitive training in people with dementia, but the majority of trials are very preliminary and better powered studies are needed.

Many commercial companies have developed and marketed brain training games. Despite the publicity surrounding the benefits of brain training games, there is extremely limited evidence to support the value of any of the current commercially available products. By far, the largest intervention study of brain training is Brain Test Britain, a 6-week online study with 11 430 participants aged between 18 and 60 years who were randomized 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 six weeks of the intervention. Participants showed a large and significant improvement in performance in the actual brain training games (Cohen's d standardized effect size 0.73 99% CI, 0.68–0.79 and 0.72 99% CI, 0.67–0.78 respectively for the 2 active interventions, but this was not translated to significant benefit in standardized cognitive assessments of executive function, attention, or working memory.[388] More recently, the longer term outcomes have been reported for the older participants in the study (6742 adults over 50), indicating significant benefits in reasoning, verbal learning and instrumental activities of daily living over 6 months with reasoning training and general brain training in comparison to the control treatment, but with significant drop-outs after 12 weeks (new ref 1).

The largest study of cognitive rehabilitation RCT evaluated 69 people with AD or mixed AD/vascular dementia, who had Mini Mental State Exam (MMSE) scores of more than 18, who were randomized to 3 arms. One group received cognitive rehabilitation (n=23) intervention to improve individualized outcomes. a second active control group of 24 people received relaxation and stress management and a third group of 22 people received no treatment. All treatments were for eight weeks. The multi-faceted cognitive rehabilitation approach consisted of weekly individual sessions utilizing teaching strategies and techniques for learning new information, maintaining attention and concentration, managing stress, and using appropriate aids. The cognitive rehabilitation intervention conferred significant benefits in goal performance and satisfaction, compared with both of the other two groups. Smaller case series have also demonstrated improvements on global activities of daily living measures using interventions based on *implicit memory*[389].

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 standardized treatment. Their intervention, Cognitive Stimulation Therapy (CST), is a group-based approach for people with mild-to moderate dementia based on the theoretical concepts of *reality orientation* and *cognitive stimulation*. designed as a very specific operationalized approach with 14 sessions of themed activities that typically run twice a week during a seven-week period[390]. A single-blind RCT of CST in 201 people with dementia (115 people receiving CST and 86 control subjects) reported significant improvements in MMSE (P = 0·04) and the Alzheimer Disease Assessment Scale—Cognition (commonly referred to as ADAS-Cog [P = 0·01]) in the treatment group relative to the control group, with additional benefits in quality of life.[391] These initial cognitive improvements following CST were sustained with maintenance CST[392]. There is also some evidence indicating the cost effectiveness of CST based on an RCT in people with mild to moderate dementia comparing 91 people receiving CST and 70 people receiving care as usual. Costs were calculated for the eight weeks before and the eight weeks after treatment. Cost effectiveness analyses usually calculate the cost of improving quality of life, usually using outcomes such as quality adjusted life years. A health economic analysis indicated that there were quality of life advantages for those receiving CST without the intervention incurring additional cost, suggesting that CST is a cost-effective intervention[393]. The positive impact of CST on quality of life has been further supported by qualitative studies[394]. Other research groups have adopted a broader definition of cognitive stimulation, and developed other intervention approaches which are less operationalized than the original Spector intervention. However, the overall evidence base for less operationalized approaches to cognitive stimulation is less clear-cut than for the specific package of CST developed by Spector and colleagues [395] [396].

Caregivers and treatment of AD

Caregivers play critical roles in the treatment of patients with AD and in research studies. For instance, caregivers' reports about their patients' cognitive impairment correlate better with objective neuropsychological evaluations than the patients' own complaints[397]. Furthermore, people with presymptomatic Alzheimer's disease whose caregivers identify that they have cognitive complaints are more than twice as likely to progress to dementia than people with caregivers who do not report such complaints (OR, 2.2; 99% CI, 1.2-3.9; P < .001), indicating that caregivers can accurately identify significant levels of cognitive dysfunction[398]. Caregivers generally provide a more accurate longitudinal history and information about daily function than can be gleaned from an office consultation. They

often can 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.

As well as being part of the therapeutic team, caregivers can become therapists themselves through cognitive stimulation techniques[399] and by managing behavioural and psychological symptoms of dementia[400]. Drug treatment for patients with AD can secondarily benefit caregivers in reducing their time commitment for supervision and assistance with daily care[401-403].

Caregivers often experience significant subjective and objective burden, high levels of stress and mood disorder, and are at increased risk of alcohol-related problems and medical co-morbidity. Supporting caregivers is therefore vital for their own wellbeing as well as to enable the best care for people with dementia. Non-pharmacological interventions play a key role in reducing stress and improving wellbeing in caregivers themselves. Several small RCTs of group Cognitive Behaviour Therapy and educational programmes that include skill training have demonstrated statistically significant improvements in mental health and coping skills[404,405]. Educational interventions without these components, carer support groups not utilizing cognitive behaviour therapy, and information provision without other key elements have conferred less convincing evidence of benefit[406].

Interventions to provide information

Information is a key part of service provision to people with dementia and those caring for them, and the importance of information and signposting is often presented as a key benefit of early diagnosis. Information can cover a broad range of topics, including the symptoms and causes of dementia, and more detailed information regarding specific symptoms, their treatment and management. Information often also covers treatment approaches, including drug therapies; the impact of dementia on caregivers, financial information, key legal issues and guidance regarding advanced directives. A number of information sources also address local service provision, charities and local groups to sign post caregivers and people with dementia to the support that they need. In a recent systematic review,[406] thirteen randomised controlled trials were identified which predominantly focused on the provision of information, although many did include additional elements such as skills training, telephone support, and direct help to navigate the medical and care system. Two of the three studies measuring quality of life indicated modest but statistically significant benefit in people with dementia and statistically significant benefits were also evident for neuropsychiatric symptoms. Surprisingly, a meta-analysis of the same 13 studies did not indicate any statistically significant benefit for caregivers with respect to caregiver burden. Whilst this evidence base does provide some support for the value of information services, future studies are needed to determine the specific elements that are effective and to optimize interventions. Designing such studies will be challenging, as it would not be ethical to deprive individuals of usual information provision. However, these studies, including a health economic component, will be essential to enable international standards to be set for the development and implementation of optimal and cost-effective information provision services.

Treatment of neuropsychiatric symptoms

There are three main types of difficult-to-manage neuropsychiatric symptoms in patients with dementia: 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, in contrast to functional psychoses, the psychotic symptoms seen in dementia are much less complex, 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.

A review of neuropsychiatric symptoms (NPS) in AD took place in 2010 under the auspices of the NPS-Professional Interest Area of the International Society to Advance Alzheimer's Research and Treatment (ISTAART)[407]. 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[408-411].

A recent systematic review[412] focusing on the value of personalized psychosocial interventions to address behavioural and psychological symptoms in persons with dementia living in care home settings highlighted the substantial evidence base supporting the importance of pleasant activities with and without social interaction for the treatment of agitation. The best established interventions include the Seattle protocols which focus upon assessing person centred activities and then introducing a care plan to ensure that individuals receive at least 60 minutes a week of enjoyable activities, with an additional focus on problem solving to maximize implementation [413]; and the approach for person centred social interaction developed by Cohen-Mansfield and colleagues [414] and the review also highlighted the value of *reminiscence therapy* to improve mood; a recent meta-analysis of RCTs of person-centred care training also demonstrates the value of specific training approaches in improving agitation and reducing antipsychotic medication use in people with dementia living in care homes. The recent WHELD trial, combining person centred care with person centred activities and exercise, has also demonstrated the potential for this intervention to reduce mortality as well as reducing antipsychotics use and improving neuropsychiatric outcomes (new ref 2). However, in the studies so far published, these training interventions did not improve well-being and quality of life for people with dementia [415]. Further work is therefore needed to try and optimize training interventions to deliver quality of life improvements, perhaps by utilizing specific elements to enable the implementation of evidence based non-pharmacological interventions in addition to more generic training to promote person centred care.

Well-being and quality of life in nursing home care

Specific figures of people with dementia living in care homes have not been calculated on a Europe wide basis. In the UK approximately 250,000 of the 750,000 people with dementia reside in care homes (Alzheimer's Society UK. Dementia UK report. https://alzheimers.org.uk/site/scripts/download_info.php?fileID=2. 2007). As the age and

dependency characteristics are similar across Europe (Alzheimer's Society UK. Dementia UK report. https://alzheimers.org.uk/site/scripts/download_info.php?fileID=2. 2007), it is therefore likely that something in the order of 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 (European Social Network. Services for older people in Europe. http://ec.europa.eu/health/mental_health/docs/services_older.pdf. 2008). Admission to a nursing home for old people with AD involves a transition with a reduction in the range of life roles, for example people are usually less involved in management of their financial affairs and may be less engaged with family, friends and hobbies outside of the care home environment. Individuals also may experience diminished engagement in meaningful activities within the care home. Life in nursing homes has often been depicted in terms of boredom, loneliness, and a disconnect between previous roles and interests and ongoing engagement in meaningful activities, for example a large observational study using dementia care mapping indicated that people spent less than 2 minutes out of 6 hours during the day engaged in social interaction and spent much of the time withdrawn[416]. 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 that suggests that best practice nursing home care involves a health-promoting approach also focusing on addressing psychosocial and existential needs through resident engagement in individualised meaningful activities[417-420]. Research shows that people with AD and other dementias in nursing homes generally have a limited opportunity to participate in individualised meaningful everyday activities [416]. The previous section briefly describes the potential benefits of personalized activities as a treatment approach for neuropsychiatric symptoms, but there is also a strong body of evidence demonstrating beneficial outcomes from interventions promoting engagement in activities adapted to cognitive and functional abilities, including improved quality of life and wellbeing, reduction in anxiety, better attention and increased alertness[418,421-427].

The essence of nursing home care is to compensate for cognitive and functional losses through assisting 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 can mean passive participation in or merely observing familiar and everyday activities, and not necessarily the use of wide-ranging activity programmes. Interventions based on promoting activities and increasing vocational tasks improve wellbeing and quality of life as well as neuropsychiatric symptoms [417,428-431].

Natural Products and Medical Foods

Studies on the potential benefits of natural products and medical food on AD have so far not yielded positive results. For Gingko Biloba, the most extensively studied product, initial studies indicated modest but statistically significant improvements in cognition, but the results were not replicated in larger and more robust studies, and the overall evidence does not indicate statistically significant benefit[432]. Intervention studies for vitamin supplements or medical foods containing vitamins have generally been disappointing.

Souvenaid is a medical food containing vitamins and other components with the aim of neuroprotection. The primary outcome measure was a composite neuropsychological evaluation battery. Souvenaid did not confer significant benefit on overall cognitive performance, and only had

very modest benefits in select areas of cognition, mainly memory. In addition, Souvenaid did not give any benefits compared to placebo in everyday functions[433]. The evidence of benefit is therefore very limited and would not meet usual standards of a recommended therapy.

The VITACOG study examined vitamin B12, B6 and folate supplementation in people with mild cognitive impairment. In the overall group there was no significant benefit with respect to neuropsychological performance or the rate of brain atrophy. There was however benefit in a post-hoc analysis focussing on the sub-group of individuals with elevated homocysteine, a homologue of the amino acid cysteine, at baseline. This is biologically plausible as elevated homocysteine is associated with low B12 and folate and has been associated with increased risk of vascular damage and dementia[434]. This could still be an important treatment approach, but a further study is needed to test and replicate these potential benefits specifically in a group of individuals with presymptomatic AD and elevated homocysteine.

The other vitamin based treatment for which there is some clinical trial evidence of potential benefit in people with Alzheimer's disease is vitamin E. The recent TEAM-AD VA study [435] examined the efficacy of memantine and vitamin E (2000iu) alone or in combination in people with AD already receiving AchEI. A statistically significant and potentially important overall clinical benefit, equivalent to six months of natural decline, was demonstrated for vitamin E alone compared to placebo on the primary outcome measure, activities of daily living. There was however no benefit in the group receiving both vitamin E and memantine, nor was there benefit in any of the secondary measures including cognition. Previous RCTs of vitamin E have produced similar mixed results. A large RCT in people with presymptomatic Alzheimer's disease (diagnosed using MCI criteria without biomarkers) suggested no benefit [436]. The ADCS study [437] did show significant benefit on the primary outcome, a composite measure of poor outcome, in people with moderate to severe AD treated with vitamin E. Bizarrely, there are many parallels to be drawn between the ADCS and the new TEAM-AD VA studies. Both reported significant benefits in the primary outcome but no benefits in any of the secondary outcome measures [please interpret these findings for the unfamiliarised reader]. Additionally, neither study showed benefit in a group combining vitamin E with another treatment in comparison to placebo. The difference between this evidence base and the evidence for other vitamins and food additives is that there are 2 well conducted RCTs showing benefit in the primary outcome measure. Nevertheless, in the absence of specific benefits in cognition or function it is very difficult to interpret or understand what factors may be contributing to the global benefit. There is also a potential safety issue to consider, as the dose of vitamin E used in these studies is 10 fold above the dose usually sold as a food additive. For these reasons the current evidence base dos not support the use of vitamin E as a clinical treatment for AD.

Fatty acids have also been a focus of interest. Two larger multi-centre RCTs each with more than 150 participants have indicated no statistically significant benefits in cognition, every day activities or global outcomes from omega 3 fatty acid-based treatments such as docosahexaenoic acid [438,439]. There has been media interest in ketogenic treatments such as axona. The theory is that the product is broken down into ketones, which could provide an alternative energy source for the brain, predicated upon the unproven assumption that the brain's ability to use glucose is impaired. The only published clinical trial, a multi-centre phase II RCT in 152 people with mild to moderate Alzheimer's disease did not indicate any significant benefits in cognition or other outcomes at the primary end point of 90 days [440].

In general, there is very little efficacy or safety evidence required to market food additives, which can have an unfortunate role in creating false expectations and potentially could lead to unforeseen safety issues. For example, there is evidence of increased mortality risk with antioxidants from a recent meta-analysis [441], and there are specific issues for vitamin E with a meta-analysis of existing evidence indicating the potential for increased mortality and an increased risk of haemorrhagic stroke [442]

There have also been promising results in cohort studies highlighting the potential benefits of *Mediterranean diet*[443], but there is potential for results to be confounded by other elements of "healthy living" and a randomized intervention study is needed.

Non-Pharmacological Interventions for people at risk of dementia

There is a growing body of literature on lifestyle and non-pharmacological interventions to prevent or delay the onset of dementia in people with pre-symptomatic AD, most of which have been undertaken by identifying people based on amnestic impairments, but without evaluation of AD biomarkers. Evidence for the benefit of social activity, weight maintenance, and diet is inconsistent or very preliminary[444]. The pivotal FINGER study[168] has demonstrated significant benefit in overall cognitive function with the largest benefits seen for attention and executive functions. FINGER is a 2 year RCT focussing on people between 60 and 77 years of age for a multi-domain intervention (diet, exercise, cognitive training, vascular risk monitoring) in comparison to a control treatment (general health advice). Although it is not clear which elements contributed to the benefits, the study provides key proof of concept that multi-domain trials are feasible and can confer cognitive benefit. The intervention did include 3 separate interventions with a total of more than 30 therapy sessions in addition to self-directed interventions. Further studies are now needed to understand and improve the cost-effctiveness of the intervention.

There is strong evidence to support smoking cessation[444], which is already widely implemented, and the effect of *cognitive reserve*[446] although this would need to be implemented as part of educational policy across the life course as the development of cognitive reserve is largely based on childhood cognition and educational attainment, together with occupation in adult life.

A number of small- and medium-sized trials have investigated the effects of exercise specifically in people with subjective memory problems, mild cognitive impairment (MCI) or pre-symptomatic AD. The main studies have identified participants based upon amnestic deficits or subjective reports of memory difficulties in the absence of Alzheimer's disease, and did not require the presence of alterations in AD biomarkers. The largest trial, conducted in Australia included 170 adults, of whom all had subjective memory complaints and 92 had -MCI, demonstrated a significant advantage in cognition on the ADAS COG at 6 months follow-u as the primary outcome. Additional benefits were seen global outcome and benefits were maintained for 18 months. The benefits were more pronounced in people with MCI[447]. Several exploratory trials of aerobic exercise in people with MCI, most of which evaluated a range of measures without stipulating a primary outcome, have also reported statistically significant improvements in cognition, function, cardiovascular fitness, motor performance, brain plasticity and AD biomarker levels [448-451] and a recent systematic review has concurred that there is consistent evidence of cognitive benefits from aerobic exercise in people with pre-symptomatic AD[452].

The evidence is already strong but larger and better powered RCTs are now required in people with pre-symptomatic AD in order to determine whether exercise can delay "conversion" to symptomatic AD and to provide evidence regarding cost-effectiveness, and to inform practice. Several studies are currently examining the potential of multicomponent interventions including exercise to prevent dementia in people with cognitive impairment and vascular disease or vascular risk factors (*e.g.*, ENLIGHTEN, THINK FIT, AETMCI, POEM, My Buddy). These trials will provide evidence to add to our understanding of cost-effectiveness, the potential additive benefits of multi-component interventions, and the specific groups of individuals where this type of intervention may confer optimal benefits. However, exercise already has a better evidence base than any other pharmacological or non-pharmacological intervention for people with presymptomatic AD, and there is a strong case that we should be routinely offering exercise interventions as a core part of the clinical management of these individuals. To give an indication of the potential public health impact, a recent review calculated that a 25% reduction in inactivity could prevent up to one million people developing AD worldwide, based upon the relative risk of incident dementia from 16 longitudinal cohort studies[96].

