Priority Medicines for Europe and the World
"A Public Health Approach to Innovation"

Update on 2004 Background Paper

Written by Saloni Tanna

Background Paper 6.11
Alzheimer Disease and other Dementias

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Table of Contents

Executive Summary

Improvements in health care in the past century have contributed to people living longer and healthier lives. This has also resulted in an increase in the number of people with noncommunicable diseases, including dementia. Although dementia mainly affects older people, it is not a normal part of ageing. Dementia is a syndrome, usually of a chronic or progressive nature, caused by a variety of brain illnesses that affect memory, thinking, behaviour and ability to perform everyday activities. Dementia is overwhelming not only for the people who have it, but also for their caregivers and families. It is one of the major causes of disability and dependency among older people worldwide.

Dementia: a public health priority

In 2008, the World Health Organization (WHO) declared dementia as a priority condition through the Mental Health Gap Action Programme. [1]

Prevalence and incidence projections indicate that the number of people with dementia will continue to grow, particularly among the oldest old, and countries in demographic transition will experience the greatest growth. The total number of people with dementia worldwide in 2010 is estimated at 35.6 million and is projected to nearly double every 20 years, to 65.7 million in 2030 and 115.4 million in 2050. The total number of new cases of dementia each year worldwide is nearly 7.7 million, implying one new case every four seconds.

Much of the increase will be in developing countries, the fastest growth in the elderly population taking place in China, India, and their south Asian and western Pacific neighbours. In 2010, Europe had an estimated 10 million disease cases and based on United Nation's demographic forecast this figure will rise to 14 million in 2030. Looking at these data, it is apparent that there is an urgent need for action. Alzheimer disease (AD) has become a major public health concern as the world's population ages. It is projected that by 2050, people aged 60 and over will account for 22% of the world's population with four-fifths living in Asia, Latin America or Africa.

The cost of Dementia

According to the WHO, treating and caring for people with dementia currently costs the world more than US$ 604 billion per year.[1] This includes the cost of providing health and social care as well the reduction or loss of income of people with dementia and their caregivers. Estimates of the future cost of dementia in Europe is a rise of 43% from 2008 reaching 250 billion euros in 2030. It is expected to rise by 43 % between 2008 and 2030 reaching 250 billion euros in 2030. [2]

In high-income countries, informal care (45%) and formal social care (40%) account for the majority of costs, while the proportionate contribution of direct medical costs (15%) is much lower. In low-income and lower-middle-income countries direct social care costs are small, and informal care costs (i.e. unpaid care provided by the family) predominate. Changing population demographics in many low- and middle-income countries (LMIC) may lead to a decline in the ready availability of extended family members in the coming decades.

A necessity to improve early risk identification, diagnosis and improve management

Alzheimer disease (AD) is the most common form of dementia. There are no available treatments that stop or reverse the progression of the disease, which worsens as it progresses, and eventually leads to death. There are currently no specific markers that can confirm with a 100% certainty AD diagnosis. A combination of brain imaging and clinical assessment checking for signs of memory impairment is used to identify patients with AD. Definitive diagnosis can only be only obtained after patients autopsy by examining brain tissues. There is a clear need for tangible advances in the area of biomarkers for assessment of risk, diagnosis and monitoring disease progression. Screening of patients still remain very expensive and new research is necessary to develop non expensive and reliable tests.

Continuing efforts are still required. This includes developing medicines that would slow progression, halt, or prevent AD and other dementias from occurring. Current studies are currently underway to identify biomarkers for diagnosis and new therapeutics to prevent or slow down disease progression. Consortia of top-level European research and industrial partners will need to act in this direction and contribute to strengthen the EU's leadership on Alzheimer disease research.

1. Introduction

Dementia is a syndrome characterized by disturbance of multiple brain functions, including memory, thinking, orientation, comprehension, calculation, learning capacity, language, and judgement. Consciousness is not clouded. The impairments of cognitive function are commonly accompanied, and occasionally preceded, by deterioration in emotional control, social behaviour, or motivation.[1,2]

Alzheimer disease is the most common form of dementia and possibly contributes to 60–70% of cases. Other types of dementias include vascular dementia, dementia with Lewy bodies, and a group of diseases that contribute to frontotemporal dementia. The boundaries between subtypes are indistinct and mixed forms often co-exist.[3]

Dementia can affect a person in different ways, and progression of the disease depends upon the impact of the disease itself and the person's personality and state of health. Dementia can be divided in three stages:

- early stage – first year or two
- middle stage – second to fourth or fifth years
- late stage – fifth year and after

These periods are given as an approximate guideline and not all persons with dementia will display the same symptoms.[4]

Table 6.11.1 illustrates the common symptoms of people with dementia.

Table 6.11.1: Common symptoms experienced by people with dementia syndrome

(from the WHO Dementia Report in reference [5].

Early stage	Middle stage	Late stage
The early stage is often overlooked. Relatives and friends (and sometimes professionals as well) see it as "old age", just a normal part of ageing process. Because the onset of the disease is gradual, it is difficult to be sure exactly when it begins. ➢ Become forgetful, especially regarding things that just happened ➢ May have some difficulty with communication, such as difficulty in finding words ➢ Become lost in familiar places ➢ Lose track of the time, including time of day, month, year, season ➢ Have difficulty making decisions and handling personal finances ➢ Have difficulty carrying out complex household tasks ➢ Mood and behaviour: may become less active and motivated and lose interest in activities and hobbies may show mood changes, including depression or anxiety may react unusually angrily or aggressively on occasion.	As the disease progresses, limitations become clearer and more restricting. ➢ Become very forgetful, especially of recent events and people's names ➢ Have difficulty comprehending time, date, place and events; may become lost at home as well as in the community ➢ Have increasing difficulty with communication (speech and comprehension) ➢ Need help with personal care (i.e. toileting, washing, dressing) ➢ Unable to successfully prepare food, cook, clean or shop ➢ Unable to live alone safely without considerable support ➢ Behaviour changes may include wandering, repeated questioning, calling out, clinging, disturbed sleeping, hallucinations (seeing or hearing things which are not there) ➢ May display inappropriate behaviour in the home or in the community (e.g. disinhibition, aggression).	The last stage is one of nearly total dependence and inactivity. Memory disturbances are very serious and the physical side of the disease becomes more obvious. ➢ Usually unaware of time and place ➢ Have difficulty understanding what is happening around them ➢ Unable to recognize relatives, friends and familiar objects ➢ Unable to eat without assistance, may have difficulty in swallowing ➢ Increasing need for assisted self-care (bathing and toileting) ➢ May have bladder and bowel incontinence ➢ Change in mobility, may be unable to walk or be confined to a wheelchair or bed ➢ Behaviour changes, may escalate and include aggression towards carer, nonverbal agitation (kicking, hitting, screaming or moaning) ➢ Unable to find his or her way around in the home.

Source: *World Alzheimer's Report 2009*. London, Alzheimer's Disease International, 2009.*Neurological disorders: public health challenges*. WHO, Geneva, 2006.

Jotheeswaran AT et al. The predictive validity of the 10/66 dementia diagnosis in Chennai, India: a 3-year follow-up study of cases identified at baseline. *Alzheimer Disease and Associated Disorders*, 2010.

1.1 Alzheimer Disease description

Alzheimer disease (AD) is characterized by a progressive decline in cognitive function. AD is substantially increased among people aged 65 years or more, with a progressive decline in memory, thinking, language and learning capacity. AD should be differentiated from normal age-related decline in cognitive function, which is more gradual and associated with less disability. Disease often starts with mild symptoms and ends with severe brain damage. People with dementia lose their abilities at different rates.[6,7,8,9,10,11]

The pathophysiology of AD is related to the injury and death of neurons, initiating in the hippocampus brain region that is involved with memory and learning, then atrophy affects the entire brain.[7] Amyloid beta, also written Aβ, is a short peptide that is an abnormal proteolytic byproduct of the transmembrane protein amyloid precursor protein (APP), whose function is unclear but thought to be involved in neuronal development. Amyloid beta monomers are soluble and contain short regions of beta sheet at sufficiently high concentration, they undergo a dramatic conformational change to form a beta sheet-rich tertiary structure that aggregates to form amyloid fibrils. These fibrils deposit outside neurons in dense formations known as senile plaques or neuritic plaques, in less dense aggregates as diffuse plaques, and sometimes in the walls of small blood vessels in the brain in a process called amyloid angiopathy or congophilic angiopathie. In Alzheimer disease abnormal aggregation of the tau protein, a microtubule-associated protein expressed in neurons is also observed. Tau protein acts to stabilize microtubules in the cell cytoskeleton. Like most microtubule-associated proteins, tau is normally regulated by phosphorylation. In AD patients, hyperphosphorylated tau P-tau accumulates as paired helical filaments that in turn aggregate into masses inside nerve cell bodies known as neurofibrillary tangles and as dystrophic neurites associated with amyloid plaques.[12]

Current evidence indicates changes in CSF levels of Aβ, tau, and P-tau, which are not static over the course of the disease. The mechanism that drives the formation of senile plaques and neurofibrillary tangles is still unknown at present. Senile plaques and neurofibrillary tangles prompt the injury and death of neurons, and as a consequence memory loss and behavioural symptomatic changes. As well, current hypotheses include circulating $\alpha\beta$oligomers as potentially neurotoxic (not just the plaques). Abnormal release of neurotransmitters such as glutamate contributes to neuronal death and inflammation.[9,10,11,13] Neuroinflammation is also involved in the complex cascade leading to AD pathology and symptoms. Considerable pathological and clinical evidence documents immunological changes associated with AD, including increased pro-inflammatory cytokine concentrations in the blood and cerebrospinal fluid.[11] Whether these changes may be a cause or consequence of AD remains to be fully understood, but inflammation within the brain, including increased reactivity of the resident microglia towards amyloid deposits, has been implicated in the pathogenesis and progression of AD.

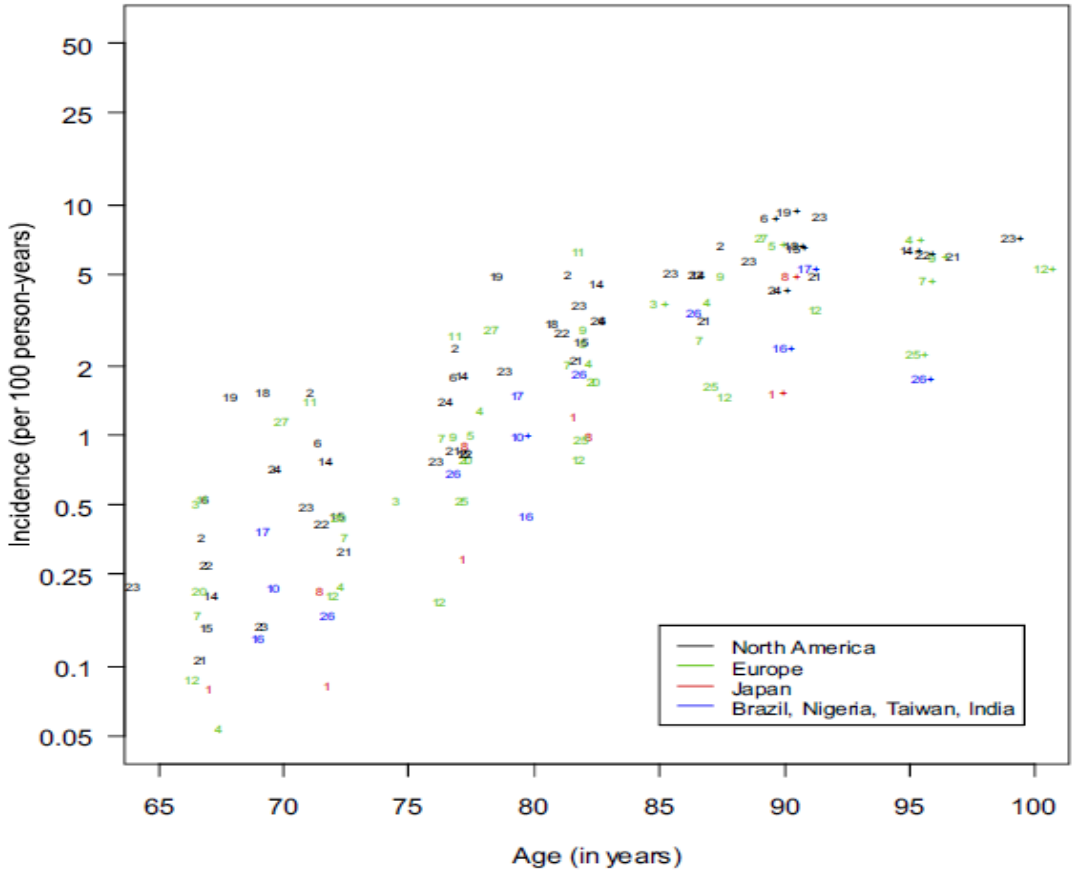
1.2 Risk Factors for AD

1.2.1 Age

The more individuals advance in age the higher is the risk they will develop Alzheimer disease. Most patients develop AD after the age of 65 years old. The risk of developing AD reaches 50% for individuals beyond age 85. Because more and more people live longer lives this disease is becoming a serious concern. The age-specific incidence rates for Alzheimer

disease demonstrate a doubling of incidence for about every six years of added life, which indicates an exponential increasing risk with increasing age. This exponential risk is fairly similar across studies, regardless of geographic region, even if the underlying absolute incidence rate differ (see Figure 6.11.1).

Figure 6.11.1: Incidence of AD (expressed as percent per year) as a function of age for each study.



Source: Ziegler-Graham, Alzheimer & Dementia 2008;4:316-328

Note: The studies are labeled with different numbers (in chronological order). Observed incidences marked with a "+" indicate that the age interval was open-ended. Regions are denoted by different colors. log(incidence) = -2.146 + 0.1271 (age-60); Incidence = .117 exp{.1271(age-60)}

1.2.2 Genetics of AD

The vast majority of Alzheimer disease is not genetically inherited although some genes may act as risk factors.[14] Genetically identified forms of Alzheimer disease, which usually have an onset before the age of 65, have been identified and account for 0.1% of disease cases.[15] The current thinking is that there are sporadic/late onset and familial/early onset cases of Alzheimer disease.

Familial/early onset

When Alzheimer disease is caused by these deterministic variations, it is called "autosomal dominant Alzheimer disease (ADAD)" or "familial Alzheimer disease". Many family

members in multiple generations are affected. Symptoms develop before age 60, and may appear among persons between 30 and 40 years old. Most of autosomal dominant familial AD can be attributed to mutations in the amyloid precursor protein (APP) and/or presenilins 1 and 2 gene.[16] Mutations in the APP and presenilin genes lead to the production of protein Aβ42 (beta amyloid 1-42) that accumulates into amyloid plaques and cause death of neurones by increasing the production of protein Aβ42.[17]

Sporadic/late onset

Other cases, that do not exhibit autosomal-dominant inheritance are termed sporadic AD. Genetic risk factors have been identified such as the inheritance of the ◎4 allele of the alipoprotein (APOE).[18] Risk genes increase the likelihood of developing a disease, but do not guarantee it will happen. Individual carrying a mutation in the APOE◎ 4 allele have a three to 15 times increase risk of developing Alzheimer disease. Table 6.11.2 shows the main genetic mutations associated with Alzheimer disease.

Table 6.11.2: Main genetic mutations associated with Alzheimer disease.