Implementation

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 there may be opportunities to further optimize the benefits of person centred care training in nursing homes, there is already clear evidence that several specific interventions to improve person centred care (eg FITS, Dementia Care Mapping) confer benefits in i neuropsychiatric symptoms and enable a reduction in antipsychotic use. Despite this, a recent survey of available person centred care interventions in the English language indicated that only 3 out of 170 (1.8%) interventions were supported by clinical trial evidence of benefit [415]. This is because many training programmes have been developed by private companies, but have not been evaluated and there is no evidence of whether they benefit people with dementia. The interventions that are effective all involve a therapist working with care home staff for a period of at least 4 months to re-inforce the training. Although some of the un-evaluated training programmes follow good educational principles, they do not generally have this additional component. Tighter criteria are needed to require 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 with presymptomatic Alzheimer's disease, where general recommendations are often made without attention to detail or structure for implementation. A programme to train and support CST therapists has been developed by University College London and has enabled some adoption 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 CST.

Future vision and goals

The G8 UK summit on dementia on December 12, 2013 emphasized the need for non-pharmacologic interventions that are effective and safe, and can be used world-wide. The future vision therefore has to be a routine implementation of evidence-based effective and cost-effective non-pharmacological

therapies for the treatment of cognition, function, neuropsychiatric symptoms and caregiver support and a better understanding of the optimal combination of non-pharmacological and pharmacological interventions as a routine part of clinical care to more optimally harness the potential of caregivers as "co-therapists" to improve outcomes for people with dementia.

Challenges

Further systematic review and international consensus are required to enable a blueprint for current best practice and to identify the non-pharmacological interventions that should be routinely available as a part of clinical care, and to identify the key research gaps. The absence of a strong commercial interest in the development of non-pharmacological interventions has resulted in a particular challenge to obtain funding for RCTs examining the additive benefits of non-pharmacological and pharmacological interventions and large adequately powered RCTs of personalized non-pharmacological interventions are time consuming, expensive and difficult to undertake. There may be opportunities to streamline other non-pharmacological interventions such as cognitive training and exercise by utilizing self-directed on-line interventions. In treating neuropsychiatric symptoms, the lack of clear research definitions for key symptoms, such as agitations, is an additional challenge, with different definitions used in different studies and by different assessment tools. 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 contributed to by non-specific benefits, increased interaction and spontaneous resolution are an additional challenge which need to be addressed. Proposed solutions include the introduction of a less intense non-pharmacological intervention lead in period for all participants, increasing the symptom threshold for entry into trials and utilizing novel approaches such as central rating through video links to reduce the number of raters and increase the inter-rater reliability for primary outcome measures.

Personalized activities for people with dementia living in nursing homes requires a shift in culture from 'doing for' towards a culture of 'doing with'. The overall philosophy of care as well as organisational demands and priorities can facilitate or obstruct resident engagement in activities and health promotion.

We need to ensure the widespread availability of good quality information in Europe, but also to learn to understand the added components of information and educational interventions that are necessary to confer benefit to people with dementia and those caring for them.

RECOMMENDATIONS

- Systematic reviews are needed and must be supported by an international *Delphi consensus* to agree on evidence-based effective non-pharmacological interventions that should be available for patients in Europe and for what indications.

- European recommendations and an infrastructure to enable 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, Cognitive Stimulation Therapy, personalized activities and Person Centred Care Training in Care Homes and Activities with or without social interaction for the treatment of agitation.

- A European consensus regarding the highest priority non-pharmacological interventions would be extremely helpful in guiding reimbursement decisions in individual countries.

- Additional RCTs are needed to address key gaps (eg non pharmacological management of sleep disturbance, pain, psychosis, apathy in people with dementia)

- Better models are needed to fund partnerships between public funders and commercial organizations to address the funding challenge and to better enable key studies examining the combination of key non-pharmacological and pharmacological interventions and to enable academic-commercial partnerships.

- Open data access to randomized clinical trials using non-pharmacologic treatments is needed to support systematic reviews and meta-analyses based on individual patient data.

- Treatment manuals and programmes should be generally available as part of dissemination for effective non-pharmacological interventions.

- Non-pharmacological interventions and activities can have an inherent ethical value in high quality care even if it is sometimes difficult to detect measurable group level outcomes. 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.

Glossary of terms non-pharma intervention

Implicit memory is an aspect of memory where previous experiences aid the performance of a task without conscious awareness of these previous experiences.

Reality Orientation is 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.

Cognitive Stimulation: The general principle based on the "use it or lose it" philosophy that it is beneficial to keep the "minds" of people with dementia active through various pastimes, interactions and activities.

Reminiscence therapy uses tools such as life histories, shared memories and familiar objects of past-periods to improve wellbeing, usually in a group setting.

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

Cognitive reserve is a concept focusing on the resistance of some individuals to the impact of brain damage (including neurodegeneration) based upon education, stimulating work and stimulating social interactions.

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

FORMAL AND INFORMAL CARE

Summary

The care of AD patients does not easily fit into typical healthcare delivery systems, especially those that rely on active patient involvement. Longterm care of dementia patients often begins at home in a collaborative partnership between informal and formal caregivers. Institutional care for severe dementia patients is demanding and costly, and little research information is available concerning the transition between informal family care and institutional care. Patient autonomy and ethical considerations are an ongoing challenge in clinical decision making in dementia care. Worldwide, the burden of care often fall on family members, but effective assisted-care and skilled nursing homes will become increasingly important, especially in Europe with shifting age demographics. Compassionate end-of-life care must respect social norms.

Current status

People with dementia need care and support in many areas of their lives. This might be provided by health care, social care, housing, transport, leisure or other sectors. Irrespective of provider, this support can be categorized into three main domains: (a) support in basic activities of daily life (ADL), (b) support in instrumental ADLs (IADLs) and (c) supervision to safeguard individuals from harm [324]. In addition to these forms of care and support, individuals with dementia may receive specific medical services such as injections, infusions, sore management medications to alleviate dementia symptoms. ADLs are dressing, eating, toilet visits, personal care activities, moving around the home or a care facility; these are very basic personal activities. IADLs relate to more complex activities with a social component: preparing food, shopping, managing money, laundry, cleaning the house, managing public transportation and communication, for example using the telephone. One challenge with IADLs is that they are influenced by context. Therefore, they are also more closely linked to technical abilities, such as the use of mobile phones, use of internet [325], or use of technical equipment in care.

Given the multidimensional needs of people with dementia, the care and support they receive often spans a number of sectors and does not easily fit into typical health-care delivery structures. It is also not always in harmony with traditional ways of organizing and financing formal care into health and social care categories. Traditional health care takes place in hospitals, specialist and primary care settings, and is provided by physicians, nurses, physiotherapists, occupational therapists, psychologists, and healthcare assistants. Long-term care in nursing homes (or similar) or in the individual's own home can be delivered by either or both health and social care providers. Similarly, day care can have a 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 or other carers), although the meaning and separation of these concepts is changing, as discussed below.

Most people with dementia will receive both formal and informal care during the course of their illness. Indeed, there is no health or social care system in the world that would be able to meet the needs of people with dementia without these informal care inputs. Consequently, strategic policy discussions, case-level planning and evaluations all need to ensure that they fully recognise the considerable contributions made by family members and other unpaid carers, and should factor into their thinking both the (opportunity) costs for carers and the consequences for their own health and quality of life[326].

An important reason for the blurring of the distinction between paid staff and family and other unpaid carers is because the latter are 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 [453]. The growth of different forms of self-directed support has been a notable feature of many social and health care systems, giving patients and their family members more control over their care; personal budgets pass responsibility for managing care resources to the patient or carer, often with both effectiveness and cost-effectiveness advantages [454]. However, in contrast to other chronic disorders, care planning and self-directed support are complicated in the case of dementia by the effects of the cognitive decline (mental capacity, lack of insight, legal issues of impaired autonomy, and risks of financial abuse). Thus, different ways and strategies of closing the gaps between all involved factors and participants including clear political strategies such as national dementia care plans, case management plans, counselling, and education are crucial for quality of care.

It should also be noted that the needs and demands of patients and their families cannot all be met by public sector health and social care agencies alone, even if the public sector tends to be dominant in most European countries. Major roles are played by organisations in the voluntary sector (often called charitable, non-profit or third sector) and in the private (for-profit) sector. The voluntary and private sectors deliver mainstream services as well as engaging 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 from charitable donations or private market transactions, selling care services directly to people with dementia or their families. Dependent on national structures and local conditions, such services could serve as either complements to or substitutes for available public sector resources. Whether such services are more cost-effective than the public services is, however, hard to say [455].

Formal (paid) care

Table 15 provides a list of formal care resources and activities, including staff support, aids and adaptations, and newer technical support such as alarms and other forms of telecare. For the purposes of policy development, local planning and commissioning, and for regulation and monitoring, it is important that each activity is measurable and quantifiable in some way (e.g. hours, days or visits). The definition of "institution" varies widely. It could be a specialised small group home for six to eight people with dementia with staff trained in dementia care providing round-the-clock support, or a supervised facility with low staffing ratios, or a large nursing home with several hundreds of people with dementia and an emphasis on medical care. The wider concept "long term care" also includes comprehensive care at home. The ultimate aim for the high-quality formal care of people with dementia is to create an environment in which the individual's needs are met, and where they are respected and can experience dignity, meaningfulness and wellbeing in spite of their difficult symptoms and limitations. Care needs to go beyond the provision of basic physical tasks and procedures to include the creation and maintenance of a person-centred, positive and welcoming climate and the support of relationships. Good formal care should have at least two dimensions: completing care tasks, and building meaningful relationships and engagement. However, there is a risk that the care tasks are given almost exclusive priority in financially-strained 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 tasks. Ethical dimensions also need consideration, even if it is difficult to gauge the outcomes of promoting dignity, meaningfulness and well-being. Good care for people with dementia means meeting physical, psychosocial and existential health needs, as well as promoting a dignified and good life. The processes of planning, organising, funding, delivering and evaluating formal dementia care need to acknowledge and support the completion of care tasks as well as build meaningful relationships and engagement in order that well-being becomes a right and a priority.

Informal (un-paid) care

Even if the analysis of the circumstances of informal carers is complex (including also for example the needs and preferences of carers), a pragmatic and narrowed approach for economic analyses is to focus on time spent on care. As mentioned above, it is important to clarify which kinds of activities are included in informal care, otherwise comparisons are not possible or meaningful. By using the division in three types; ADL, IADL and supervision it is possible to get a good overview of how informal carers´ time is used. The quantity of informal care can be measured in different ways. A direct and continuous observation timed is the best way since then it can be directly measured, but for practical reasons it is useful only in validation and exploration studies [327]. Diaries and recall are the most frequently used methods to quantify informal care, although recall may overestimate caregiver time [328].

Instruments for assessing the amount of care may be generic or diagnosis-specific. Data may be also collected in different ways: interviews, diaries, medical records, registries, *etc*. There may be legal and ethical aspects involved in how to get access to data that can vary a lot between and within countries. In dementia/AD, the Resource utilization in dementia (RUD) instrument [329, 330] and the Client Service Receipt Inventory (CSRI) [331] are comprehensive and frequently used instruments to collect data on resource utilization. When combined with appropriate unit cost, these instruments aim to calculate costs from a societal viewpoint, including use of health and social care resources as well as informal care time. Examples of other instruments are the Caregiver Activities Time Survey (CATS) [332], the

Caregiver Activity Survey (CAS) [333], and the Resource Use Inventory (RUI) [334]. The CATS captures formal and informal caregiver time use across a range of tasks and activities, while the CAS measures caregiver time and some aspects of caregiver burden. The RUI from the US asks about resource use in the past three months and is designed for AD prevention trials.

It is not easy to get a view of how formal and informal care resources are used by people with dementia worldwide. Such data are to a great extent available from high-income countries. However, the Alzheimer´s Disease International (ADI) with its 10/66 group, Alzheimer´s Association, as well as Alzheimer Europe has in recent years broadened the picture. ADI´s World Alzheimer Report 2010 and linked publications [1, 4, 335] were based on a very comprehensive review of the use of formal and informal resources worldwide. Informal care was very often comprehensive and in low and middle income countries the most important form of care. In low income countries, the social care sector (home care, nursing homes, day care) was almost non-existent and 90-100% of dementia cases were estimated to live at home (about 50-90% were estimated to live at home in high-income countries). Women were the most frequent carers, 55-91% with a tendency of a lower female proportion in high income regions [456]. However, in the ADI report it was concluded that the education of women in low and middle income countries and their increasing participation in the workforce (which generally should be seen as a positive human development indicator), tend to reduce womens´ availability for informal caregiving. Spouses were the most common informal caregivers but with considerable variations (daughters or daughters in law are in some countries/cultures more frequent as caregivers). Data on formal and informal care of people with dementia from Eastern Europe are also rare, but as part of the EuroCoDe project (administrated by Alzheimer Europe) [5, 336] data from Hungary were presented and, as part of the ICTUS study, [337] similar resource-use figures came from Romania**.** Although figures from Eastern Europe must be judged cautiously due to the limited number of studies, it seems as the contribution of informal care is higher in Eastern Europe than Western Europe and in parallel, the proportions of people with dementia that are living and cared for in nursing home is lower in Eastern Europe.

Future goals and vision

For many persons with dementia and their families, the dominant priority is *timely access to care*. This is clearly demonstrated, for example, in the EU-funded projects RightTimePlaceCare [457] and ACTIFCare [338], which explore how a timely care planning and a timely diagnosis can facilitate care and help patients and their families to have control of their situation. Care that is inadequate and arrives too late is ineffective, as well as being very burdensome for some families, while too much care too early can create dependency and wasted resources. National strategies for dementia, such as those in France, the USA, UK, the Netherlands, Sweden and many other countries [458] all emphasise the need for timely diagnosis. More generally, those national policy frameworks aim to set out how to improve care and support, including strategies for implementation across health, social care and other sectors.

One clear need is for better information on the multidimensional needs and related preferences of people with dementia and their families. Information and advice can help those individuals gain some understanding of the disorder and its consequences, while self-directed support – if it is possible within a particular national or local context – can contribute significantly to empower them to be active partners in care. Principles of person-centred care, where the individuality of the person with dementia

is acknowledged in all aspects of care and treatment, are vital to improve quality of life both for the patients and for their family members[339].

Formal care support for family members and informal caregivers, such as day care [340], respite care [341], counselling, [342] as well as various case management programmes [343] (+ new REF) is crucial for better quality of life, and can also represent a cost-effective use of resources. Timely diagnosis of dementia [344,458] is obviously necessary to arrange for timely care. Timely does not necessarily mean as early as possible (such as in a preclinical state) and it does not indicate mass screening programmes since there may be great problems with false positive cases [345]. However, opportunistic screening for dementia where people who, for example, are offered a cognitive tests in a primary health center may be an alternative option [346]. Although care is organized and financed differently across Europe, early detection of dementia and timely access to post-diagnostic support demands some kind of care infrastructure, including diagnostic resources, support programmes for people living at home, and resources for long-term care in (hopefully) home-like institutions with staff available around the clock or as needed.

Challenges

Two of the main challenges are how to organize care in order to achieve the vision of timely care, and how to ensure the effectiveness and cost-effectiveness of care systems.

The diagnosis rate of dementia varies within and between countries, but the iceberg metaphor [347] seems appropriate. It is not only an issue of resources, but also a question of awareness and attitudes [348]. The main arguments for an early diagnosis today are linked to care planning in a narrow context (what do we need to do and plan for in the immediate future?) and to planning across the life-course in a broader context (what are the long-term consequences of the diagnosis?) [346]. Policy statements such as from the G8 summit in London in December 2013, or from the World Health Organization [1] in 2012 and the European Parliament in 2009 [2] are important for raising the profile of dementia and ensuring that it is high up on political agenda; while national strategies and local dementia plans are obviously important for turning those high-level aspirations into the reality of care and support as experienced by individuals with dementia and their families. One enduring challenge in the diagnostic process is accuracy, particularly in the 'grey zone' transitions from normal cognition to mild cognitive impairment to very early dementia. It is unclear how well today's diagnostic pathways avoid the problems of false positives and false negatives: either of these misdiagnoses could be enormously distressing, with negative psychological consequences from a false positive and delayed support and care planning from a false negative.

Long-term care of people with dementia is very demanding on staff time and therefore very costly. Long-term care refers not only to institutional provision but also support, often quite intensive, in community settings[459]. Most people with dementia, especially as their condition gets more severe, need support not only in instrumental ADL but also in basic ADL and more general supervision, and overall this can amount to a much heavier need than in other chronic disorders where cognition is not affected [460] . As the numbers of people with dementia grows, the funding of long-term care becomes a greater challenge, which in turn is forcing national governments to seek new strategies for

sustainable long-term care[459] . However, there is an obvious tension between the need to contain future costs and the desirability of better education and training of care staff in order to improve the quality of care. Offering better working conditions and higher salaries in order 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. For example, in a Swedish study on day care for people with dementia with special trained staff it was shown that nursing home admissions were reduced [461]

Since a high proportion of care at home is already provided by family members, and given the high cost of even maintaining current patterns of formal care into the future, another major challenge is to ensure the continued availability of unpaid carers. This is especially difficult given 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 those families, and higher employment rates for women [462]. Informal carers also need to be supported to help them manage the heavy personal burden of caring. Encouraging results have emerged from a support programme in England which 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 [349, 350]. The basic components of support ought to be reproducible in other country contexts. Counseling programmes have also been shown to be effective both in terms of quality of life of carers and to postpone nursing home admission [463].