Gene	Main alteration	Presumed mechanism
Amyloid precursor protein (*APP*)	Mutation	Autosomal dominant, mostly early onset
Presenilin 1 (*PSEN1*)	Mutation	Autosomal dominant, mostly early onset
Presenilin 2 (*PSEN2*)	Mutation	Autosomal dominant, mostly early onset
Apolipoprotein-E (*APOE*)	Common variant	Familial and sporadic, late onset
Sortilin-related receptor, L(DLR class) A repeats-containing (*SORL1*)	Common variant	Familial and sporadic, late onset
Clusterin (*CLU*)	Common variant	Sporadic, late onset
Phosphatidylinositol binding clathrin assembly protein (*PICALM*)	Common variant	Sporadic, late onset
Complement component (3b/4b) receptor 1 (*CR1*)	Common variant	Sporadic, late onset
Bridging integrator 1 (*BIN1*)	Common variant	Sporadic, late onset

Source: Alzheimer Europe. Available at http://www.alzheimer-europe.org/?lm1=D8105B21BD2C

Alzheimer disease is a complex multi-factorial and multi-mechanism disease merging genetics and epistasis that can unravel novel pathways.

1.2.3 Role of environment for AD

Several studies indicate a role for environmental effects on AD development. In a recent review Richard Mayeux and Yaakov Stern summarized the role of diet, activities, or diseases that potentially play a role in the onset of Alzheimer disease.

Diabetes, hypertension, smoking, obesity, and dyslipidemia have all been found to increase risk as well a history of brain trauma, cerebrovascular disease, and vasculopathies. A higher level of education, as well as Mediterranean diet were shown to decrease the risk of developing AD. Table 6.11.3 shows identified risks factors for AD.

Table 6.11.3: Factors that modify the risk of Alzheimer disease.

Antecedent	Direction	Possible mechanisms
Cardiovascular disease	Increased	Parenchymal destruction Strategic location ↑ Aβ deposition
Smoking	Increased	Cerebrovascular effects Oxidative stress
Hypertension	Increased and decreased	Microvascular disease
Type II diabetes	Increased	Cerebrovascular effect Insulin and Aβ compete for clearance
Obesity	Increased	Increased risk of type II diabetes inflammatory
Traumatic head injury	Increased	↑Aβ and amyloid precursor protein deposition
Education	Decreased	Provides cognitive reserve
Leisure activity	Decreased	Improves lipid metabolism, mental stimulation
Mediterranean diet	Decreased	Antioxidant, anti-inflammatory
Physical activity	Decreased	Activates brain plasticity, promotes brain vascularization

Source: *Epidemiology of Alzheimer DiseaseRichard Mayeux and Yaakov Stern Cold Spring Harb Perspect Med 2012;2:a006239*

2. Size and Nature of Disease Burden

Dementia mainly affects older people, although there is growing awareness of cases that start before the age of 65. Population ageing is having a profound impact on the emergence of the global dementia epidemic, influencing awareness and driving demand for services.

2.1 Incidence and prevalence

Exact estimates of the prevalence of dementia depend on the definition and specific threshold used. The syndrome affects approximately 5%-8% of individuals over age 65, 15%-20% of individuals over age 75, and 25%-50% of individuals over age 85. Alzheimer disease is the most common dementia, accounting for 50%-75% of the total, with a greater proportion in the higher age ranges.[10] Vascular dementia is probably next most common, but its prevalence is unknown. The remaining types of dementia account for a much smaller fraction of the total.

Dementia Worldwide

The WHO 2012 Report "Dementia: a public health priority" estimates there are at present 35.6 million people living in dementia worldwide. Alzheimer disease is the most frequent cause of dementia in Western societies.

As the world population ages, the frequency is expected to double by 2030 and triple by 2050.[19] Neither healthcare nor financial systems are prepared to face the magnitude of the situation.

Late onset dementia (from the WHO Dementia Report)

In 2005, Alzheimer's Disease International (ADI) commissioned a panel of experts to review all available epidemiological data and reach a consensus estimate of prevalence in each of 14 world regions. The panel estimated 24.3 million people aged 60 years and over with dementia in 2001, 60% living in LMIC. Each year, 4.6 million new cases were predicted, with numbers affected nearly doubling every 20 years to reach 81.1 million by 2040. Incidence was estimated from prevalence and mortality. The estimates were provisional, due to limited data.[20] *Coverage was good in Europe, North America, and in developed Asia-Pacific countries. Studies from China and India were too few and estimates too variable to provide a consistent overview. There was a dearth of studies from Latin America, Africa, Eastern Europe, Russia and the Middle East, and a consequent reliance on the consensus judgment of the international expert panel. This supported a tendency, noted in the few LMIC studies available at that time, for the age-specific prevalence of dementia to be lower in developing countries than in developed ones.*

*Global prevalence is being reappraised for the revision of the Global Burden of Disease (GBD) study 2010 (http://www.globalburden.org/), with findings summarized in ADI's 2009 World Alzheimer Report.*3 *The evidence base was expanded considerably with more studies from LMIC and from other regions and groups previously underrepresented in the literature. Enhancements included a fully systematic review of the world literature on the prevalence of dementia (1980–2009) in 21 GBD regions, a critical appraisal of study quality, and an attempt, where possible, to generate regional estimates from quantitative meta-analysis.*

Meta-analysis of dementia prevalence within GBD regions

There were sufficient studies of good quality to conduct meta-analyses for 11 of the 21 GBD regions; Western Europe, North America, Latin America (combining Andean, Central, Southern and Tropical regions), Asia Pacific high-income, Australasia, East Asia, South-East Asia and South Asia. For Latin America, we considered it pragmatic and appropriate to pool studies from across the four GBD regions to conduct a single continent-wide meta-analysis. Given that the North American region comprised just Canada and the USA, and that Canada was represented by a large and well-conducted survey on a nationally representative sample, the national prevalence figures for Canada were applied to Canada and the USA studies were meta-analysed to generate estimates for that country.

Modelling the prevalence of dementia

Age-specific and age- and sex-specific meta-analysed dementia prevalence estimates are described for each region in Annex 6.11.1. Prevalence increased exponentially with age in each region, doubling with every 5.5 year increment in age in Asia Pacific, Latin America and North America, with every 5.6 year increment in East Asia, every 6.3 years in South Asia and Western Europe, and every 6.7 years in Australasia and South-East Asia. In all regions other than Asia Pacific and North America, the predicted prevalence for men was lower (by 19–29%) than that for women. There was a tendency in all regions for the divergence in prevalence between men and women to increase with increasing age; however, this was statistically significant only for the Asia Pacific region. There was statistically significant heterogeneity (variation in prevalence between studies within regions) for all regions other than South-East Asia; it was most marked for South Asia (alpha=0.39), Western Europe (alpha=0.19) and Asia Pacific (alpha=0.18).