Despite developments in recent years, research evidence is scarce on the interaction between formal and informal care, on the interactions between different elements of health 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.

RECOMMENDATIONS

National policy strategies and implementation guidelines for dementia care, aiming for a later development into EU/global guidelines, are needed in all countries. Such frameworks should include at least the following:

- Timely diagnosis of dementia.
- Wider availability of evidence-based post-diagnostic support and information programmes for people with dementia, families and other carers.
- Better coordination between health, social care and other relevant sectors (such as welfare benefits and housing).
- Development of case management and coordination programmes to help people with dementia and carers to access the services they need at the time they need them.
- Strategies for recruiting, educating, training and retaining staff skilled in dementia care.

- Action to improve awareness of dementia among health and social care staff, and across society more generally.

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

ETHICAL CONSIDERATIONS

Summary

Ethical considerations are important in dementia risk assessment, treatment and routine care. The inherent loss of patient autonomy and competency that coincides with the clinical progression of AD and other dementias is a complicating factor. Ethical considerations can raise important challenges for the design of clinical trials, especially in large clinical therapeutic trials where regulatory organizations must work hand-in-hand with academic and industry partners.

With quickly expanding basic knowledge and ongoing innovation in diagnostic and management options in AD, new ethical issues require careful attention to realize improved quality of life and wellbeing for this vulnerable patient group. These issues affect both research and patient care in the fields of prevention, diagnosis, guidance and treatment, as well as policy making.

The rapidly growing number of AD patients results in considerable increase in expected health care costs, while the growth of health care expenditures has to be limited. The quest for sustainability in health care gives an extra urgency to the ethical and societal choices that have to be made for technical and psychosocial advances needed in dementia care. This section is focused on the ethical issues directly involving patients with AD or prodromal stages, their proxies and the professionals delivering dementia care services (**Table 16**). These issues are mainly deduced from the internationally accepted perspective of Beauchamps and Childress. [464] Their main principles, which are the widest accepted tools of reasoning in solving ethical dilemmas in health care, can be abbreviated as: doing well, not causing harm, respecting the individual's autonomy, or striving for justice for all.

Linking these principles to the widely accepted paradigm of evidence based medicine results in very important messages for policy making. The first is that introduction of new diagnostic tools should be evaluated on proven net benefit for patients, which extend beyond reaching sufficient added diagnostic value to also realising added value by being better informed and improved wellbeing. The second concerns shared decision making and maximising the patient's autonomy. This has to be based on sound assessment of the patient's competency to consent, which should be a required skill for all physicians caring for patients in all stages of cognitive impairment. A diagnosis of dementia does not mean that patients are incompetent and patient involvement is desirable in shared decision-making in all diagnostic and treatment decisions. Thirdly, advanced care management and advance directives should be discussed already at an early stage in the disease regardless of whether patients live in low, middle or high income countries. These ethical and public health questions may be a greater challenge in low income countries where the number of AD patients will grow most dramatically.

Increased international collaboration puts a demand on harmonized ethical committee decisions on a higher level, ie national/EU level.

Prevention and early diagnosis: Ethical considerations

As mentioned in previous sections, recently some evidence has been delivered on the potential beneficial effects of exercise, nutrition and other lifestyle changes [267, 285, 288, 296, 306-09, 465]. Moreover, long lasting drug trials such as the DIAN study have started to focus on prevention of AD in people at high risk. This sort of study raises new ethical questions, some of which were addressed in the section on ethical concerns on genetic testing.

In research studies, Alzheimer's disease pathology is more and more detected using new biomarkers well before dementia is clinically diagnosed and even before symptoms of serious cognitive decline occur [298,466]in line with the proposed research criteria. There is currently no evidence that these criteria should be used outside the realm of scientific research. Apart fom the lack of knowledge on the predictive value of these criteria for the development of clinically overt dementia in an average outpatient clinic population, there is currently insufficient evidence that early or "preclinical" diagnosis will improve patients' health and well-being [467,468]. The question is whether we should inform persons that they are possibly at high risk for developing dementia, for which still no effective treatment is available. To answer this difficult question, individual benefits should be weighed against possible disadvantages. Once there is sufficient certainty on the diagnosis, early disclosure paves the way for timely psychosocial interventions ameliorating symptoms in dementia, which may be more effective when started early. It may also reduce strain in carers as they may be able to adapt more successfully to the cognitive and behavioural changes occurring during the natural course of dementia [469]. Moreover, knowledge about being at risk for dementia empowers patients and carers to make important decisions about future treatment, care and life in general [470,471]. On the other hand, the decision to enter a diagnostic process may be burdensome and provoke anxiety, and may be harmful when it raises false expectations of a potential cure [471]. Pre-symptomatic diagnosis might also lead to early stigmatization, social and emotional isolation, and have important practical consequences for daily life, such as on obtaining insurance and not being allowed to maintain a driving licence [472].

Empirical data on the benefits of early or pre-symptomtic diagnosis are largely lacking. People differ in how they cope with perceived cognitive decline, and in their needs and preferences for an early diagnosis. General practitioners' experience is that many patients do not want additional diagnostic evaluation when they present themselves with cognitive disorders in primary care [471]. Memory Clinics and Alzheimer's Centres are visited by a selected group of persons, most of whom are highly motivated to receive an early diagnosis, and are willing to undergo all diagnostics available. It is the responsibility of the clinician to clearly explain 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 may result in professionals implicitly assuming this active statement to be the preference of all patients with memory complaints, thereby overlooking those who prefer a more conservative approach.

Pepersack and Gauthier propose a framework for diagnostic disclosure to reduce practice variation and improve average quality of care[472,473], which they divide into three phases. In the 'before phase,'

key objectives include determining whether the patient and his/her family members wish to know the diagnosis, identifying the coping style of the patient (here defined as the ability to develop adaptive strategies in the face of emotional distress); the psychological profile of the patient and his/her entourage, as well as 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 'during phase' include establishing what the patient and his/her family know about AD, using terms such as ''Alzheimer's disease, or memory complaints'' instead of ''senile dementia'' and avoiding the use of words such as ''incurable.'' In addition, the diagnosis is to be directed first and foremost to the patient, with the proviso that, should the disease be in its initial stages, the patient's family is not to be informed of the diagnosis without the patient's consent. Objectives for the phase following the disclosure include ensuring that the information presented is understood by the patient and his/her family; providing contact information for psycho-education programmes, and scheduling a follow-up meeting.

For the whole process of diagnosis and disclosure, doctor and patient together should best balance the potential benefits and costs required for an early disclosure, before the diagnostic process is started or continued with new techniques (*e.g.*, imaging and biomarkers). To arrive at this level, new research frameworks for evaluation of diagnostic tests should be applied, in which the value of a diagnostic test is not simply measured by its diagnostic accuracy alone, but also on how it affects patients' health and wellbeing [474]. In patient care a tailor-made approach is the best way to meet the expectations for both patient and family, prevent disappointment about the outcome of diagnostic work-up and subsequent treatment. This is not yet standard clinical practice and great inter-doctor, as well as inter-patient variability, is present. Awareness of the patients' needs and expectations is a necessary precondition for such shared decision making, and appropriate use of decision aids such as evidence based outcome tables support this shared decision making with patient and family [475]. Cultural differences in weighing doing well, not causing harm, respect for autonomy and giving all persons equal opportunities for good dementia care may lead to different outcomes in shared decision making across countries [476]. As long as evidence for a net benefit of very early diagnosis is lacking, efforts could be made into the development of guidance for optimal decision making around early diagnosis, taking into account the point of view of all involved (patient, proxies, clinicians and other professionals). Changes in general practice on early diagnosis should be monitored by collecting data on their effects on quality of care, quality of life and cost-effectiveness.

Competency to consent

Clinical assessment of competency to consent requires new consideration as more and more complex decisions have to be made on early diagnostic testing, treatments that are potentially harmful, and genetic testing, with the latter also affecting family members. This competency requires attention both in clinical management options and in recruitment for research, but tools that may be used in these different settings have to meet different criteria. Here we focus on the assessment of competency to consent in research, as new ethical questions will be met first in experimental contexts. Adequate informed consent is the cornerstone of shared decision making at all these stages. It is now well accepted that the diagnosis of dementia does not mean that a person is by definition incompetent to consent. Therefore, it is crucial to be able to judge the capacity to consent on an individual basis. Classically, what is considered necessary at least for competency judgement is: 1) ability to receive and understand information, 2) ability to process information, 3) ability to appreciate the situation and its

consequences, 4) ability to weigh benefits, risk and alternatives, and 5) ability to make and communicate a decision.

Several instruments are available for the evaluation of competency to consent based on the specific research question that motivated assessment of capacity to consent, such as the Aid to Capacity Evaluation [477], and the MacArthur Competence Assessment Tool (MacCAT) [478,479]. Other instruments are based on vignettes providing a hypothetical description of a research situation, which include elements that are in general considered crucial in decision making in dementia treatment, such as whether or not injections are given or serious adverse events have taken place. The variety in instruments to assess competency to consent reflects the major variation in routine practice on informed consent assessment. On the one hand one can try to make a judgement on capacity to consent in general; on the other hand one can aim to judge the ability for a very specific situation. General decision making capacity assessment is still often practised, while the mental functions that are needed for this competency highly differ depending on the complexity of the question at stake. In general, helping the individual to understand specific research information as fully as possible and checking whether the individual indeed understood the information (*e.g.*, by some standardized questions), are the first prerequisites for a valid assessment of informed consent, which is also the basis of the MacCat instrument. Important conditions to reach these goals are: sufficient time for the information process, and information which is compatible with the cognitive, visual and hearing capacities of the older patients.

If an individual is judged unable to provide independently informed consent on a certain issue, proxy (*i.e.*, family) or double consent (of patient and proxy) are good alternatives. However, simplified information for the patient, and asking verbal consent or assent, always remains relevant. The patient's behaviour should be closely monitored and in patients who demonstrate objection or signs of refusal, the procedures planned should at least be reconsidered. Ultimately, application of the best competency assessment instrument, which is 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. Combining these elements will give physicians and researchers the best chances for an ethically justified answer on the diagnostic or management questions raised, while maximizing the patient's autonomy.

A range of complex issues in genetic testing has been mentioned in the genetics section of this paper. However, we did not yet refer to the fact that research projects often also have a major impact on relatives' self-assessment of their health currently or in the future [480]. Currently, relatives do not have a role in the standard individualized informed consent procedure of patients with dementia in most European countries. However, the question arises whether it should be required to give relatives always a voice in the informed consent procedure along with the consent of the research subjects themselves, especially when the diagnostic information also has impact on their dementia risk and therefore on the lives of these family members [481]. In case of clinical genetic diagnostics, mostly an investigation of all family members at risk and all patients involved is preferred to realize an overview of the familial risk status and the different phenotypes present. This familial investigation 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 patients do, this will result in incomplete data collection.

From this short overview it becomes clear that properly addressing informed consent in AD patients is a routinely required complex competency, which therefore should be an obligatory part of the training of all physicians working with AD patients. It is a first and essential step towards realizing shared decision making in the dementia care dilemmas that patient and professionals should try to establish at each important step during the disease trajectory.

End of life care

When AD or dementia syndrome due to other causes is the main health problem at the end of life, more and more compelling 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 the increased societal awareness on dementia, will probably result in an important increase of the ethical, political and societal dilemmas around end of life care for AD patients. The weighing of benefits and disadvantages of diagnostic and treatment proposals at end-of-life stage is more and more actively carried out by patients, family members and caregivers. For physicians it is increasingly relevant to personalise end of life care in order to do well, cause no harm and safeguard autonomy as much as possible. Here we will mainly discuss the decision-making process in the use of advance directives *(see e-appendix)*, as these directives may highly improve the quality of end of life care, and are reasonably well evidenced (see E-appendix on systematic review of this topic). For the delicate debate on euthanasia and end of life care the reader is referred to other papers [482,483].

In advanced care planning for patients with advanced AD, a key example of what is often debated as appropriate *versus* unnecessary care is the delivery of artificial nutrition and hydration. Decisions in this area are among the most challenging of the various decisions that confront family members and physicians with regards to the medical care of patients with advanced AD [472,484]. Family members frequently state that the 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. Interestingly, the use of feeding tubes has not been shown to prevent or delay death, nor has it been shown to improve functional status, quality of life, or life expectancy while being associated with dysphagia, aspiration pneumonia, and malnutrition [485]. Despite the existing evidence, many physicians still feel that such measures benefit patients with advanced AD.

Given the progressive nature of the decline seen in AD, the completion of advanced directives may improve guidance in such decision making from the patients’ perspective. While desirable, in the event that advance directives were not drafted, or that they are incomplete, decision-making can be guided by a consensus-based approach that incorporates the patient’s preferences, as stated or as determined by close family members and others who knew the patient well, with the wishes of family members and the opinion of the attending physician [486]. In the event of an impasse in this process, ideally clinical ethics consultants can be involved, or the local clinical ethics committees to provide counsel and assistance. However, in most European countries these services are not available in regular dementia care. Finally, it is imperative that end-of-life decisions, whether guided by advance directives or via a consensus-based approach, are guided by the principles to minimize harm and maximize comfort of the patient.

As stated in several international surveys, the majority of older subjects consider it relevant and desirable to get more information on the health-related scenario’s that can be expected in the course

of the disease [487,488]. Currently, advance directives are already widespread and routinely documented on hospital admissions, and in most nursing home admissions. However, the majority of the elderly in the community still do not have an advance directive, while in this population the benefits, for example by realizing more control on one's own future hospital care, probably will be the largest. There is solid evidence that in older adults a support service guided by primary care professionals will lead to a substantial increase of the number of advance directives realised [489], up until almost full coverage of all older subjects in specific regions in the USA, Canada and Australia with a ten-year tradition of advance directive support in primary care [490]. It has also been demonstrated that advance directives indeed have a large impact on the care supplied. For example the Physician Orders for Life-Sustaining Treatment-form (POLST), which is now a legally recognized form in about ten states in the US, proved to guide substantially the care in older subjects [491,492]. As hospital admission is usually stressful and acute or semi-acute, this is not the best moment to start such an advance care assessment, which much better can be implemented pro-actively in primary care. However, current practice shows important barriers for advance directives support by general practitioners in primary care in Europe, which may require national advance directive support services that educates professionals (see E-appendix) and supplies them with well evidenced facilitators such as information leaflets, and clear advance directive forms.

In The Netherlands up until now 5-10% of all elderly subjects in general practice has a form of an advance directive or advance care planning [492]. However, in other European countries this figure may be much lower. In older subjects with advanced dementia and chronic obstructive pulmonary disease or another terminal illness the number of directives rises to 10-40% in The Netherlands [493], but internationally the average is probably much lower. Therefore, there still is substantial room for improvement. In summary, many advance directives and advance care planning can still be much improved as a crucial step towards better end of life management and palliative care in AD. There are suggestions that this may not only improve quality of care, but also reduce use of health care resources in realizing most appropriate care for dementia patients [494,495].

RECOMMENDATIONS

- For early diagnostic procedures in very early symptomatic persons with cognitive complaints or decline, new research frameworks for evaluation of diagnostic tests should be applied in which the overall benefits and disadvantages of a new diagnostic test are evaluated both from the biomedical and the patients' perspective.

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

- Assessment of competency to consent cannot be based on a diagnosis, neither on staging or neuropsychological testing alone, but requires an individual assessment, specified for the decision to be made, performed with the aim to maximise autonomy.

- End of life care in dementia can still be substantially improved by advanced care management and if advance directives were routinely discussed in primary care.

- Harmonized national/EU ethical committee decisions.

E-appendix

SYSTEMATIC REVIEW on Advance Directives (AdvD), with special focus on AD

We found four systematic reviews of the literature on advance directives over the last ten years (Durbin 2010, Patel, 2004; Ramsaroop, 2007; Bravo 2008), of which three used meta-analytic techniques to address the question whether interventions stimulating the use of AdvDs are effective, and if so what kind of interventions are most effective in specific subpopulations (Patel, 2004; Ramsaroop, 2007; Bravo 2008). We completed our review of the literature with a search on new trials on AdvD until September 2014.

The reviews together surveyed the literature until 2009 and together analysed 55 prospective studies, of which 18 were RCTs, 10 non-randomized comparative studies and 27 non-comparative studies. Because of the reported age and in- and exclusion criteria, patients suffering from dementia were probably included in these studies, but dementia was not specifically addressed in these reviews. All four systematic reviews concluded that interventions stimulating the completion of formal AdvDs are effective, especially when interventions incorporated direct interactions between patients and healthcare professionals, and best when this is spread over multiple visits. Such interventions reached an effect size of 0.50 (95% CI=0.17-0.83), and the average pooled odds ratio for increase of formal AdvD completion rates by means of an support intervention varied from 4.0 (CI: 1.6-10.4) across randomized trials to 2.6 (CI: 1.3-5.4) when all comparative studies were included. Expressed differently, the trials showed that the increase in the percentage of persons having an AdvD following a support intervention varied from 23% to 36% (Bravo, 2008). Age was not a significant effect modifier, however over the last decades there is increased readiness to use a formal AdvD (on more issues than just resuscitation) in most recent years, and the non-clinical, community based and nursing home populations showed the highest success rate (46-49%), when compared with hospitalized inpatients (18%), which is only partially explained by the lower percentage of AdvDs at the start. This strongly suggests that a pro-active primary care approach probably is more effective than starting an AdvD intervention at a major clinical event such as a hospital admission. Only the study of Bravo et al. studied selection bias. Both with statistical testing and funnel plots there was little suggestion of selection bias in these data sets. These systematic reviews found only one random-control trial (RCT) study focusing on cost-effectiveness (Molloy, 2000). Molloy et al. found substantial less resource use after introducing and AdvD stimulation plan in a nursing home population in Canada. However, an older systematic review on cost effectiveness of AdvD support interventions found no definite evidence for reduced health care expenditures in three prospective and three retrospective studies in tertiary hospitals in the US (Taylor 1999). Another non-randomized trial on a complex AdvD intervention in America confirmed both the success of realizing AdvDs after educating subjects with advanced disease, as part of a much broader advanced illness coordination plan, and the compliance to these AdvDs (Engelhardt 2009). A recently published RCT showed that emotion-focused and an individualized approach, facilitated care planning, however these patients were all in in early AD stage(Hilgeman et al., 2104). The most recent survey on advanced care planning was carried out on a national base in Canada, which showed that only 160 (16%) of the 1021 respondents were aware of the meaning of this term while 530 (52%) and 105 (10%) discussed it with family or health care providers, respectively (Teixeira et al, 2013). This resulted in an advanced care plan in 205 patients (20%), but this was general population, and did not address the specific issues of AdvD. All these recent data underline that there is still much work to be done to reach the level that AdvD is discussed in all AD patients.

In our systematic review another four articles on RCTs with AdvD interventions were found but none of these was specifically focusing on dementia patients. First, *Sudore et al.* presented additional evidence on the importance of presenting AdvD information in a simple format to meet most (n=205) older subjects' literacy needs, by reaching a high preference rate (N=149) for this simple AdvD format and a higher AdvD completion rate (in 39 *vs* 16 subjects) in an adequately conducted RCT (Sudore, 2007). However, they studied a multicultural American population in a general medicine clinic (San Francisco), not a community based sample.

Two other hospital-based RCTs on legally competent inpatients from settings in Australia and Thailand also proved effectiveness of advanced care planning, and showed improved patient and family satisfaction and reduced stress, anxiety, and depression in surviving relatives (Detering 2010; Sittisombut 2008).

In a last RCT among the specific population of homeless subjects of all ages in Minneapolis (USA), AdvD completion could also be stimulated both by a simple information based intervention, and by a more complex counselling intervention (Song, 2010).

Additional to the review of literature, we also checked the most frequently used clinical trial databases (ClinicalTrials.Gov, Current Controlled Trials and the Cochrane Central Register of Controlled Trials (CENTRAL). However, we could not find and RCT planned for (in literature databases, or in trial registration databases) testing the cost-effectiveness of an AdvD related intervention. The three most relevant planned or ongoing AdvD intervention trials in older subjects are focusing on the concordance between the patients' AdvD and surrogate decision making by a proxy (Bravo, 2012; Trial Registration: Isrctn 89993391), and on a more extensive advanced care planning in hospitalized veterans (PI: Sudore: ClinicalTrials.gov: NCT01990236). In sum, the eight trials found do not add evidence on AdvDs in community based older subjects.

Concerns have been raised on the potential adverse effects of AdvDs because these might result in less quality of care delivered to these subjects from the time onwards that they decided on their AdvD, which might even result in worse survival. However a recent prospective observational study in 485 subjects in Colorado (USA) did not find any difference in survival or harm of the patients with an AdvD (Fischer 2011). We must conclude however that the evidence on AdvD specifically for AD patients is limited, and much more research is required.

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G8 TARGETS: *NOBLESSE OBLIGE* TO REALIZE AN INTERNATIONAL DEMENTIA DATA SHARING NETWORK

One of the main targets, expressed by the recent G8 meeting on dementia is to have researchers work together, and share data from the research they are conducting, including sharing initiatives for big data [496]. This is still a major challenge, as sharing research and clinical data for dementia research still faces many huge barriers to safeguard relevant privacy and legal issues, regulate valid and trustworthy re-analyses, warrant ethical conduct and transparency for sponsors and last but not least guarantee high quality research practice for the subjects who participated in the trials and other research. Still, considering the enormous challenges in the dementia health care domain, data sharing is the only way forward to really make progress and to meet the promises the G8 made to our aging societies[497].

As such, it can be applauded that the European call for research proposals in the Horizon 2020 programme also promotes data sharing [498] although the European Union at the same time is steering in the direction of effectively hindering secondary data use by requiring the patients' approval with increasingly strict privacy legislation that makes no exception for research use [496]. With regard to dementia research, however, there are some points, which require specific attention.

Challenges

The first challenge is how to reach an International Database for Longitudinal Studies on Aging and Dementia (IDAD), in which harmonization of the data collection over all domains to be covered is sufficiently addressed. As genetic, molecular, imaging, epidemiological, observational, and trial data are important, this is a huge undertaking. Adequate description of the data and the characteristics of setting in which these are collected ("metadata") in a standardized way is crucial but not straightforward [498].

The second challenge is how to safeguard proper informed consent for such a broad and gradually extending data-application in subjects who already have great problems in being capable to consent for the trial in which they participate. Subjects should both be facilitated to contribute to scientific progress and have what is called a "Right to innovation"[499], which refers to the notion that in principle all patients should be able to profit from scientific progress and be allowed to contribute to it, if they want to, and at the same time be sufficiently protected if they do not wish to participate.

The third challenge is to organize quality control and management of such an endeavor [500]. Interests of participating subjects, researchers, pharma and other companies, universities and research institutes, the general public and society should be balanced, by organizing transparency on the parties' interests. This overall quality control is a prerequisite to really be able to conduct high quality and reliable research on big data that has the expected impact and value, and which is certainly possible as put eloquently by futurist John Naisbitt: "we are drowning in information, but starved for knowledge" [501]. Interests in proprietorship over databases and the competitive demand to increase published output also may hinder data sharing, and should be tackled by a smart and transparent management structure.

Fourth, and not the least, the technical process of sharing the data should be made feasible, and safe, both for research databases and clinical records.

Solutions

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 positive changes in public health strategies, and support and improve the preventive strategies that are very promising already [69], but also in other research areas this approach might create breakthroughs. These advantages have become increasingly recognised throughout scientific communities, consequently prompting 17 major European funders of public health research coordinated by the Wellcome Trust to draft a joint statement supporting public data repositories [501]. Importantly, the AD neuroimaging initiative cohort study (ADNI), showed that large scale data sharing is possible and if carried out professionally and pre-planned can be highly successful [502]. We also addressed potential obstacles in data sharing for the Dutch National Care for the Elderly Programme in the TOPICS-MDS (The Older People and Informal Caregivers Survey-Minimum DataSet) initiative: a national project on data sharing in 64 research projects in elderly care [503]. Some lessons learned here are that first, to comply with data protection legislation, external users will only be permitted to access a fully anonymised database [504]. To circumvent issues related to publication rights and to prevent uses of the data for which they are unsuitable, a selected group of members from the research consortium evaluate all applications for secondary use for scientific feasibility and overlap with the studies that are already being performed or planned for. Rather than erecting barriers to secondary use, this brief assessment aims to improve secondary use because it tries to identify potential synergies with studies that are already ongoing, tries to connect applicants with researchers already on the topic, and tries to optimize the methodology of a proposed study to the possibilities offered by TOPICS-MDS. To further protect the interests of external users and to guarantee the involvement of patient representatives and to improve societal relevance of the requests, a Societal Board was established. The Societal Board acts as a safeguard against preferential release of data and evaluates the societal relevance of proposals.

Conclusion

International data sharing in dementia research is challenging, but recent examples show that it is possible. However, the development of overarching research data-bases takes time, money, effort, and expertise. *Therefore, the aim of data sharing would benefit from the establishment of an international dementia research network 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, this *noblesse obliges* to support financially and organize such a unique international dementia data sharing network sets the framework for the ambitious goal of finding a cure within 15 years.

SUMMARY AND CONCLUSION

Alzheimer's disease (AD) is the leading cause of dementia, and since the primary risk factor for AD is old age, the prevalence of the disease is increasing dramatically in most developed countries with aging populations. Even in the developing world, the incidence of AD and other dementias are probably grossly underestimated. Despite recent evidence that the incidence of AD in the "younger old" population might be levelling off or declining, possibly due to the results of mitigation of concurrent risk factors like cardiovascular disease, the cost of future medical care and associated societal burdens related to AD will soon become overwhelming.

Basic biomedical science has provided significant insights about the underlying pathophysiology of AD and other neurodegenerative diseases. Epidemiological studies have identified many risk factors for AD and the quality of care of AD patients has improved due to increase emphasis on early detection and integrated team-oriented care and treatment of co-morbid conditions. The pharmaceutical industry and government-sponsored research programmes in partnership with multinational academic consortia have advanced several promising therapeutic leads, but success has been elusive and overall progress has been disappointing.

At present, there is no therapeutic drug available to treat the underlying pathology of established AD, and there is no therapeutic option to delay the inevitable progression of AD. Human subjects research on AD is extremely complex and expensive due to a number of factors, including limitations of study design, a lack of accessible early biomarkers and ethical consideration. Drug development programmes now pose unacceptably high financial risks to investors. Because of the lack of progress in developing a cure for AD and due to the increasing financial and societal burden of AD, policy decision makers and governments have a powerful incentive to provide more resources to develop AD therapeutics. In fact, the coordination of the additional resources through multinational public-private organisations focused on the development of therapeutics should be linked to clinical care programmes at multiple levels. Multiple therapeutic targets and approaches should be pursued in parallel to mitigate risk. Even relatively minor advances to delay progression or ameliorate symptoms might have significant financial and societal benefits.

Unlike many other diseases where survival rates can be used to judge success, the progressive cognitive impairment and functional decline of AD patients takes a huge toll on individual autonomy and dignity and profoundly affects entire families.

With this background concerning the challenges of AD, we recommend a dramatic overall increase in government and private investment in the care of AD patients and the search for AD therapeutics. The individual sections of this compendium have provided specific recommendations. Here we summarize the key points of the Commission and propose how we recommend that patient care and research should be organized in the future. Given the dramatic advances in information technology, bioinformatics, molecular biology and genetics and statistical approaches to analyse mega-data, we are optimistic that geometric progress can be made if investment in the relevant clinical science is increased substantially and if a long-term commitment (15+ years) can be made to maintain the investment.

The overarching aim of this Commission is to provide information and expert recommendations to policy decision makers and political leaders about the growing problem of AD and related dementias

of aging. Unlike many other medical conditions where patients themselves can be advocates for enhanced care and focused research, the progression of AD causes a relentless decline in cognitive function and often, family members become overwhelmed as well, so that direct advocacy by those directly affected is often not possible. As the cost of care for AD patients increases, funds must not be shunted from basic research, clinical research and drug discovery programmes. In fact, dramatic increases in long-term funding for multidisciplinary research programmes is absolutely essential to decrease the burden of individual suffering and society cost from AD. Only targeted increases in investment in AD research will provide any hope of curative therapeutic drugs or other strategies to delay the onset or slow the progression of AD.Below, we have summarized some of the most important recommendations from the different chapters in this commission paper.

KEY RECOMMENDATIONS

- All individuals should have access to reliable and timely diagnosis and treatment, independent of social inequalities. Accurate and timely diagnosis is a prerequisite for cost-effective care with currently available therapies. The cost-effectiveness of new therapies will be uncertain at the time they are introduced and should not be a limiting factor for treatment of this patient group.

- There is a need to establish harmonized international databases for existing population-based longitudinal studies on ageing and dementia. This will provide powerful resources for further understanding the burden (*e.g.*, prevalence, incidence, and mortality), nature history (*e.g.*, genetic and clinical markers for early detection), and etiopathogenetic hypotheses (*e.g.*, psychosocial stress, nutrition, and frailty) for AD and dementia.

- Prevention studies need to start early in (mid)life and have a long duration in order to identify windows of opportunity for effective interventions. Many modifiable risk factors such as high blood pressure, obesity, physical inactivity and unhealthy diet are shared among dementia/AD and other major late-life chronic conditions like heart disease and stroke. Public health efforts promoting healthier lifestyles have the potential to improve generally health status in advanced age.

- Scientific collaborations among research groups in Europe require the development of appropriate infrastructures to facilitate more effective use of existing data, and rapid recruitment of participants in multinational intervention trials. Increased collaboration among governments, public, and private institutions is required to facilitate AD/dementia prevention research.

- Genetics plays a major role in current understanding of AD and will play an important role in the general prevention and care of the disease in future. To allow for optimal utilization of genetics in prevention of dementia, pre-symptomatic and early diagnoses, and present and future treatment approaches, there is a need to:

    - Systematically collect and store DNA and clinical data from epidemiology, clinical settings and clinical trials
    - Develop a legal framework that regulates the use of data for research, as well as protects the individual and the family

- Currently available biomarkers need to be validated and standardized. At the same time, the search for novel biomarkers with higher predictive value at pre-dementia stages needs to be continued. It is also necessary to develop more simple biomarkers (eg in blood) to be used in general practice.
- To find a cure or an effective therapy for AD remains imperative. For that, there is need of ambitious programmes in basic research. Without new breakthroughs in understanding AD pathogenesis, the development of a cure seems unachievable.

IMPROVE THE CLINICAL DEVELOPMENT INFRASTRUCTURE:

- *Increase collaboration* among governments, public, and private institutions is required to facilitate clinical research. There is substantial redundant research in AD drug development.

- *Increase drug discovery, development and clinical trial research budgets.* Establish international methodology, cohorts, and ethical and regulatory frameworks to facilitate trials. Clinical drug development and clinical trials should be coordinated internationally. Recognize and support the different approaches to drug development.

- *Improve public, private, corporate funding such that decisions are made based on evidence*, scientific merit, rather than by advocacy, opinion, persuasion.

- Recommendations from authorities and an infra-structure to enable non-pharmacological interventions for which clear evidence of benefit already exists should be put into practice with appropriate training, support and maintenance of fidelity.

- National policy strategies and implementation guidelines for dementia care are needed in all countries. Such frameworks should include e.g.,
    - Better coordination between health, social care and other relevant sectors (such as welfare benefits and housing).
    - Affordable long-term funding plans for dementia care that span health, social care, housing and other relevant sectors.

- For early diagnostic procedures in asymptomatic AD, new research frameworks for evaluation of diagnostic tests should be applied in which the overall benefits and disadvantages of a new diagnostic test are evaluated both from the biomedical and the patients' perspective.

Future European Perspectives

In the field of AD research, Europe suffers from several limitations that constitute bottlenecks:

1. Low level of investment and human resources compaired to the rest of the world and to other diseases.
2. Fragmentation and low coordination (in Europe, research policy is carried out by the European Commission and by the 28 member states at national level.
3. Knowledge application: Europe must introduce innovation, metholodogies and processes for promoting the application of research results.
4. European research infrastructures should be strengthened.
5. Research careers and mobility with full freedom of researchers' movement needs to be improved.

While it is clear that much more basic biomedical research will be required to understand the biology of dementia, it is important to develop and implement new approaches for pharmaceutical research and development to target Alzheimer's disease and other dementias. In the setting of current knowledge, and with currently available resources, it is unlikely that any individual pharmaceutical company (or even an alliance of companies), will 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 there is no clear strategy to mitigate risk when a profit motive that emphasizes shareholder return predominates. Therefore, we advocate public-private partnerships in which large consortia of pharmaceutical companies and public-governmental agencies can deploy capital resources and share risk.

Only agencies such as the US National Institutes of Health or an alliance of European Union health research agencies in partnership with the pharmaceutical industry will be able to assemble the required expertise and expend the capital to initiate and advance large-scale drug discovery and development programmes. Essentially all major clinical trial initiatives that target early-onset or familial dementia syndromes are US led, with at least partial NIH support. A complementary European strategy should be extremely productive; perhaps to target sporadic cases in which onset of symptoms occurs at older average ages. Such a strategy might be most effective if several approaches are 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 systematized and considered as a core principle, rather than play second-fiddle to a search for a magic-bullet therapy. For example, would controlling known intrinsic risk factors decrease the incidence or severity of disease? Do elderly subjects with normal cognition and mental function harbour some protective factors like 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 only exist currently within the European Union 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 required. In fact, it is likely if not probably that treatment of dementia syndromes might evolve to be multidimensional, with combinations of treatments for a

specific diagnosis, or numerous treatment options depending on a particular ”molecular” or genetic diagnosis. As an example, cancer treatment is now often ”patient-specific” and cancer is no longer considered to be a single entity, but rather 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 would 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 caring sciences and support cannot be over-emphasized. Relatively low-cost innovations and interventions are likely to have a huge impact on the quality of life for patients and their families and caregivers.