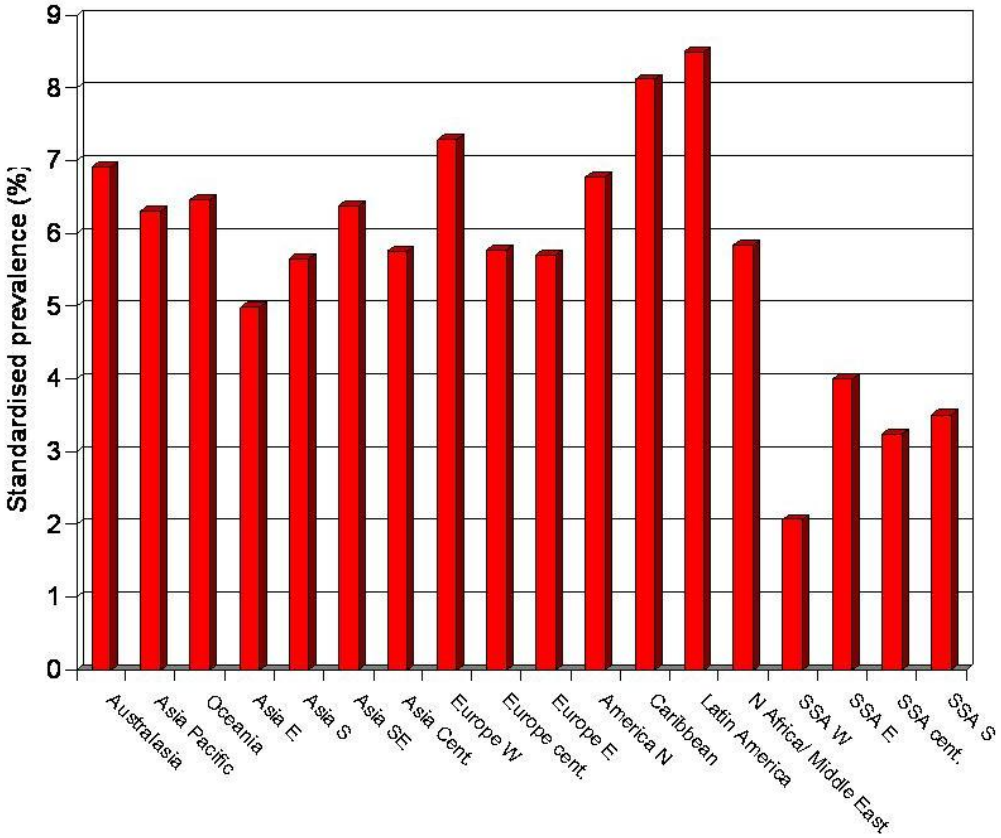
Generation of prevalence estimates for other GBD regions

Where it was impractical to conduct a meta-analysis due to insufficient data, the default option was to apply relevant estimates from the Delphi consensus of 2005, representing the best available estimates of likely dementia prevalence in those regions.[20]

Estimated prevalence of dementia

Estimated prevalence of dementia for all those aged 60 years and over, age-standardized to the Western Europe population structure, can be compared directly between the 21 GBD regions (Annex 6.11.1,6.11.2 and Figure 2-2 in Annex 1). There is a four-fold variation, from 2.07% (West sub-Saharan Africa) to 8.50% (Latin America). However, most of the estimated age-standardized prevalence figures lie in a band between 5% and 7%. The major source of variation is the very low estimated prevalence for the four regions of sub-Saharan Africa.

Figure 6.11.2: Estimated prevalence of dementia for persons aged 60 and over, standardized to Western Europe population, by Global Burden of Disease region



Source: Source: Dementia: a public health priority. WHO, 2012.
Note: **Regions used here are those used in the Global Burden of Disease 2010 Study.*

Estimation of numbers of people with dementia

Having applied the age-specific, or age- and sex-specific, prevalence estimates to UN population projections, it was estimated that 35.6 million people worldwide were living with dementia in 2010 (Annex6.11.3). Western Europe is the GBD region with the highest number of people with dementia (7.0 million), closely followed by East Asia with 5.5 million, South Asia with 4.5 million and North

America with 4.4 million. The nine countries with the largest number of people with dementia in 2010 (1 million or more) were China (5.4 million), USA (3.9 million), India (3.7 million), Japan (2.5 million), Germany (1.5 million), Russia (1.2 million), France (1.1 million) Italy (1.1 million) and Brazil (1.0 million).

The total number of people with dementia is projected to almost double every 20 years, to 65.7 million in 2030 and 115.4 million in 2050. Much of the increase is attributable to increases in the numbers of people with dementia in LMIC (Figure 6.11.3); in 2010, 57.7% of all people with dementia lived in LMIC, and this proportion is expected to rise to 63.4% in 2030 and 70.5% in 2050. The projections are driven mainly by population growth and demographic ageing (Annex6.11.3). World regions fall into three broad groups. High-income countries start from a high base, but will experience only a moderate proportionate increase – a 40% increase in Europe, 63% in North America, 77% in the southern Latin American cone and 89% in the developed Asia Pacific countries. Other parts of Latin America and North Africa and the Middle East start from a low base but will experience a particularly rapid increase – 134–146% in the rest of Latin America, and 125% in North Africa and the Middle East. China, India and their neighbours in South Asia and Western Pacific start from a high base and will also experience rapid growth – 107% in South Asia and 117% in East Asia. Projected increases for sub-Saharan Africa (70–94%) are modest and are consistent with limited demographic ageing in view of persistently high child mortality and the effects of the HIV epidemic.

Young onset dementia (early oncet dementia)

Young onset dementia (YOD), defined typically as onset before the age of 65 years, is a rare condition. Few population-based surveys have been carried out, since large sample sizes are needed to estimate prevalence with precision. Instead, researchers typically conduct registry-based studies, reporting prevalence calculated as the number of cases known to local service providers divided by the total local population from the census. The assumption is that all of those with YOD seek help early in the disease course. This is not always the case, and therefore such studies will underestimate the true prevalence of dementia.

Review

The European Collaboration on Dementia group (EuroCoDe) carried out a systematic review of prevalence of YOD.[21] In addition to two registry-based studies from the United Kingdom, the group identified a registry-based study from the USA,[15] and a population-based survey of late-onset dementia from Rotterdam, Netherlands, in which the youngest age group was 55–59 years.[22] The reviewers commented on the scarcity of data and variability of estimates, and did not attempt a meta-analysis. A Delphi consensus had previously been attempted for the Dementia UK report, using the two United Kingdom studies, one carried out in Cambridgeshire, and the other in four London boroughs[023,24,25] The prevalence of persons aged 45-64 was, for males, 120/100 000 in London and 101/100 000 in Cambridgeshire; and for females 77/100 000 in London and 61/100 000 in Cambridgeshire. For YOD, as with late onset dementia, the expert consensus was that prevalence increased exponentially with increasing age, roughly doubling every five years from 9/100 000 at age 30 to 156/100 000 at age 60–64 years. Two-thirds (68%) of all young onset cases were aged 55 and over. Among this larger, middle-aged group of people with YOD, males predominated over females with a gender ratio of 1.7 to 1.

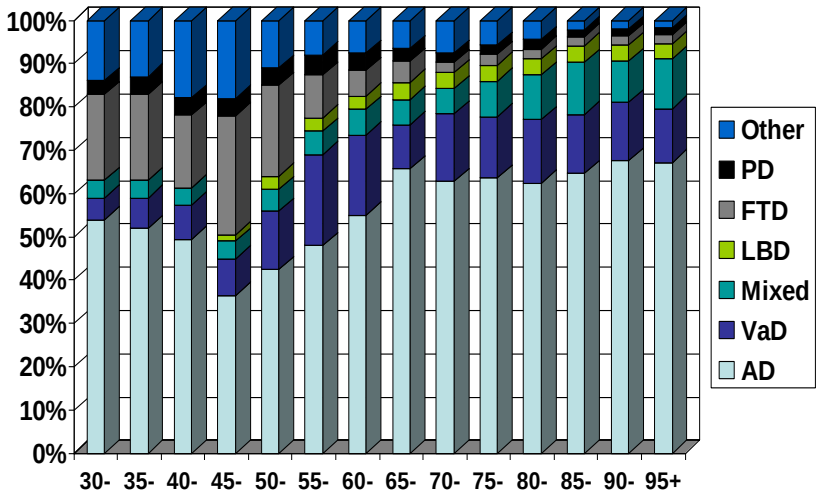
The consensus group's estimate for 60–64 years (156/100 000, or 0.16%) is one-ninth rather than, as expected, one half of the late-onset prevalence for the next five-year age band (1.3% for those aged