The discovery of informative biomarkers should be a priority and the science of disease biomarkers in Alzheimer’s disease and related dementias is still in its infancy. New biomarkers and diagnostic strategies to detect synaptic loss and apoptotic cell death in the CNS are urgently needed. The search for biomarkers might take place in large patient cohorts even independent 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 at present 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 like blood, CSF and genetic analysis plus advanced memory, cognitive and behavioural testing might lead to significant 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 of clinical trial design, for both diagnostic and therapeutic modalities, are paramount when informed consent cannot be readily or reliably obtained from human subjects, at least in more advanced stages of the disease.

In summary, effective strategies to prevent or cure Alzheimer’s disease and other dementias will require an urgent reassessment of traditional paradigms of health care practice. Although basic biomedical research as initiated by individual investigators can lead to breakthroughs and discoveries, and the pharmaceutical industry has had an unparalleled series of successes over many decades, a disease threat as large and complex as Alzheimer’s disease in an aging population cannot be left to chance on unfocused research programmes on the one hand, or to the whims of corporate risk-return business analysis on the other hand. A massive large-scale public-private partnership on a multinational scale is required, and the European Union is well-positioned due to its excellent health-care delivery system, basic single-payer model, outstanding research infrastructure, and stung pharmaceutical industry base, to take the world lead, in partnership with international organizations, to develop new paradigms to prevent or cure dementing illnesses and to provide models of compassionate care of dementia patients.

Table 1: Costs involved in diagnosing a case with Alzheimer's disease and a calculation of the cumulative costs as each new diagnostic procedure is added. Source: Wimo et al [18] Costs in Swedish Kronor (SEK) converted to Euros at 9 SEK/EUR.

Primary care level	**Unit cost (EUR)**	**Cumulative cost (EUR)**
Visit to family physician	122	122
Routine blood tests	33	156
Computed tomography (CT) scan	200	356
Visit to occupational therapist	144	500
Specialist care level		
Visit to specialist physician	367	867
Neuropsychologic testing	422	1289
Electroencephalogram (EEG)	100	1389
Cerebrospinal fluid (CSF) tests	622	2011
Magnetic resonance imaging (MRI)	289	2300
Single photon emission computed tomography (SPECT)	378	2678
Position emission tomography (PET) scan	1711	4389
Amyloid marker	1166	5555

Table 2. The intangible cost of Alzheimer's disease and other dementias, by World Bank income level

	World	High Income	Upper Middle Income	Lower Middle Income	Low Income
Total DALYs (million)	1,523	122	121	452	828
DALYs due to AD and other dementias (million)	11.16	4.39	1.04	3.73	2.00
DALYs due to dementia (% of total DALYs)	0,7%	3,6%	0,9%	0,8%	0,2%
GDP per capita (USD)	0	38,182	7,289	1,924	596
Intangible cost (billion USD) valued at 3xGDP per capita per DALY	550	503	23	22	4

Table 3. Population-based surveys and systematic reviews of population surveys on the temporal trends of dementia occurrence by continents

Study (city, country)	Study design	Study population (time periods)	Outcome (diagnostic criteria)	Key findings on the trend
NORTH AMERICA				
Langa et al. 2008 (USA)	Repeated surveys in the Health and Retirement Study	Age ≥70 for both waves; Wave 1 (1993), n=7406 Wave 2 (2002), n=7104	Prevalence of cognitive impairment (≤10 of 35-point cognitive scale)	Prevalence decreased from 12.2% to 8.7%
Hall et al. 2009 (Indiana, USA)	Repeated cross-sectional surveys	African Americans, age ≥70 Wave 1 (1992), n=1500 Wave 2 (2001), n=1892	Prevalence of dementia and AD (ICD-10)	Prevalence was stable for dementia (6.75% to 7.45%) and AD (5.47% to 6.77%)
Hebert et al. 2010 (Chicago, USA)	Repeated cross-sectional surveys every 3 years	Cycle 1: age ≥65, n=6158 All cycles: age ≥65, n=~10000 Time period: 1997-2008	Incidence of AD (NINCDS-ADRDA)	Risk of AD was stable over time (OR for trend variable 0.97, 95% CI 0.90-1.04)
Rocca et al. 2011 (USA)	Review	Time period: 1993 to 2002	Prevalence or incidence of dementia and AD	Prevalence or incidence of dementia or AD was stable
EUROPE				
Lobo et al. 2007 (Spain)	Repeated cross-sectional surveys	Age ≥65 for both waves; Wave 1 (1988-1989), n=1080 Wave 2 (1994-1996), n=3715	Prevalence of dementia (DSM-IV)	Prevalence was stable in all (5.2% to 3.9%); decreased in men (5.8% to 2.3%)

Schrijvers et al. 2012 (Rotterdam, The Netherlands)	Repeated cross-sectional surveys	Age ≥60 for both waves; Wave 1 (1990), n=5727 Wave 2 (2000), n=8384	Incidence of dementia (DSM-III-R)	Incidence decreased (age-adjusted IRR: 0.75, 95% CI 0.56-1.02, p=0.06)
Qiu et al. 2013 (Stockholm, Sweden)	Repeated cross-sectional surveys	Age ≥75 for both waves; Wave 1 (1987-1989), n=1700 Wave 2 (2001-2004), n=1575	Prevalence and survival of dementia (DSM-III-R)	Prevalence: stable (17.5% to 17.9%); Suggestive declining in incidence
Wiberg et al. 2013 (Gothenburg, Sweden)	Repeated cross-sectional surveys	Wave 1 (1976-1977): age=70, n=404; age=75, n=303 Wave 2 (2000-2001): age=70, n=579; age=75, n=753	Prevalence of dementia (historical criteria-wave 1; DSM-III-R-wave 2)	Prevalence: stable (70-year-olds: 2.0%-2.4%; 75-year-olds: 5.0%-6.0%)
Matthews et al. 2013 (England, UK)	Repeated cross-sectional surveys	Age ≥65 for both waves; Wave 1 (1989-1994), n=7635 Wave 2 (2008-2011), n=7796	Prevalence of dementia (Geriatric Mental State scale)	Prevalence decreased (8.3% to 6.5%)
ASIA				
Li et al. 2007 (Beijing, China)	Repeated cross-sectional surveys	Age ≥60 for both waves; Wave 1 (1986-1989), n=1090 Wave 2 (1997-1999), 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)	Review	Age ≥70; Time period: 1995 to 2006	Prevalence of dementia (ICD-9, 10)	Prevalence increased from 4.5% to 9.3%
Chan et al. 2013 (Mainland China)	Systematic review of 75 cross-sectional surveys	Age ≥55, n=340247; Time periods: 1990 to 2010	Prevalence of dementia and AD	Prevalence increased in all age groups
Wu et al. 2014 (Mainland China, Hong Kong, and Taiwan)	Systematic review of 70 prevalence studies	Age ≥60 Time periods: 1990 to 2012	Prevalence of dementia by survey years, age groups, and birth cohorts	Controlling for methodological factors, there is a slight increase from 1995 to 2012, and a birth cohort effect.
Sekita et al. 2010 (Hisayama, Japan)	Repeated cross-sectional surveys	Age ≥65 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)	Systematic review of 8 cross-sectional surveys	Age ≥65, n=13396 Time period: 1985 to 2008	Prevalence of dementia (DSM-III, DSM-III-R, DSM-IV)	Prevalence increased (6.7% to 11.3%)

Table 4. Putative risk and protective factors for late-onset dementia and Alzheimer's disease

Risk factors	Protective factors
Older age	**Genetic**
Genetic factors	Different genes (e.g. *APP*, *APOE* ε2) have been proposed (www-alzgene.org)
Familial aggregation	
APOE ε4 allele	
Different genes (*e.g*., *CR1, PICALM, CLU, TREM2,* TOMM40) have been proposed (www-alzgene.org)	**Psychosocial factors**
	High education and socioeconomic status
	High work complexity
Vascular and metabolic factors	Rich social network and social engagement
Atherosclerosis	Mentally-stimulating activity
Cerebral macro- and microvascular lesions	
Cardiovascular diseases	**Lifestyle factors**
Diabetes mellitus and pre-diabetes	Physical activity
Midlife hypertension	Light-to-moderate alcohol intake
Midlife overweight and obesity	
Midlife high serum cholesterol	**Diets and nutritional factors**
	Mediterranean diet
Lifestyle factors	Polyunsaturated fatty acid and fish-related fats
Sedentary lifestyle	Vitamin B_6, B_{12}, folate
Smoking	Antioxidant vitamins (A, C, E)
Heavy alcohol consumption	Vitamin D
Diet related factors	**Drugs**
Saturated fats	Antihypertensive drugs
Homocysteine	Statins
	Hormone replacement therapy
Others	Non-steroidal anti-inflammatory drugs
Depression	
Traumatic brain injury	
Occupational exposure (heavy metals, ELF-EMFs)	
Infectious agents (e.g., herpes simplex virus type I, clamydophila pneumoniae, and spirochetes)	

APP: amyloid precursor protein. *APOE*: apolipoprotein E. *CLU*: clusterin. *CR1*: complement component receptor 1. ELF-EMFs: extremely-low-frequency electromagnetic fields. *PICALM*: phosphatidylinositol binding clathrin assembly protein. *TOMM40*: Translocase of outer mitochondrial membrane 40 homolog. *TREM2*: triggering receptor expressed on myeloid cells 2.

A large number of risk and protective factors for dementia and AD have been investigated, and there are greater and lesser degrees of evidence to support these various factors.

Table 5. Characteristics of selected RCTs for prevention of cognitive impairment, dementia and Alzheimer disease based on multidomain interventions

RCT	**FINGER** [505]	**MAPT** [506]	**PreDIVA** [507]	**HATICE** [508]
Sample size	1260 community dwellers, from previous population-based observational cohorts	1680 community dwellers	3533 community dwellers	4600 community dwellers
Main inclusion criteria	Dementia 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 without dementia in GP practices	Non-demented older adults with increased risk of cardiovascular conditions and dementia
Age at enrolment	60–77 yrs	≥70 yrs	70–78 yrs	≥ 65 yrs
Study design	Multicentre, randomized, parallel-group controlled trial	Multicentre, randomized, controlled trial	Multisite, cluster-randomized, parallel-group controlled trial	Multinational, multicentre, randomized parallel-group controlled trial
Intervention	Multidomain: nutritional guidance, physical activity, cognitive training, social activity and management of vascular risk factors	Multidomain: vascular care, nutritional advice, exercise advice, cognitive training and/or DHA 800 mg/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 optimize management of vascular and lifestyle-related risk factors
Duration	2 yrs + 5-yrs follow-up	3 yrs + 2-yrs follow-up	6 yrs	1.5 yrs
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 utilisation, change in AD biomarkers	Primary: dementia, disability Secondary: cognitive decline, depression, cardiovascular events	Primary: optimization of cardiovascular and dementia risk management Secondary: change in cognitive function, dementia, cardiovascular conditions, mortality, hospitalization, depression, disability, cost-effectiveness
Status	Ongoing, completed in 2014	Ongoing, completed in 2014	Ongoing, completed in 2015	Ongoing, completed 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,

Table 6. CAIDE Dementia Risk Score: Probability of dementia in 20 years according to midlife risk score categories.

Risk factor		Points	Total score	Dementia risk
Age	< 47 years	0	**0-5**	**1.0%**
	47-53 years	3	**6-7**	**1.9%**
	> 53 years	4	**8-9**	**4.2%**
Education	> 10 years	0	**10-11**	**7.4%**
	7-9 years	2	**12-15**	**16.4%**
	< 9 years	3		
Sex	Female	0		
	Male	1		
Blood pressure	<140 mmHg	0		
	>140 mmHg	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		

Table 7. List of known genes and loci implicated in Alzheimer disease.

OR: Odds Ratio; CI: Confidence Interval; MAF: Minor Allele Frequency; PAF: Population Attributable Fraction

Chr	Gene in the region	Transmission	OR[95%CI]	MAF	PAF	PAF Type	Putative function	Possible pathways	Ref.
21	amyloid beta (A4) precursor protein, ***APP***	autosomal dominant / recessive	Complete penetrance	Rare	–	causal	Precursor of Aβ peptide, Tau phosphorylation, GSK-3β activation	Amyloid cascade, Aβ pathway Tau pathway	[176]
14	Presenilin 1, ***PS1***	autosomal dominant	Complete penetrance	Rare	–	causal	γ-secretase activity, intracellular signaling, transmembrane protein processing	Aβ pathway, synaptic plasticity, neuronal survival	[180]
1	Presenilin 2, ***PS2***	autosomal dominant	Complete penetrance	Rare	–	causal	γ-secretase activity, intracellular signaling, transmembrane protein processing	Aβ pathway, synaptic plasticity, neuronal survival	[181]
21	amyloid beta (A4) precursor protein, **APP**	codominant rare	A673T variant 0.24, p= $4.19x10^{-5}$	< 1%	–	preventive	Precursor of Aβ peptide, Tau phosphorylation, GSK-3β activation	Amyloid cascade, Aβ pathway Tau pathway	[204]
6	Triggering receptor expressed on myeloid cells, ***TREM2***	codominant rare	R47H variant 4.59 [2.49-8.46]	< 1%	–	risk	Homozygous loss-of-function mutations in an autosomal recessive form of early-onset dementia (Nasu–Hakola disease)	Immune response, Aβ pathway, neuroinflammation	[200,201]
19	Phospholipase D3, ***PLD3***	codominant rare	V232M variant 2.10 [1.47-2.99]	< 1%	–	risk	Member of the PLD superfamily	Aβ pathway	[202]
19	Apolipoprotein E, ***APOE***	codominant frequent	ε4 ε4 : 14.9 [10.8-20.6] ε3 ε4 : 3.2 [2.8-3.8] ε3 ε2 : 0.6 [0.5-0.8]	ε4 allele 13.7% ε2 [289]allele 8.4%	27.3	ε4 risk ε2 preventive	Aβ aggregation, Aβ clearance, Aβ metabolism, Aβ accumulation,Tau phosphorylation,Tau accumulation,Tau aggregation, lipid metabolism, inflammation, neuronal repair, synaptic plasticity	Lipid pathway, Aβ pathway, synaptic plasticity, neuroinflammation, oxydation	[177,178]
11	Sortilin-related receptor, L(DLR class) A repeats containing, ***SORL1***	susceptibility loci	0.77 [0.72-0.82]	4.4%	1.1	preventive	Lipid transport, endocytosis and cargo sorting, trafficking and metabolism of APP	Lipid pathway, Aβ pathway	[44,289]
8	Clusterin, ***CLU*** *(APOJ)*	susceptibility loci	0.86 [0.81-0.90]	39.8%	5.3	preventive	molecular chaperone, synapse turnover, Aβ clearance, Aβ metabolism, Aβ accumulation, Aβ toxicity	Lipid pathway, Aβ pathway, neuroinflammation, oxydation, apoptosis, immune pathway	[44,186,187]
1	Complement Receptor 1, ***CR1***	susceptibility loci	1.21 [1.14-1.29]	19.1%	3.7	risk	activator of complement system, Aβ clearance, Aβ metabolism	immune system, Aβ pathway	[44,186]

11	Phosphatidylinositol binding clathrin assembly protein, ***PICALM***	susceptibility loci	0.88 [0.81-0.96]	36.5%	5.3	preventive	clathrin mediated endocytosis	protein trafficking, synaptic cell functioning, Aβ toxicity	[44,187]
2	Bridging Integrator 1, ***BIN1***	susceptibility loci	1.13 [1.06-1.21]	36.6%	8.1	risk	synaptic vesicle endocytosis, formation tubular membrane structure	synaptic cell functionning, Tau pathway, caspase independent apoptosis	[44,188]
7	Ephrin receptor A1, ***EPHA1***	susceptibility loci	0.90 [0.85-0.95]	35.0%	3.1	preventive	synaptic development and plasticity	immune system	[44,189,190]
19	ATP-binding cassette, subfamily A, member 7, ***ABCA7***	susceptibility loci	1.23 [1.17-1.28]	16.2%	2.8	risk	substrate transporter across cell membrane	Cholesterol pathway, APP processing, immune pathway	[44,189,190]
11	Membrane spanning 4-domains, subfamily 4, ***MS4A6A/MS4A4E***	susceptibility loci	0.91 [0.88-0.93]	40.6%	4.2	preventive	No known function	cell surface signaling (?)	[44,189,190]
19	CD33 molecule, ***CD33***	susceptibility loci	0.89 [0.84-0.95]	30.7%	–	preventive	clathrin mediated endocytosis	immune system, synaptic cell functioning	[189,190]
6	CD2-associated protein, ***CD2AP***	susceptibility loci	1.11 [1.04-1.18]	25.5%	2.3	risk	receptor mediated endocytosis	synaptic cell functionning, actin skeleton	[44,189,190]
6	Major histocompatibility complex, class II, DR beta 5 and DR beta 1, ***HLA-DRB5 and DRB1***	susceptibility loci	1.11 [1.08-1.15]	27.7%	3.2	risk	clathrin mediated endocytosis	Immune response and infl ammation	[44]
8	Protein tyrosine kinase 2 beta, ***PTK2B***	susceptibility loci	1.10 [1.08-1.13]	35.8%	3.1	risk	Hippocampal synaptic function, cell migration	Synaptic cell functioning	[44]
14	Solute carrier family 24 (sodium/potassium/calcium exchanger), member 4, ***SLC24A4***	susceptibility loci	0.91 [0.88-0.94]	21.2%	1.5	preventive	iris development and hair and skin colour variation, risk of hypertension	Neural development	[44]
7	Zinc finger, CW type with PWWP domain 1, ***ZCWPW1***	susceptibility loci	0.91 [0.89-0.94]	29.3%	3.2	preventive	Epigenetic regulation	–	[44]
11	CUGBP, Elav-like family member 1, ***CELF1***	susceptibility loci	1.08 [1.05-1.11]	31.2%	2.4	risk	pre-mRNA alternative splicing, mRNA editing, and translation	–	[44]
14	Fermitin family member 2, ***FERMT2***	susceptibility loci	1.14 [1.09-1.19]	7.9%	1.5	risk	Actin assembly, cell shape modulation, angiogenesis	Tau pathology	[44]
20	Cas scaffolding protein family member 4 , ***CASS4***	susceptibility loci	0.88 [0.84-0.92]	8.8%	1.1	preventive	Cytoskeletal function and axonal transport	–	[44]
2	Inositol polyphosphate-5-phosphatase 145kDa, ***INPP5D***	susceptibility loci	1.08 [1.05-1.11]	46.2%	4.6	risk	Negative regulator of myeloid cell proliferation	Immune response and infl ammation; APP metabolism	[44]
5	Myocyte enhancer factor 2C, ***MEF2C***	susceptibility loci	0.93 [0.90-0.95]	38.9%	2.7	preventive	Hippocampal synaptic function	Synaptic cell functioning	[44]
7	NME/NM23 family member 8 , ***NME8***	susceptibility loci	0.93 (0.90-0.95]	36.8%	2.9	preventive	Cytoskeletal function and axonal transport	–	[44]

Susceptibility genes and loci that still need to be confirmed

10	FERM Domain Containing 4A, ***FRMD4***	susceptibility loci	1.68 [1.43–1.96]	3.4%	–	risk	cell structure, transport and signalling functions	Aβ pathway	[509]
6	Triggering receptor expressed on myeloid cells like, ***TREML2***	susceptibility loci	0.93 [0.91-0.96]	29.7%	–	preventive	enhances T-cell activation, innate and adaptive immune response	immune system	[44,510]
15	Thyroid Receptor-Interacting Protein 4, ***TRIP4***	susceptibility loci	1.29 [1.17-1.42]	2.0%	–	risk	transcription coactivator activity and ligand-dependent nuclear receptor binding	–	[44,341]
1	***Intergenic***	susceptibility loci	1.09 [1.05-1.13]	16.9%	–	risk	–	–	[44]
4	***Heparan sulfate glucosamine 3-O-sulfotransferase 1, HS3ST1***	susceptibility loci	1.08 [1.05-1.11]	30.0%	–	risk	rate limiting enzyme for synthesis of anticoagulant heparan	–	[44]
5	***Sequestosome 1, SQSTM1***	susceptibility loci	1.35 [1.20-1.52]	1.6%	–	risk	regulates activation of the nuclear factor kappa-B, associated with frontotemporal lobar degeneration with ubiquitin-positive inclusions	–	[44]
8	***NADH Dehydrogenase (Ubiquinone) Complex I, Assembly Factor 6, NDUFAF6***	susceptibility loci	1.07 [1.04-1.10]	46.9%	–	risk	Mitochondria protein, role in the assembly of complex I , associated with complex I enzymatic deficiency	Mitochondrial pathway	[44]
10	***Enoyl CoA Hydratase Domain Containing 3, ECHDC3***	susceptibility loci	1.07 [1.04-1.10]	38.7%	–	risk	catalytic activity	–	[44]
11	***Adaptor-Related Protein Complex 2, Alpha 2 Subunit, AP2A2***	susceptibility loci	0.93 [0.91-0.96]	36.6%	–	preventive	retrograde neurotrophin signalling and Clathrin-dependent protein traffic	–	[44]
12	***ADAM Metallopeptidase With Thrombospondin Type 1 Motif, 20, ADAMTS20***	susceptibility loci	1.07 [1.04-1.10]	40.6%	–	risk	zinc-dependent proteases	–	[44]
14	***Immunoglobulin heavy locus, IGH@***	susceptibility loci	0.87 [0.83-0.92]	10.3%	–	preventive	Immune response	–	[44]
15	***Signal Peptide Peptidase Like 2A, SPPL2A***	susceptibility loci	0.93 [0.91-0.96]	33.9%	–	preventive	aspartic-type endopeptidase activity and protein homodimerization activity. May play a role in the regulation of innate and adaptive immunity	–	[44]
17	***SLP Adaptor And CSK Interacting Membrane Protein, SCIMP***	susceptibility loci	1.10 [1.06-1.15]	12.1%	–	risk	Lipid tetraspanin-associated transmembrane adapter/mediator involved in major histocompatibility complex (MHC) class II signaling transduction.	–	[44]
17	***Angiotensin I Converting Enzyme, ACE***	susceptibility loci	1.34 [1.20-1.50]	1.8%	–	risk	Converts angiotensin I to angiotensin II by release of the terminal His-Leu, this results in an increase	–	[44]

of the vasoconstrictor activity of angiotensin.

Table 8. Classification of the identified loci with genetic association to AD according to their genetic impact on risk for AD

	Frequency of associated gene/locus variant		
Classification:	**Very rare (MAF <0.1%) familial variants present almost exclusively among AD patients**	**Variants present at low frequency (MAF <1%) in the population**	**Variants present as common polymorphisms in the population (MAF >10%)**
Disease gene	*APP* *PSEN1* *PSEN2*		
High impact (OR≥2)	*SORL1*	*TREM2* *PLD3* *APP* A673T (protective)	*APOE ε4* *APOE ε2 (protective)*
Low impact (OR<2)			*CLU, CR1, PICALM, BIN1, EPHA1, ABCA7, MS4A6A/MS4A4E, CD33, CD2AP, HLA DRB5 – DRB1, SORL1, PTK2B, SLC24A4, ZCWPW1, CELF1, FERMT2, CASS4, INPP5D, MEF2C, NME8, FRMD4, TREML2,TRIP4, Intergen, HS3ST1, SQSTM1, NDUFAF6, ECHDC3, AP2A2, ADAMTS20, IGH@, SPPL2A, SCIMP, ACE*.

Table 9. Differences between presymptomatic genetic testing for deterministic monogenic mutations and testing for susceptibility loci.

	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 (~10^{-4})	From rare to common
Test result	Highly predictive	Probabilistic
Individual impact	Strong	Weak
Family impact	High	Small
Potential population impact	Low	High
Risk	Simple (binary: yes/no)	Complex
Life-style factors	May not affect risk in general	Modify risk

TABLE 10. THE LEXICON PROPOSED BY THE IWG

Alzheimer's disease:

- starts with the first specific symptoms,
- encompasses both the prodromal and dementia phases:
- **AD dementia**: phase of AD with an impact on ADL (it corresponds to "AD dementia" in the NIA-AA criteria)
- **Prodromal AD**: the early symptomatic, predementia phase of AD. This condition corresponds to "MCI due to AD".

Typical AD:

- common clinical phenotype of AD,
- characterized by an early amnestic syndrome of the hippocampal type that can be isolated or associated with other cognitive/behavioural changes

Atypical AD:

- less common but well characterized clinical phenotypes: logopenic aphasia, posterior cortical atrophy, frontal variant of AD;
- the diagnosis of AD needs in vivo evidence of pathophysiological markers

Mixed AD:

- patients who fulfill the criteria for AD with clinical and biomarkers evidence of other co-morbid disorders

Preclinical stages of AD

- they include 2 different conditions in cognitively normal individuals (different from the NIA-AA criteria):
- **Asymptomatic at risk:** cognitively normal individuals with in vivo pathophysiological biomarkers of AD
- **Presymptomatic AD**: cognitively normal individuals with a proven autosomal dominant mutation

Alzheimer's pathology:

- neurobiological changes responsible for AD
- (different from the NIA/AA criteria where the presence of Alzheimer's pathology defines the presence of an Alzheimer's disease)

Pathophysiological markers:

- in vivo biological changes that reflect the underlying AD pathology;
- they consist of CSF Abeta and tau and PET-amyloid;
- they are markers of diagnosis, more targeted at identifying AD.

Topographical biomarkers:

- downstream markers of neurodegeneration
- they can be structural (atrophy/MRI) or metabolic (hypometabolism/FDG);
- they are markers of progression, more targeted at assessing changes over time and predicting outcomes.

MCI:

- now includes individuals who do not meet criteria for prodromal AD.
- It is also valuable to patients for whom there is no disease clearly identified, including individuals who have memory deficit characteristic of prodromal AD but where biomarker evidence of AP is absent

Table 11. Different stages and classification of AD subtypes across NIA-AA and IWG criteria

NIA-AA criteria	IWG criteria	Comments
Preclinical AD Asymptomatic cerebral amyloidosis (ACA) ACA + evidence of neuronal injury (NI) ACA + NI + subtle cognitive decline	**Asymptomatic at risk with AD pathology** [1] **Preclinical AD** [2]	*[1] Normal cognition with a pathophysiological marker* *[2] Normal ognition with an autosomal dominant AD-causing mutation*
MCI due to AD MCI due to AD high likelihood [1] MCI due to AD intermediate likelihood [2] MCI possibly due to AD [3] MCI unlikely due to AD [4]	**Alzheimer's disease (Prodromal stage)** [5]	*[1] Biomarkers of amyloidosis and neuronal injury are positive* *[2] Biomarker of amyloidosis positive or biomarker of neuronal injury untested* *[3] Biomarker of amyloidosis positive and biomarker of neuronal injury are untested or give conflicting results* *[4] Biomarker of amyloidosis positive and biomarker of neuronal injury are negative* *[5] Episodic memory impairment or atypical AD-compatible syndrome with one pathophysiological marker (CSF or abnormal amyloid imaging)*
Dementia caused by AD Probable AD dementia with increased level of certainty – 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 etiology Probable AD dementia with evidence of AD pathophysiological process – High likelihood of AD etiology (biomarkers of amyloid abnormalities and neurodegeneration both present) – Intermediate likelihood of AD etiology (biomarker of amyloid abnormalities or neurodegeneration is present) Possible AD dementia with evidence of the AD pathophysiological process – High likelihood of AD etiology (biomarkers of amyloid abnormalities and neurodegeneration both present) – Intermediate likelihood of AD etiology (biomarker of amyloid abnormalities or neurodegeneration is present)	**Alzheimer's disease (Dementia stage)** [1]	*[1] Episodic memory impairment or atypical AD phenotype with impaired activities of daily living* *AND a pathophysiological marker*

Pathophysiologically proved AD dementia (Clinical phenotype of probable AD with neuropathology findings indicative of AD)		

Table 12. Approval (A) or reimbursement (R.) of the four drugs on the market for Alzheimer´s Disease (source: update of Alzheimer Europe: Dementia in Europe Yearbook 2012 – National Dementia Strategies (diagnosis, treatment and research), ISBN-13: 978-2-9599755-8-5, 2012)

Country	Donepezil		Rivastigmine		Galantamine		Memantine	
	A	R	A	R	A	R	A	R
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	No	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
United Kingdom	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Table 13. Prescription regulations of the four drugs on the market for Alzheimer´s Disease: Source Alzheimer Europe: Dementia in Europe Yearbook 2012 – National Dementia Strategies (diagnosis, treatment and research), ISBN-13: 978-2-9599755-8-5, 2012)

	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	NA	NA	NA	NA
Croatia	YES*	NO	YES*	YES*
Cyprus	NA	YES	NA	NA
Czech Republic	YES	NO	YES	NO
Denmark	YES	NO	YES	YES
Estonia	NA	NA	NA	NA
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	NA	NA	NA	NA
Ireland	YES	YES	YES	YES
Italy	YES	NO	YES	NO
Jersey	NA	NA	NA	NA
Latvia	NA	NA	NA	NA
Lithuania	NA	NA	NA	NA
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
United Kingdom	YES	NO	YES	YES

* Memantine only

** Support by statement from a specialist

*** Not donepezil
**** Restrictions for donepezil

Table 14 – . Drugs in late-stage clinical development (phase 2, 3 or 4 RCT) for Alzheimer´s disease: selected ongoing RCTs.

Data source: www.clinicaltrials.gov

Drugs tested in subjects at-risk of AD	Ongoing RCTs (examples)
Drugs targeting amyloid: ↓ production	
Pioglitazone: PPARγ agonist, acts as β-secretase inhibitor by stimulating PPARγ.	TOMORROW: phase 3 RCT in 5800 cognitively normal seniors (65-83 years) at risk of developing MCI due to AD. Risk stratification: algorithm including age and TOMM40 and APOE genotype. Subjects with high and low risk are included. To be completed by 2020, duration is 5 years.[3] A blinded long-term extension phase 3 RCT is also planned, enrolling participants who will complete the TOMORROW RCT and will have a diagnosis of MCI due to AD. The RCT is expected to recruit 316 subjects; duration is 2 years, and it will be completed in 2021.[511]
Drugs targeting amyloid: ↑ clearance	
Passive immunotherapy	
Solanezumab: anti-amyloid monoclonal antibody.	ADCS-A4: Anti-Amyloid Treatment in Asymptomatic AD. Phase 3 RCT enrolling 1150 subjects (500 with evidence of brain amyloid accumulation), with normal cognition, age 65-85 years. To be completed by 2020 (3 years + 2 years extended follow-up planned).[1] DIAN-TU: Dominantly Inherited Alzheimer Network Trial. Phase 2-3 RCT enrolling 210 members of families with early-onset AD (age 18-80 years); 105 subjects carry a mutation in one of three genes (PSEN1, PSEN2, APP) causing autosomal dominant AD. To be completed by 2019 (2 years + 3 years extended follow-up planned)[148]
Crenezumab: anti-amyloid monoclonal antibody.	API-ADAD: Alzheimer's Prevention Initiative - Autosomal Dominant AD. Phase 2 RCT in 300 members of Colombian families, (200 carriers of autosomal dominant mutation in the PSEN1 gene causing AD, age 30-60 years). To be completed by 2020 (3 years + 2 years).[4]

Gantenerumab: anti-amyloid monoclonal antibody.	Tested in the DIAN-TU RCT (see above).
Drugs tested in symptomatic, pre-dementia stages (prodromal AD, MCI due to AD)	Ongoing RCTs (examples)
Drugs targeting amyloid: ↓ production	
E2609: BACE1 inhibitor.	Phase 2 RCT in 700 subjects with prodromal AD or mild AD dementia (age 50-85 years). 18 months duration, to be completed in 2016.[20]
AZD3293: BACE1 inhibitor.	AMARANTH: Phase 2/3 RCT in 2202 subjects with MCI due to AD or mild AD dementia (age 55-85 years). 2 years duration, to be completed in 2019.[22]
Verubecestat (MK-8931, MK-8931-009): BACE1 and BACE2 inhibitor.	APECS: phase 3 RCT in 1500 subjects with prodromal AD (age 50-85). Two years duration, to be completed in 2018.[57]
JNJ-54861911: BACE1 inhibitor.	Phase 2 RCT enrolling 100 subjects with early AD (age 50-85). Ten months duration, to be completed in 2016.[512] Further, a phase 2 extension study of subjects who participated in previous phase 1 and 2 RCTs with the drug is also ongoing. It is expected to last 2 years, and to enrol 100 subjects with early AD (50-85 years). It will be completed in 2024.[513]
Drugs targeting amyloid: ↓ aggregation or oligomerization	
PQ912: glutaminyl cyclase inhibitor, which counteract the production of amyloid peptides (i.e., pyroglutamate-modified Aß peptides) highly prone to aggregation.	SAPHIR: phase 2 RCT in 110 subjects with MCI or mild dementia due to AD (age 50-89). Three months duration, to be completed in 2016.[514]
Drugs targeting amyloid: ↑ clearance	
Passive immunotherapy	
Gantenerumab: anti-amyloid monoclonal antibody.	Phase 3 RCT in 799 subjects (50-85 years), 2 years duration, to be completed at the end of 2015.[515]
BAN2401: anti-amyloid monoclonal antibody.	Phase 2 RCT in 800 subjects (MCI due to AD or mild AD dementia, age 50-90 years), 18 months duration, to be completed by 2018.[6]
Aducanumab (BIIB037): anti-amyloid human monoclonal antibody originally derived from healthy older adults.	2 phase 3 RCTs (EMERGE, ENGAGE), in 1700 subjects (MCI due to AD or mild AD dementia, age 50-85 years), about 18 months duration, to be completed in 2020.[145,146]
Intravenous immunoglobulin: derived from healthy donors, contain naturally occurring polyclonal anti-Aβ antibodies.	MCI: phase 2 RCT in 50 subjects with MCI (age 50.84). two years duration, to be completed in 2017.[516]