65–69). This discrepancy is likely to be artefactual, arising from an underestimation of population prevalence in the YOD studies, which ascertained cases from service contact only. This explanation is supported by the Rotterdam population-based survey prevalence of 423/100 000 for those aged 55–59 and 418/100 000 for those aged 60–64.[22] Thus, there may be an underestimation by registry-based studies of the true prevalence of YOD by a factor of 2.5 to fourfold. While it was estimated that YOD accounts for only 2.2% of all people with dementia in the United Kingdom, the true proportion may be closer to 6–9%.[23]

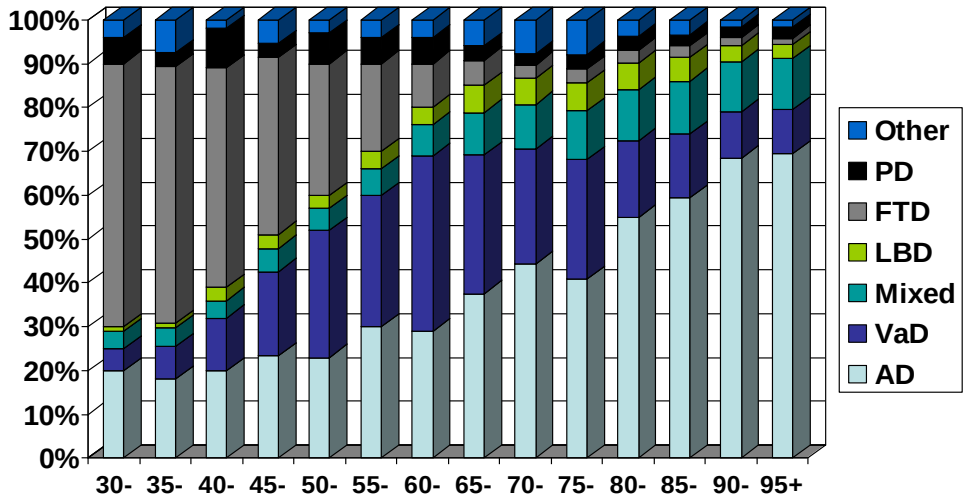
It is sometimes suggested, chiefly on the grounds of lower life expectancies at birth, that ageing begins earlier in LMIC. These differences are mainly accounted for by early life mortality and there is little evidence that YOD is more common in LMIC. Three prevalence studies from India included participants aged less than 65 years, and prevalences of YOD were as low as those seen in high-income population-based surveys: 328/100 000 (60–64 years) in Kerala,[21] 249/100 000 in Ballabgarh (55–64 years), and 63/100 000 (50–59 years) and 280/100 000 (60–64 years) in Mumbai.8[26,27] However, this statement must be qualified given the likely impact of the HIV epidemic which is concentrated among younger people in low-income countries, particularly in southern and eastern Africa. HIV-associated dementia is an AIDS-defining illness, with a prevalence of 15–30% in untreated populations, presenting with neurocognitive impairments (forgetfulness, poor concentration and slowed mental processing), emotional disturbances (agitation, apathy), and motor dysfunction. The condition is also seen among those receiving Highly Active Antiretroviral Therapy (HAART) with a prevalence of 10% and an annual incidence of 1%.[28,29]

Figures 6.11.2.4a and 2.4b: Dementia UK report: consensus estimates of the proportion of all dementia cases accounted for by different dementia subtypes, by age and gender)

a) Women



b) Men



Source: *Dementia: a public health priority.* WHO, 2012.
PD. Parkinson's disease, FTD Frontotemporal dementia, LBD Lewy bodies dementia, VaD Vascular disease, AD Alzheimer disease:

2.2 Discussion - prevalence of dementia

The current estimates provide an indication of the numbers of people aged 60 years and over with dementia worldwide and in different world regions. There is much more uncertainty as to the prevalence of YOD but, if such cases were to be included, the total numbers affected might be up to 6–9% higher. The current estimates for the prevalence of dementia among those aged 60 years and over are approximately 10% higher than those from the earlier ADI Delphi consensus, accounted for by a higher age-standardized prevalence for South Asia (5.7% versus 3.4%), Western Europe (7.3% versus 5.9%) and the Latin American regions (8.5% versus 7.3%).[30] *These increases were partly offset by the lower estimated prevalence for East Asia (5.0% versus 6.5%). The new estimates are likely to be an improvement on those provided earlier, given the extension in the evidence base from LMIC. It was possible to include seven studies from South Asia, 52 from Western Europe, 34 from East Asia and 11 from Latin America in the regional meta-analyses. There was previously just one prevalence study available from Latin America.*[31] *The decision to pool the data across the four GBD regions in Latin America was supported by the relatively low level of heterogeneity in estimates between sites. The evidence base from China was considerably extended by a recent systematic review that included data from publications previously available only in Chinese journals.*[32] *The previous estimates for South Asia were perhaps disproportionately influenced by one large study, from rural Ballabgarh in northern India, which recorded an unusually low prevalence.*8 *Earlier estimates for Europe* [33] *were strongly influenced by two previous reviews by the European Community Concerted Action on the Epidemiology and Prevention of Dementia Group (EURODEM).*[19,34,35] *The current systematic review is much more comprehensive, and the new estimates coincide with the 7.1% prevalence derived from a recent systematic review by the EuroCoDe group.*[21]

Data was insufficient for certain regions, particularly Eastern Europe, North Africa, the Middle East, Russia, and sub-Saharan Africa. As such, the estimates must still be considered provisional. The current estimates have drawn on previous Delphi consensus estimates for these regions. A limitation of this review could be using two methodologies to quantify prevalence estimates for different GBD regions, i.e. meta-analysis for 11 out of 21 regions where sufficient studies were available and for

others (due to insufficient data), use of relevant estimates from the Delphi consensus. Meta-analysis methods that allow estimates for regions without data by borrowing strength from those with data would allow updated estimates for all regions. This also emphasizes the need of more data of good quality for the GBD regions where sufficient studies were not available.

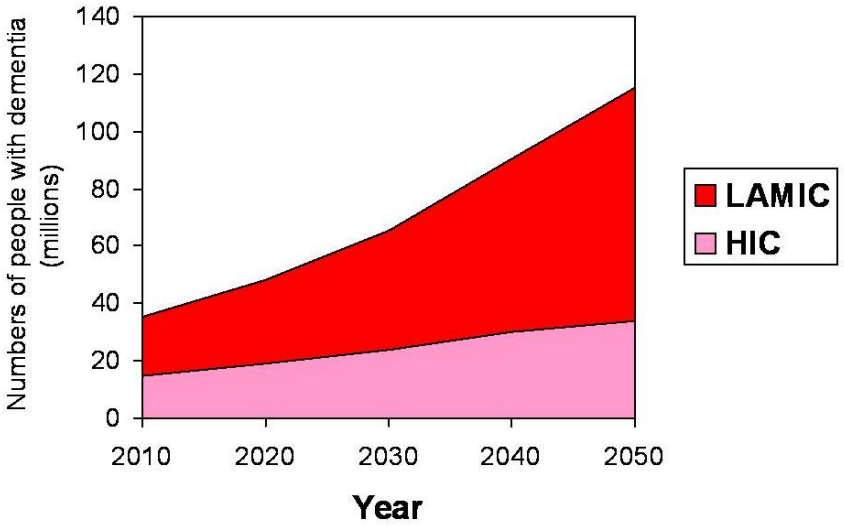
The low prevalences for sub-Saharan Africa are mainly determined by the one good-quality study (Ibadan, Nigeria) that was available when the review was conducted in 2009.[15] Subsequent studies from francophone countries in western and central Africa, and one further study from northern Nigeria suggest a more variable prevalence, higher in urban than in rural sites, and higher in central compared with western Africa.[36,37,38,39] The Nigerian study recorded a low prevalence that is consistent with findings from the earlier USA/Nigeria study (2.4% for those aged 65 and over, age-standardized to Western Europe, with an age-standardized prevalence of 1.9% for those aged 60 and over assuming that the prevalence for those aged 60–64, which was not assessed, was half that of those aged 65–74).[39] Prevalence was similarly low in rural Benin (2.4% age-standardized for age 65+ and 2.0% for age 60+ similarly estimated).[36] The prevalence in urban Benin was higher (4.3% and 3.5%) and that recorded in cities in the Central African Republic (10.1% and 8.2%) and the Republic of the Congo (7.2% and 6.0%) was substantially higher.[38,39]