Drugs targeting tau: ↓ p-tau production, ↓ fibrillization or ↓ deposition	
Exendin-4 (Exenatide): anti-diabetic agent (glucagon-like peptide-1 receptor agonist), can restore intracellular transport of tau, prevent tau phosphorylation and improve insulin signalling.	Phase 2 RCT in 100 subjects with MCI or mild AD dementia (age 60+). About 18 months duration, to be completed in 2016.[24]
Drugs modulating neurotransmission	
Atomoxetine: licensed drug which acts as norepinephrine uptake inhibitor; increases noradrenaline brain levels.	ATX-001: phase 2 RCT in 40 subjects with MCI (age 50-90 years). Six months duration, to be completed in 2017.[27]
Ladostigil (TV-3326): derivative of rasagiline and rivastigmine, acts as an AChEI and MAO inhibitor; also has antioxidant properties and can modulate APP processing and cellular signalling pathways.	Phase 2 RCT enrolling 200 subjects with MCI (age 55-85 years). Three years duration, to be completed at the end of 2015/2016.[49]
DAOIB: modulates glutamatergic transmission by regulating NMDA receptors.	Phase 2 RCT in subjects with 50 MCI (age 50-90). Six months duration, to be completed in 2016.[517]
PXT00864: combination of acamprosate and baclofen (both licensed drugs), which regulates GABAergic transmission.	PLEODIAL-I: phase 2 RCT in 45 subjects with mild AD dementia, aged 60 or older. 12 weeks duration, completed in 2015, 24-week open label extension started (PLEODIAL-II).[50,51]
Drugs with other mechanisms of action	
Benfotiamine: thiamine derivative, supports brain glucose metabolism and can reduce amyloid accumulation.	Phase 2 RCT in 76 subjects with MCI or mild AD dementia (age 65+). To be completed in 2018, 1 year duration.[116]
Insulin (including rapid-acting-insulin glulisine): regulate glucose metabolism, can also counteract amyloid accumulation.	SNIFF: phase 2/3 RCT testing insulin in 240 subjects with MCI or mild AD dementia (age 55-85). 18 months duration, to be completed in 2016.[26] Another phase 2 RCT is testing glulisine in 90 subjects with MCI or mild AD dementia (age 50-90). 6 months duration, to be completed in 2017.[38]
Cilostazol: phosphodiesterase III inhibitor licensed as antiplatelet drug, can reduce amyloid toxicity	Phase 2 RCT in 200 subjects with MCI (age 55-84). About 2 years duration, to be completed in 2018.[33]
BI 409306 (SUB 166499): phosphodiesterase 9 inhibitor, can	Two phase 2 RCTs in 624 subjects with MCI due to AD (age 55+ years). Twelve weeks duration, to be completed in 2016.[518,519]

enhance synaptic plasticity and reduce amyloid toxicity.	
Simvastatin: licensed cholesterol lowering drug, can lower Aβ brain production and reduce Aβ-mediated neurotoxicity, as well as having antioxidant and anti-inflammatory properties.	SIMaMCI: phase 4 RCT in 52o subjects with MCI (age 55-90). Two years duration, to be completed in 2018.[19]
VX-745: inhibitor of p38a mitogen-activated protein kinase, modulates inflammation.	2 phase 2 RCTs in subjects with MCI due to AD or mild AD dementia (32 participants in total, age 60-85 years). Duration from 6 to 12 weeks, to be completed in 2016[36,37]
Drugs tested in subjects with dementia due to AD	Ongoing RCTs (examples)
Drugs targeting amyloid: ↓ production	
E2609: BACE1 inhibitor.	Tested in a RCT including subjects with mild AD dementia or prodromal AD (see above).
AZD3293: BACE1 inhibitor.	Tested in a RCT (AMARANTH) including subjects with mild AD dementia or MCI due to AD (see above).
Verubecestat (MK-8931, MK-8931-009) BACE1 and BACE2 inhibitor.	EPOCH: phase 2-3 RCT enrolling 1960 subjects with mild to moderate dementia due to AD (age 55-85). 18 months duration followed by double-blind extension phase (additional 5 years); the first phase will be completed in 2017.[520]
Bryostatin-1: macrocyclic lactone that has already been investigated as an antineoplastic drug; it can stimulate α-secretase and reduce brain amyloid burden.	Phase 2 RCT enrolling 150 subjects with moderate to severe dementia due to AD (age 55-85). Seven months duration, to be completed in 2017.[521]
Drugs targeting amyloid: ↓ aggregation or oligomerization	
Carvedilol: nonselective ß-adrenergic receptor blocker, approved for the treatment of congestive heart failure and hypertension. It can prevent formation of amyloid oligomers.	Phase 4 RCT in 50 subjects with mild dementia due to AD. Six months duration, to be completed in 2016.[522]
PQ912: glutaminyl cyclase inhibitor, which counteract the production of amyloid peptides (i.e., pyroglutamate-modified Aß peptides) highly prone to aggregation.	Tested in a RCT including subjects with mild AD dementia or MCI due to AD (see above)

Drugs targeting amyloid: ↑ clearance	
Passive immunotherapy	
Solanezumab: anti-amyloid monoclonal antibody.	EXPEDITION-3: a phase 3 RCT enrolling 2100 cases of mild AD dementia, 18 months duration, to be completed in 2018.[7] EXPEDITION-EXT: phase 3, open-label extension study to evaluate safety in 1275 subjects with dementia due to AD (age 55+) who previously participated in Phase 3 RCTs with Solanezumab. Two years duration, to be completed in 2018.[523] Also tested in subjects at risk of AD (ADCS-A4, DIAN-TU, see above).
Gantenerumab: anti-amyloid monoclonal antibody.	Phase 3 RCT in 1000 patients with mild AD dementia, age 50-90 years. About 2 years duration, to be completed in 2018.[144] Tested also in subjects at risk (DIAN-TU) and patients with prodromal AD (see above)
BAN2401: anti-amyloid monoclonal antibody.	Tested in a RCT including also MCI due to AD(see above).[6]
Aducanumab (BIIB037): anti-amyloid human monoclonal antibody originally derived from healthy older adults.	Tested in 2 RCTs including also MCI due to AD (see above).[145,146]
Crenezumab: anti-amyloid monoclonal antibody.	Phase 2 long-term, open-label safety extension study in 360 subjects with mild to moderate dementia due to AD who previously participated in phase 2 RCTs testing the antibody. About 2 years duration, to be completed in 2017.[524]
Albumin and Immunoglobulin associated with plasmapheresis.	AMBAR: phase 2/3 RCT in 350 subjects with mild to moderate AD dementia (age 55-85 years). 14 months duration, to be completed in 2016.[46]
Drugs targeting tau: ↓ p-tau production, ↓ fibrillization or ↓ deposition	
TRx0237: inhibitor of tau aggregation	2 phase 3 RCTs in about 1533 patients with mild to moderate AD dementia, age <90 years. About 18 months duration, to be completed in 2016.[124,147]
Exendin-4 (Exenatide): anti-diabetic agent (glucagon-like peptide-1 receptor agonist), can restore intracellular transport of tau,	Phase 2 RCT including also subjects with MCI (see above).

prevent tau phosphorylation and improve insulin signalling in the brain.	
Liraglutide: glucagon-like peptide-1 receptor agonist, approved for the treatment of diabetes mellitus type 2. It improves insulin brain signalling and can prevent tau hyperphosphorylation.	ELAD: phase 2 RCT enrolling 206 subjects with mild dementia due to AD (age 50-85). Twelve months duration, to be completed in 2017.[525]
Drugs modulating neurotransmission	
Donepezil. AchEI already approved for the treatment of dementia due to AD.	3 phase 4 post-marketing surveillance studies evaluating safety and effectiveness in 1600 subjects with AD dementia from mild to severe. Up to 4 year duration, to be completed between 2015 and 2016.[526-528]
Encenicline (MT-4666, EVP-6124): agonist of the nicotinic α7 receptor, increases cholinergic transmission.	4 RCTs (Phase 2 and 3) in 1930 subjects with mild to moderate AD dementia (age 50-85 years). Duration is from six months (phase 2 and 3) to one year (phase 3), to be completed in 2016[529] and 2017[25,530,531] A 6-months extension phase 3 RCT is also planned for subjects participating in the RCTs mentioned above. It is expected to recruit 1000 participants and it will be completed in 2017.[532]
MK-7622: it is hypothesized to act as allosteric modulator of muscarinic receptors, enhancing the response to AchEIs.	Phase 2 RCT in 830 subjects with mild to moderate dementia due to AD (age 55-85). Duration is up to one year, and the RCT will be completed by 2020.[533]
Rasagiline: MAOB inhibitor licensed for the treatment of Parkinson disease.	R2: phase 2 RCT including 50 subjects with mild to moderate dementia due to AD (age 50-90). Six months duration, to be completed in 2016.[534]
RG1577 (RO4602522): acts as MAOB inhibitor.	Phase 2 RCT enrolling 544 subjects with moderate AD dementia (age 50-90 years). One year duration, to be completed in 2015[535]
Idalopirdine (Lu AE58054, SGS 518): serotonin 6 (5-HT6) receptor antagonist, can enhance cholinergic, glutamatergic, noradrenergic, and dopaminergic neurotransmission.	STARSHINE, STARBEAM, STARBRIGHT, STAR Extension: 4 phase 3 RCTs in 2490 subjects with mild to moderate AD (1770 subjects enrolled for STAR Extension) aged 50+ years. Six months duration (then additional 8 months for subjects recruited in the extension study), to be completed between end of 2015 and 2016.[35,52-54]
Riluzole: modulator of the glutamatergic transmission.	Phase 2 RCT in 48 subjects with mild dementia due to AD (age 60-85). Six months duration, to be completed in 2017[536]

DAOIB: modulates glutamatergic transmission by regulating NMDA receptors.	Phase 2 RCT enrolling 90 subjects with AD or vascular dementia from mild to moderate-severe stage (age 50+). Six weeks duration, to be completed in 2016.[537]
Methylphenidate: licensed drug acting as a dopamine-norepinephrine reuptake inhibitor, promotes dopaminergic and noradrenergic transmission, thus acting as stimulant.	ADMET 2: phase 3 RCT in 200 subjects with mild to moderate AD dementia and apathy. Six months duration, to be completed in 2019.[48]
Formoterol: drug approved for the treatment of asthma and chronic obstructive pulmonary disease. This compound act as long-acting agonist of adrenergic receptors ß2, which can improve synaptic plasticity and reduce amyloid burden	Phase 2 RCT in 60 subjects with mild to moderate dementia due to AD (age 50-85). One year duration, to be completed in 2016.[538]
Drugs with other mechanisms of action	
Sagramostim: licensed synthetic form of the hematopoietic growth factor granulocyte-macrophage colony-stimulating factor (GM-CSF); can promote amyloid removal by stimulating phagocytosis.	Phase 2 RCT in 40 subjects with mild to moderate AD dementia (age 55-85). 6 months duration, to be completed in 2016.[115]
Benfotiamine: thiamine derivative, supports brain glucose metabolism and can reduce amyloid accumulation.	Tested also in subjects with MCI (see above).
Adenosine triphosphate (ATP): small molecule enhancing metabolism, can protect against amyloid-mediated cytotoxicity.	Phase 2 RCT in 20 subjects with moderate to severe AD dementia (age 55-85). 3 months duration, to be completed in 2016.[539]
Azeraligon (PF-04494700 , TTP488): small molecule acting as RAGE inhibitor, can counteract amyloid brain accumulation and modulate inflammation.	Phase 3 RCT in 800 subjects with mild AD dementia (age 50+). 18 months duration, to be completed in 2018.[117]
T-817MA: small molecule showing neurotrophic and neuroprotective properties related to protection against amyloid and tau-mediated toxicity.	Phase 2 RCT 450 In subjects with mild to moderate AD dementia (age 55-85). About one year duration, to be completed in 2016[39]

Cerebrolysin: peptide mixture with neurotrophic-like properties related to the regulation of cell signalling, control of amyloid metabolism and anti-apoptotic effects mediated by expression of endogenous neurotrophic factors. A meta-analysis of 6 RCTs suggested beneficial symptomatic effects in subjects with mild to moderate dementia due to AD.[540]	DAT: phase 4 RCT in 510 subjects with mild to moderate dementia due to AD (age 50+). Six months duration, to be completed in 2016.[541]
Nilvadipine: licensed anti-hypertensive drug, is a dihydropyridine calcium channel blocker. Can enhance brain circulation, and also prevent amyloid accumulation/increase its clearance.	NIVALD: phase 3 RCT enrolling 500 subjects (age 50+) with mild to moderate AD dementia. 18 months duration, to be completed in 2017.[21]
Insulin (including rapid-acting-insulin glulisine): regulate glucose metabolism, can also counteract amyloid accumulation	Phase 2/3 RCTs including also subjects with MCI (see above).
AZD0530 (Saracatinib): inhibitor of Fyn-kinase, can attenuate amyloid and tau-mediated neuronal damage.	Phase 2 in 152 subjects with mild AD dementia (age 55-85). One year duration, to be completed in 2016.[542]
Masitinib (AB1010): selective tyrosine kinase inhibitor, can modulate neuroinflammation by regulating mast cells activity. It can also promote neuroprotection by targeting Fyn-kinase.	Phase 3 RCT in 396 subjects with mild to moderate AD dementia (age 50+). Six months duration, to be completed in 2016.[543]
VX-745: inhibitor of p38a mitogen-activated protein kinase, modulates inflammation.	2 phase 2 RCTs including also subjects with MCI due to AD (see above).

Abbreviations: AChEI: acetylcholinesterase inhibitor; AD: Alzheimer´s disease; APOE: Apolipoprotein E; APP: amyloid precursor protein; BACE1: B-site APP-cleaving enzyme; MAO: monoamine oxidase inhibitor; MCI: mild cognitive impairment; NMDA: N-Methyl-D-aspartate; PPARγ: peroxisome-proliferator activated receptor γ; PSEN1: Presenilin 1; PSEN2: Presenilin 2; RAGE: receptor for advanced glycation endproducts; TOMM40: translocase of outer mitochondrial membrane 40 homolog.

Table 15. Formal Resources of interest to analyse in economic evaluations of dementia care

Formal care
Living situation (at home, institutions)
Respite care
Home social care visits
Home medical care visits
Home rehabilitation care visits
Visits to clinics: physicians: specialist
Visits to clinics: GP (similar)
Visits to clinics: registered nurses (similar)
Visits to clinics: rehabilitation (similar)
Hospital care (various specialities/departments)
Day Hospital care (such as day surgery)
Day Care special for dementia
Day Care (non-specified)
Use of drugs
Technical device/equipment
Food support/meals on wheels
Transport services

Table 16. Ethical questions in dementia care, currently most important for patients, proxies and professionals.

Domain	Patients	Proxies/Caregivers	Professionals
Prevention	Is lifelong medication and lifestyle change beneficial? Should recommendations be targeted for those at risk or be promulgated to the population at large?	What may be the effects of early risk assessment (genetic, vascular, Alzheimer biomarkers) for dementia with respect to changes in work, family planning, behaviour of relatives, insurances?	How long, extensive and rigorous can prevention trials be? How can health care providers be encouraged to advocate for these changes to their patients?
Predementia diagnosis	What is the benefit of early biomarker and/or genetic testing? Should the whole family be tested genetically? Whether or not to participate in prevention trials?	Should a patient with a prodromal AD diagnosis without symptoms be treated as a patient by his/her proxies or not? Should relatives also be tested for risk factors?	What is the added value of a pre-dementia diagnosis based on biomarkers? How to realize shared decision making on the preferred diagnostic route?
Diagnostic disclosure	What are the pros and cons of knowing versus not knowing the dementia diagnosis? Truth telling versus paternalistic protectiveness? Is there evidence that earlier diagnosis is beneficial?	To tell or not to tell the diagnosis to relatives and other family members, especially in prodromal AD?	How to balance advantages and disadvantages of predementia AD disclosure, and minimize stigma of an early diagnosis?
Management	Whether or not to participate in drug trials? What to do independently, and what not (e.g. driving), and how to balance own versus societal interests?	Whether or not to give informed consent by proxy?	How to assess competency to consent?
End of life care	How and when to realize advance directives? Whether or not to have advance directives, and limit use of health services? How active to be at and of life planning?	How to maximize autonomy at home and following institutionalization? When to stop active and supportive treatments? How to assist good quality of dying?	How strictly to adhere to advance directives? When to stop active and supportive treatments? How to assist good quality of dying?

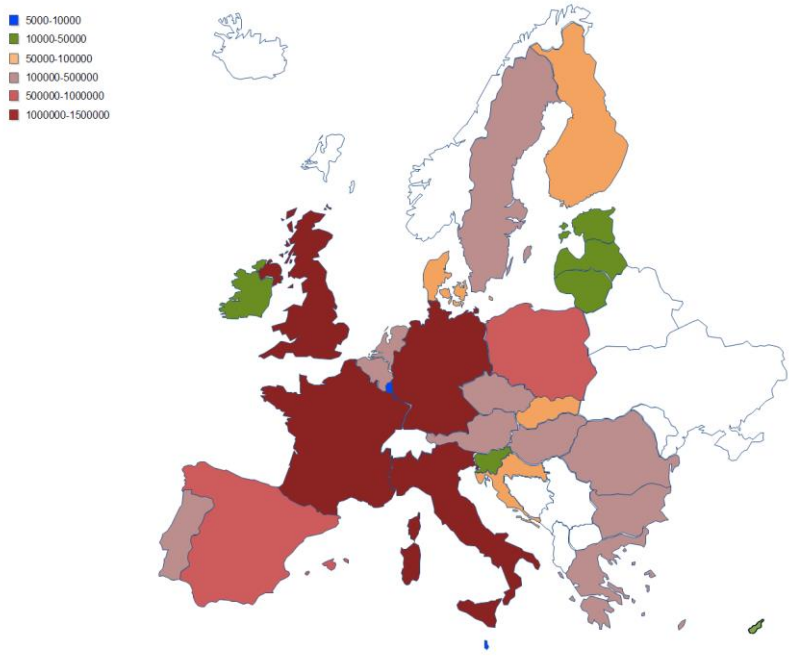

Figure 1. Number of dementia cases in 28 European countries in 2013 (www.alzheimer-europe.org/Publications/Dementia-in-Europe-Yearbooks).