Current evidence therefore challenges the previous consensus that the prevalence of dementia was lower in LMIC, and strikingly so in some studies.9,11 Methodological factors may be implicated.6,7,8 In the 10/66 Dementia Research Group studies, the group's 10/66 dementia diagnosis – developed, calibrated and validated in a 26-site pilot study – was both more prevalent than that according to DSM-IV criteria, and more consistent between sites.[40] The prevalence of DSM-IV dementia was particularly low in rural and less developed sites.[41] It may be that milder dementia is under-detected in LMIC because of low awareness, high levels of support routinely provided to older people, and reluctance to report failings to outsiders, which could all contribute to difficulties in establishing the DSM-IV criterion of social and occupational impairment.8,41 In Cuba, the criterion validity of the 10/66 diagnosis was superior to that of DSM-IV which selectively missed mild and moderate cases.[42] In India, the predictive validity of the 10/66 diagnosis was supported by high mortality after three years of follow-up, with survivors showing expected progression of cognitive impairment, disability and needs for care;[43] this suggested that the true prevalence at baseline was likely to be much closer to the 7.5% recorded for 10/66 dementia than the 0.9% prevalence according to DSM-IV criteria.[41]

Extracted from the WHO dementia Report 5.

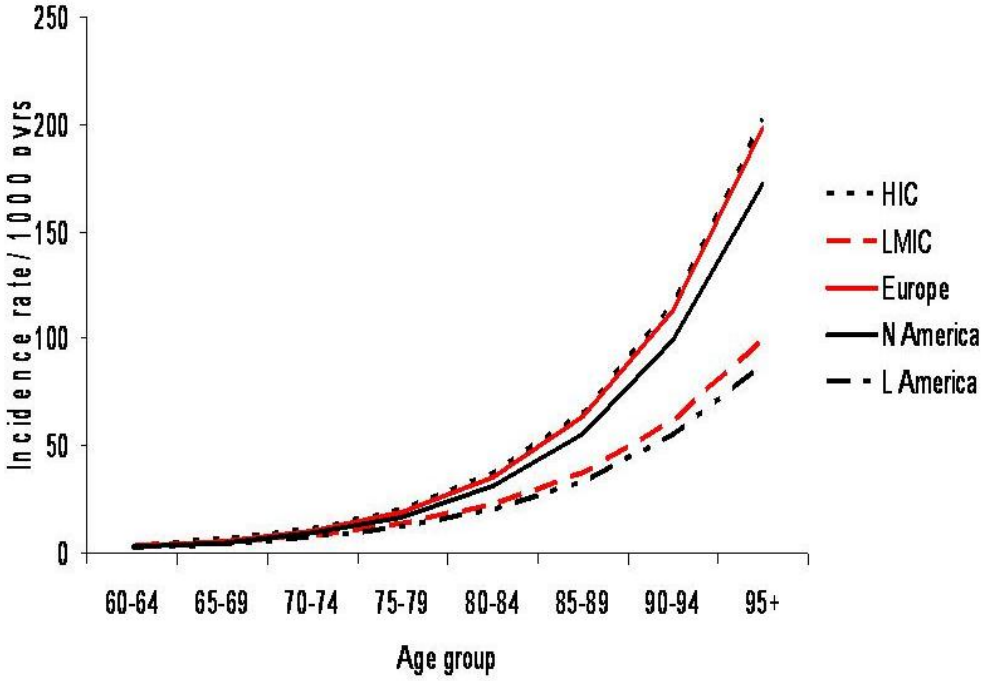
Recent epidemiological surveys report that *"North America and Western Europe have at age 60, the highest prevalence of dementia (6.4 and 5.4% of the population at age 60), followed by Latin America (4.9%) and China and its developing western-Pacific neighbors (4.0%). The annual incidence rates (per 1000) for these countries were estimated at 10.5 for North America, 8.8 for Western Europe, 9.2 for Latin America and 8.0 for China and its developing western-Pacific neighbors, increasing exponentially with age in all countries, especially through the seventh and eighth decades of life"*.[14]

Figure 6.11.3: Growth in numbers of people with dementia in high-income and low- and middle-income countries.



Source: D*ementia: a public health priority.* WHO, 2012.

Figure 6.11.4: Estimated age-specific annual incidence of dementia, derived from mixed-effects Poisson meta-regression, for world regions for which meta-analytical synthesis was feasible



Source: D*ementia: a public health priority.* WHO, 2012.

2.3 Dementia in Europe

According to Alzheimer Europe Association and following UN's demographic forecast number of demented patients in Europe will rise substantially in the following years.6
There are over six million people with dementia in the EU. Currently, 40% of those with late-stage Alzheimer disease live at home, while 60% live in healthcare establishments.6 Families have often to take care of a relative with Alzheimer disease, which is a challenging experience. With the ageing of the baby boomer generation, managing dementia in elderly is one of the greatest challenges that Europe will have to face in the next 50 years.

From The WHO dementia Report:

The most sophisticated analysis of dementia subtype was that carried out for the Dementia UK report. Authors estimated the proportion of dementia cases accounted for by different subtypes according to age and sex, using a Delphi consensus of United Kingdom and other European evidence.[23] Three of six United Kingdom population-based studies of late-onset dementia included information on subtype diagnoses (Alzheimer disease, VaD or mixed dementia and "other").[44,45,46] A more recent community-based study provided information on the relative frequency of a wider range of subtypes;[47] Alzheimer disease (41%), VaD (32%), dementia in Parkinson Disease (3%), FTD (3%) and DLB (8%); Only the EURODEM meta-analysis of studies in the 1990s provided gender- as well as age-specific proportions with Alzheimer disease and VaD.[35] In that study, while the proportion with Alzheimer disease among females remained constant at around 70%, among men the proportion increased progressively from 38% among those aged 65–69 years to 80% in those over 90 years of age. Two YOD studies included detailed information on the full range of dementia subtypes, based on specialist dementia clinic assessments.[24,25] Two further YOD studies provided limited information on the relative frequency of Alzheimer disease, VaD and mixed dementia. [48,49]

The results indicate that the FTD is a common subtype in YOD, particularly among men among whom it is the commonest subtype up to age 55 (Figures 6.11.2-4a and 2-4b). Vascular dementia is also relatively more common among men aged 45–75 years of age. While the proportion of dementia cases attributable to Alzheimer disease, the commonest subtype overall, is relatively constant among women varying between 40–60% across the age range from 30 years and over, among men the proportion increases steadily with age from around 20% at age 30 to around 70% at ages 95 and over.

Studies in developed countries have consistently reported Alzheimer disease to be more prevalent than VaD. Early surveys from South-East Asia were an exception, though more recent studies suggest that the pattern may now have reversed.[50] This may be due to increasing longevity and better physical health. Alzheimer disease, with typically a later age of onset than VaD, increases as the number of very old people increases. Better physical health reduces cerebrovascular disease and hence the numbers with VaD. These changes also tend to shift the sex ratio towards a preponderance of female cases.

Detailed graphs regarding DALYs and mortality caused by Alzheimer disease and other dementias by regions and sex are in Annex 6.11.7 and 6.11.8.

Global incidence of dementia

Studies of the incidence of the Alzheimer disease subtype were recently systematically reviewed.[51] Twenty-seven studies were identified, of which only seven were conducted outside of North American and Europe – three from Japan, and one each from China (Province of Taiwan), India, Nigeria and

Brazil. Hence, only three studies were performed in LMIC. Incidence at age 80 was higher in North America (20.6/ per 1 000 person years) and Europe (15.1) than in other countries (8.3). However, the doubling time was shorter in other countries (5.0 years) than in North America (6.0) or Europe (5.8). Incidence was slightly higher among women (13.7 per 1 000 person years) than in men (10.6/ 1 000 person years). The last review of the incidence of dementia was conducted in 1998, in which 23 studies were identified, with only one from LMIC.[52] Incidence in Europe increased from 9 per 1 000 person years at ages 60–64 to 180 per 1 000 person years at ages 90–94. A new review was conducted to estimate annual incidence rates and expected annual numbers of new cases in 21 GBD regions.

Search results

The search yielded 1 718 abstracts, from which we identified 34 fully eligible studies. Of these, 16 had been conducted in Western Europe, five in North America (four in the USA and one in Canada), four in East Asia (four in China, including one in the Province of Taiwan), six In Latin America or the Caribbean (Brazil, Cuba, Dominican Republic, Mexico, Peru and Venezuela), one in Australasia (Australia), one in the Asia Pacific region (Republic of Korea), and one in West sub-Saharan Africa (Nigeria). Collectively, the studies included 72 224 older people "at risk" and accumulated 214 756 person years of follow-up. The median cohort at risk was 1 769 (interquartile range 937–3 208) and the median person years was 4679 (interquartile range 2 795–9 101). Most studies applied DSM-III-R (n=14), DSM-IV (n=14) or ICD-10 (n=3) criteria. The six 10/66 Dementia Research Group studies applied both DSM-IV and 10/66 dementia criteria.

Coverage

While the evidence base from Europe and North America dominated, 13 of the 34 studies were from outside these regions, and 10 studies were conducted in countries with low or middle income regions. There was no coverage for nine GBD regions: Oceania, South-East Asia, Central Asia, Central Europe, Eastern Europe, North Africa/Middle East, Southern sub-Saharan Africa, Central sub-Saharan Africa and Eastern sub-Saharan Africa. Five studies (four in Europe and one in the USA) focused on persons aged 80 years or over. The Western European studies contributed 52% of the total person years, the North American studies 21% and the Latin American studies 15%, with just 12% contributed by studies from other regions.

Modelling the incidence of dementia

The incidence of dementia increases exponentially with increasing age. For all studies combined, the incidence of dementia doubles with every 5.9 year increase in age, from 3.1 per 1 000 person years at age 60–64 to 175.0 per 1 000 person years at age 95+ (see Figure 6.11.4). The incidence of dementia appears to be higher in countries with high incomes (doubling every 5.8 years from 3.4 per 1 000 person years to 202.2 per 1 000 person years) than in LMIC (doubling every 6.7 years from 2.9 per 1 000 person years to 99.4 per 1 000 person years). Overall the incidence of dementia in LMIC was 36% lower (RR 0.64, 95% CI 0.48–0.85) than in high-income countries. However, if the 10/66 Dementia Research Group's cross-culturally validated 10/66 dementia criteria were applied rather than DSM-IV criteria, then this difference was no longer apparent (RR 0.99, 95% CI 0.74–1.33). There was significant heterogeneity in the incidence estimates when all studies were combined (alpha = 0.16). Heterogeneity was greater for studies in countries with high incomes (0.17) than in countries with low or middle incomes (0.02).

Estimation of annual numbers of incident cases of dementia

Numbers of new cases increase and then decline with increasing age in each region; in Europe and the Americas peak incidence is among those aged 80–89 years, in Asia it is among those aged 75–84 years, and in Africa among those aged 70–79 years (Table 6.11.4). The researchers estimated nearly 7.7 million new cases of dementia each year worldwide, implying one new case every 4 seconds. Some 3.6 million (46%) would impact in Asia, 2.3 million (31%) in Europe, 1.2 million (16%) in the Americas, and 0.5 million (7%) in Africa.

Discussion - the incidence of dementia

Incidence rates and numbers of new cases are particularly relevant to efforts to develop, initiate and monitor prevention strategies. Prevalence differences between populations and trends in prevalence over time are difficult to interpret since they may arise from differences in underlying incidence or duration (survival with dementia). The current estimate of 7.7 million new cases per year is an important benchmark, globally and regionally, particularly given the relatively low levels of heterogeneity between studies.

Various explanations have been advanced for previous observations of very low prevalences of dementia in some LMIC sites. Estimates of the incidence of dementia were also exceptionally low in the US-Nigeria and US-India studies, suggesting that differences in survival could have been only part of the explanation for the low prevalence recorded in those sites.[53,54] Differences in levels of exposure to environmental risk factors may also have contributed (e.g. the healthy cardiovascular status of older Nigerians).[55,56] Differing patterns of mortality in early life might also be implicated; older people in very poor countries are exceptional survivors, and some of the factors that confer survival advantage may also protect against dementia onset in late life. However, the evidence from our meta-analysis suggests that differences in dementia incidence between developed and developing countries may not be as large as had previously been suggested, and that methodological factors, particularly the use of DSM-IV diagnostic criteria, may have contributed. For the 10/66 Dementia Research Group studies, as with prevalence, the incidence of 10/66 dementia is higher than that of DSM-IV dementia, and when that criterion is applied in this meta-analysis the developed/developing country incidence rates converge.[41] Clearly more research is required into the incidence of dementia in order to provide more evidence on the extent of the problem in different world regions.

Mortality associated with dementia

Dementia shortens the lives of those who develop the condition. One of the best studies in the field estimated median survival with Alzheimer disease at 7.1 years (95% CI 6.7–7.5 years) and for VaD 3.9 years (3.5–4.2 years).[57] There is much individual variability around these median estimates. The independent contribution of dementia to mortality is difficult to assess. Death certificates are unreliable, since dementia is rarely considered as a direct or underlying cause of death. People with dementia often have comorbid health conditions that may or may not be related to the dementia process and which themselves may hasten death. Hence deaths of people with dementia cannot automatically be considered to be deaths attributable to dementia.

Review

A meta-analysis of studies principally from high-income countries estimated a two-and-a-half-fold increased mortality risk for people with dementia (RR 2.63, 95% CI 2.17–3.21).[58] The EURODEM incidence studies reported a constant relative risk of 2.38 up to age 89 years, declining to 1.80 in

females and 1.60 in males over the age of 90 years. Estimates from LMIC suggest a slightly higher relative mortality hazard: in the10/66 Dementia Research Group studies, the pooled HR was 2.77 (95% CI 2.47–3.10), with a modest degree of heterogeneity, while even larger relative risks have been recorded in studies in Nigeria (HR 2.83, 95% CI 1.10–7.27) [56] and Brazil (HR 5.16, 95% CI 3.74–7.12).[59, 60] In the three studies published to date that have compared dementia with other health and sociodemographic factors influencing mortality in countries with low or middle incomes, dementia emerged as the leading contributor among health conditions.[59,60,61]

In the Dementia UK report, the EURODEM mortality relative risks were used to calculate the proportion of deaths at different ages independently attributable to dementia.[23] This proportion increased steadily from 2% at age 65 years to a peak of 18% at age 85–89 years in men, and from 1% at age 65 to a peak of 23% at age 85–89 in women. Overall, 10% of deaths in men over 65 years, and 15% of deaths in women are attributable to dementia, the majority occurring among those aged 80–95 years.

Estimates of deaths attributable to dementia from the GBD Report [60] are much more conservative – 4.0% of deaths (275 000) among those aged 60 and over in high-income countries, 0.6% (19 000) in upper-middle-income countries, 0.6% (72 000) in lower-middle-income countries and 1.3% (111 000) in lower-income countries, amounting to 477 000 annual deaths worldwide, just 1.6% of the global total for this age group.
Extracted from the WHO dementia Report.