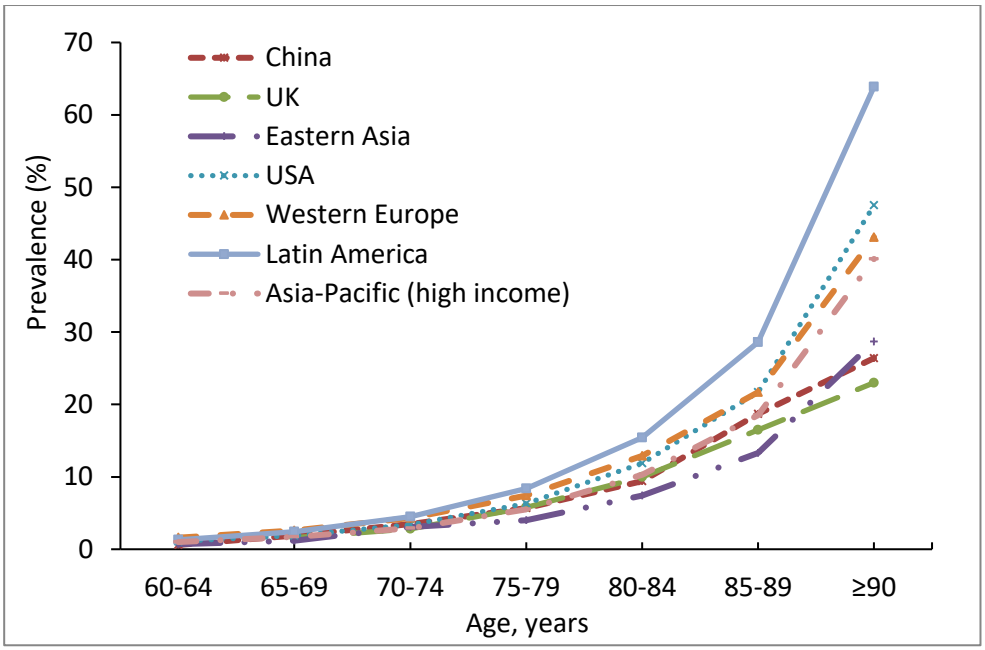

Figure 2. Prevalence of dementia by regions and major countries in the world (Source: Fratiglioni L and Qiu C [108], with modifications)

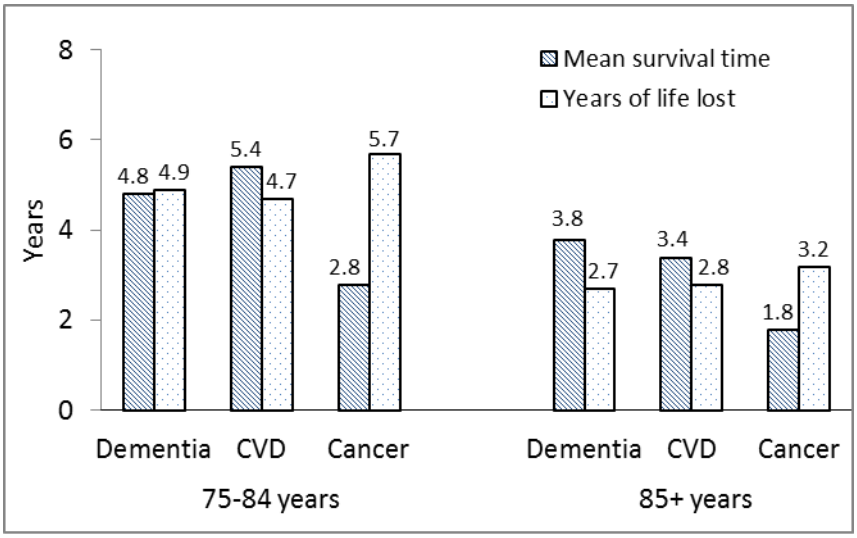

Figure 3. Mean survival time and years of life lost due to dementia, cardiovascular disease (CVD), and cancer stratified by two age groups [44]

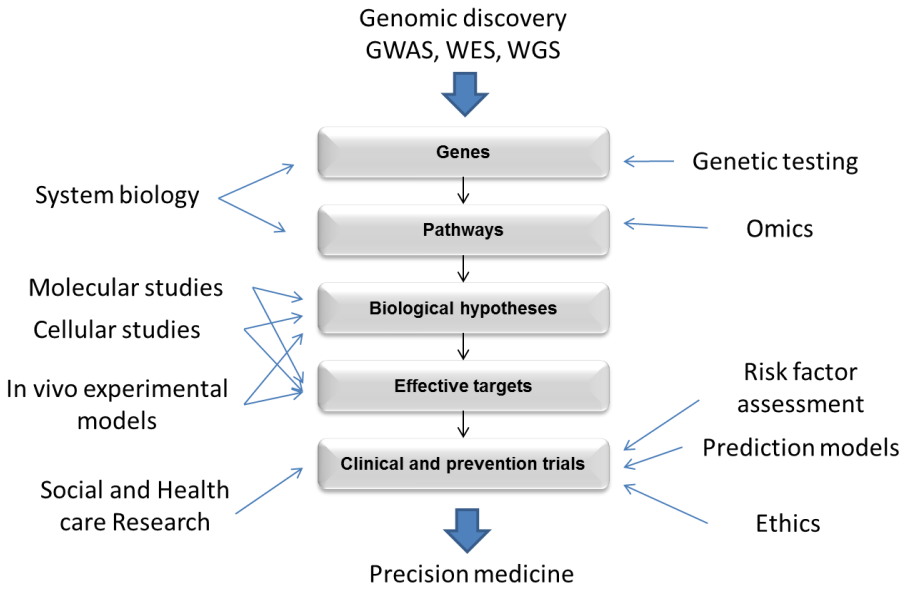

Figure 4. Starting from the genetic and genomic discoveries, future research studies need to integrate data from all research areas in order to make intelligible interpretations of the functional consequences of the known AD associated genes and loci. These integrated analyses will lead the research frontier forward and generate personal risk profiles as well as point towards individual interventional regimes.

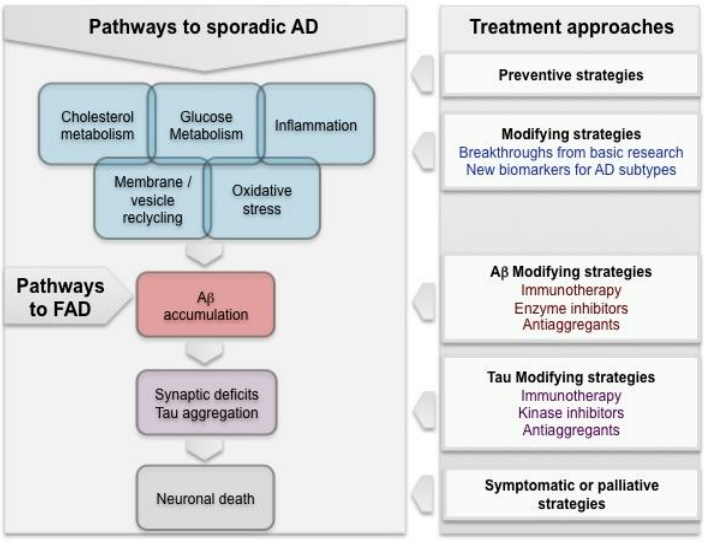

Figure 5. Pathways to Alzheimer disease. Epidemiological and genetic studies of AD individuals have categorized mechanism resulting in brain Aβ accumulation, neuronal tau hyperphosphorylation and synaptic deficits and leading to non-genetically inherited AD (sporadic AD). In Familial AD (FAD), AD begins with Aβ pathology. It is likely that different causing pathways would result in different disease subtypes, which should be treated differently. The identification of patient subtypes, with homogenous etiology and prognosis, will result in more accurate and personalized treatments.

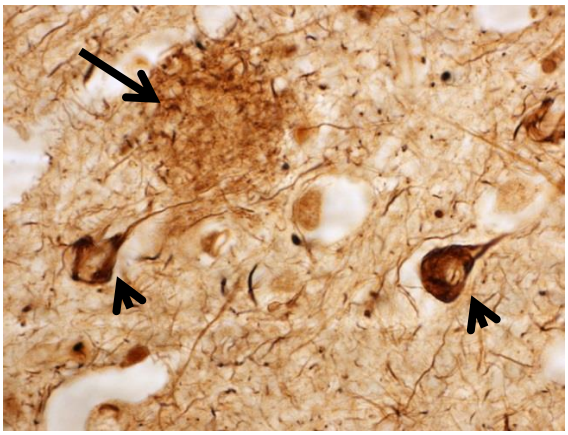

Figure 6. Neuropathology (Bielschowsky silver staining of frontal cortex of a patient with Alzheimer disease illustrating the presence of a neuritic amyloid plaque (arrow: consisting of aggregated extracellular Aβ-amyloid fibrils) and intraneuronal neurofibrillary tangles (arrow-heads: consisting of hyperphosphorylated tau-protein) characteristic for the disease.

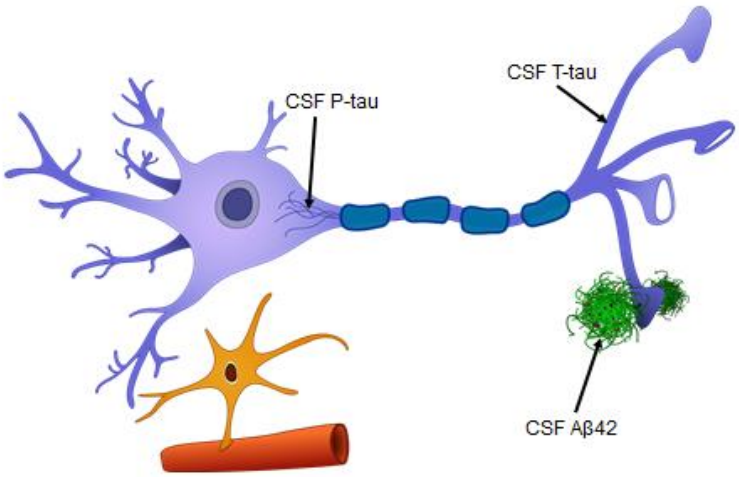

Figure 7. Schematic representation of a neuron showing the pathological changes that the three core cerebrospinal fluid (CSF) biomarkers for AD reflect: total tau (T-tau), axonal degeneration; phosphorylated tau (P-tau), neurofibrillary tangles; the 42 amino acid form of amyloid β (Aβ42), senile plaque pathology.

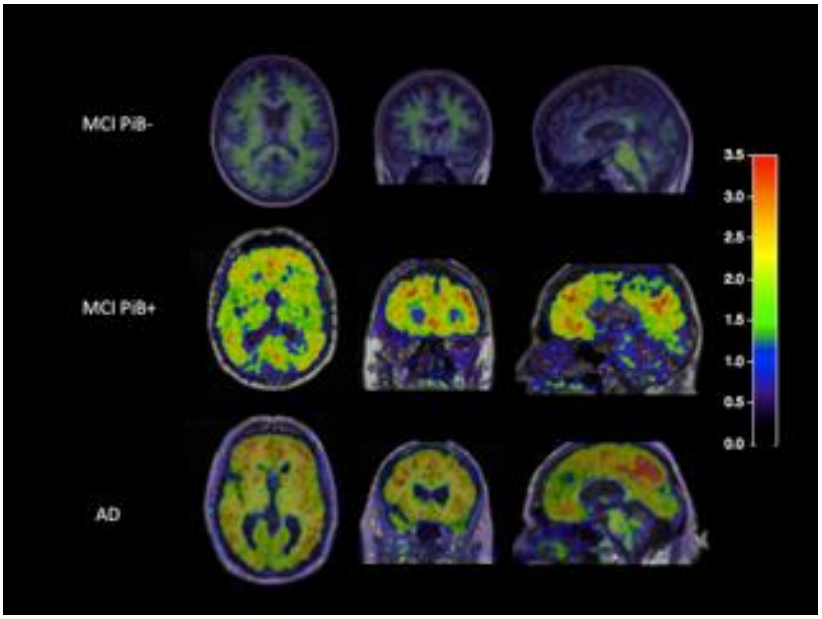

Figure 8. Fusion images from co-registered PET and MRI scans. Deposition of fibrillar amyloid plaques measured with ^{11}C-PIB PET in two patients with MCI and one patient AD. The fusion images are presented in transverse (left panel), coronal (middle panel) and sagittal (left panel) sections. The MCI patients were clinically longitudinally followed. The MCI patient with low PIB retention (PIB negative) remained as MCI while the MCI patient with high PIB retention (PIB +) converted to AD. Standard uptake values (SUV) in relation to cerebellum are expressed in colour scale.
Abbreviations: MCI =mild cognitive impairment; AD= Alzheimer´s disease; PIB=Pittsburgh Compound B (photo; A Nordberg, Karolinska Institutet).

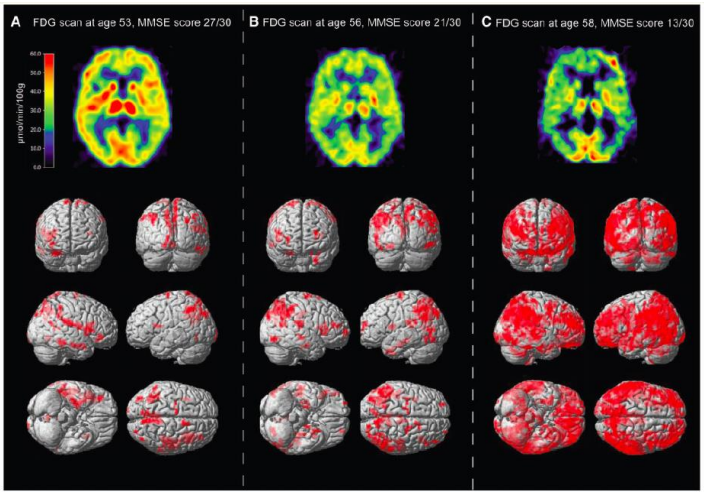

Figure 9. (From Kadir A et al.[544]) Upper row illustrates the positron emission tomography (PET) images of the regional glucose metabolism (umol/mi/100g) as measured by ^{18}F-fluorodeoxyglucose (^{18}F-FDG)in an AD patients at age of 53(A),56 (B) and 58 (C) years. The red colour indicates high, yellow medium and blue low ^{18}F-FDG uptake. Lower row illustrates the 3D brain rendering representation of statistical parameters mapping 18F-FDG- PET images. Areas of red depict areas in which the regional cerebral glucose metabolism was significantly decreased in the patients with Alzheimer´s disease during the progression of the disease compared with a group of healthy control subjects (P=0,001). MMSE=mini-mental state examination.

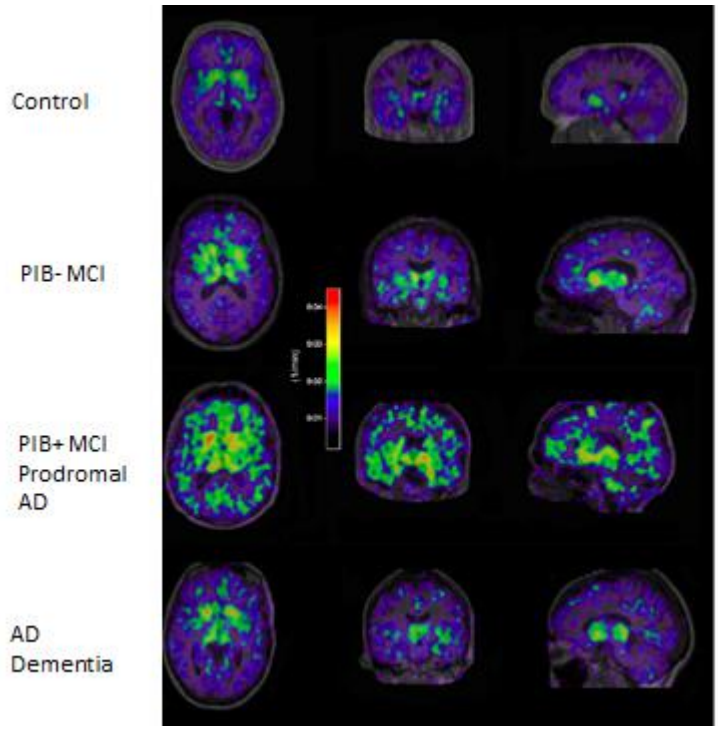

Figure 10. (From Carter et al.[545]). High Astrocytosis measured by ^{11}C-d-deprenyl and PET in brain of MCI patients with high amyloid plaque load in brain measured with PIB (PIB positive)(prodromal AD according to Dubois et al 2014) compared to MCI with no amyloid plaques (PIB negative) and AD patients and controls . The colour scale indicates red =very high, yellow=high, green =medium, blue =low binding.

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