2.4 Economic impact: the global societal cost of dementia

Dementia is expensive. The financial costs of managing AD are enormous. The cost of illness is high in terms of both public and private resources. Families and caregivers who are required to provide care and patients affected by dementia also pay a high price in terms of their quality of life. **"***In high-income countries, informal care (45%) and formal social care (40%) account for the majority of costs, while the proportionate contribution of direct medical costs (15%) is much lower. In low-income and lower-middle-income countries direct social care costs are small, and informal care costs (i.e. unpaid care provided by the family) predominate. Changing population demographics in many LMIC may lead to a decline in the ready availability of extended family members in the coming decades***"** states the 2012 WHO report "Dementia: a health priority".[3]

Most European countries are spending about 1% of their gross domestic product (GDP) on dementia. Sweden spends over 2.5%. The biggest driver of costs is nursing homes or residential care.[3]

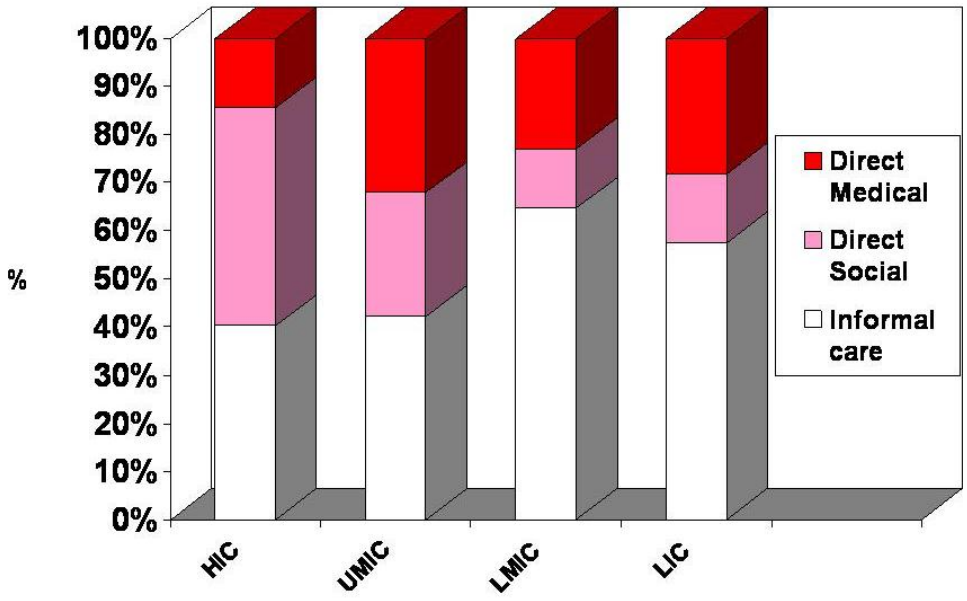
From the WHO dementia Report 5:

A proper understanding of the societal costs of dementia, and how these impact upon families, governments and their health and social care systems, is fundamental to raising awareness, achieving proper prioritization, and focusing efforts to improve the lives of people with dementia and their caregivers. Cost-of-illness studies for dementia have been carried out for some, mainly high-income, countries such as Australia, Canada, Sweden, United Kingdom and the USA, as well as the European Union.[23,62,63,64,65,66] The consensus is that dementia is already imposing huge economic burdens, both through direct (medical and social care) and indirect costs (unpaid caregiving by families and friends). Evidence is also emerging of the extent of the economic burden in middle-income countries.[67,68,69,70]

Cost-of-illness studies are descriptive, quantifying the total societal economic burden of a health condition and highlighting its impact on different health and social care sectors. The distribution of costs between countries and regions can also be estimated and compared, and trends over time can be monitored or, tentatively, projected into the future. Comparison of costs of illness across health conditions is more challenging; it has also been argued that prioritization for investment should be determined more by the relative cost-effectiveness of available interventions than by the economic burden of the disease.[71]

Three previous reports of the global economic burden of dementia were each based on the best available data for the prevalence of dementia and care inputs.[72,73,74] *The most recent of these estimated global costs at US$ 422 billion in 2009, 74% contributed by high-income countries. The aim of this recent cost-of-illness study was to generate evidence-based estimates of resource utilization for each country. Thus, country-specific annual per capita costs (direct medical and social care costs, and informal care) were applied to estimated numbers of people with dementia in each country, and aggregated up to the level of WHO regions, and World Bank country income-level groupings. The costs (as well as the prevalence of dementia) reflect estimates for 2010. Cost estimates based on previous years are inflated appropriately. Costs are expressed as US dollars, converted from local currencies based on current exchange rates. Where no estimates were available for a country, estimates from other similar countries within the same region or adjacent regions were used. For direct costs, the strong relationship between the direct costs per person with dementia and per capita Gross Domestic Product (GDP) was used to predict total direct costs for countries within regions with no data. The split between medical and social care costs was estimated by applying data from China, the one LMIC with available data.*

Figure 6.11.5: Distribution of total societal costs (%) by World Bank Income level



Source: *Dementia: a public health priority.* WHO, 2012.

Table 6.11.4: Per capita (US$) and aggregated costs (billions US$) by Global Burden of Disease region and World Bank income classification

GBD world region	Per capita costs (US$)	Number of people with dementia	Aggregated costs (US$ billion)				Total costs as % of GDP	Direct costs as % of GDP
			Informal care (all ADLs)	Direct medical costs	Direct social costs	Total costs		
Australasia	32 370	311 327	4.30	0.70	5.07	10.08	0.97%	0.56%
Asia Pacific, High Income	29 057	2 826 388	34.60	5.23	42.29	82.13	1.31%	0.76%
Oceania	6 059	16 553	0.07	0.02	0.01	0.10	0.46%	0.12%
Asia, Central	2 862	33 0125	0.43	0.28	0.24	0.94	0.36%	0.20%
Asia, East	4 078	5 494 387	15.24	4.33	2.84	22.41	0.40%	0.13%
Asia, South	903	4 475 324	2.31	1.16	0.57	4.04	0.25%	0.11%
Asia, South-East	1 601	2 482 076	1.77	1.48	0.73	3.97	0.28%	0.15%
Europe, Western	30 122	6 975 540	87.05	30.19	92.88	210.12	1.29%	0.75%
Europe, Central	12 891	1 100 759	8.59	2.67	2.94	14.19	1.10%	0.44%
Europe, Eastern	7 667	1 869 242	7.96	3.42	2.94	14.33	0.90%	0.40%
North America, High Income	48 605	4 383 057	78.76	36.83	97.45	213.04	1.30%	0.82%
Caribbean	9 092	327 825	1.50	0.78	0.71	2.98	1.06%	0.53%
Latin America, Andean	3 663	254 925	0.35	0.31	0.28	0.93	0.43%	0.27%
Latin America, Central	5 536	1 185 559	1.58	2.61	2.37	6.56	0.37%	0.28%
Latin America, Southern	8 243	61 4523	2.36	1.42	1.29	5.07	1.02%	0.54%
Latin America, Tropical	6 881	1 054 560	2.17	2.67	2.42	7.26	0.42%	0.29%
North Africa/Middle East	3 296	1 145 633	1.90	2.05	0.54	4.50	0.16%	0.09%
Sub-Saharan Africa, Central	1 081	67 775	0.04	0.02	0.01	0.07	0.06%	0.02%
Sub-Saharan Africa, East	1 122	360 602	0.28	0.08	0.04	0.40	0.17%	0.05%
Sub-Saharan Africa, Southern	6 834	100 733	0.52	0.11	0.06	0.69	0.24%	0.06%
Sub-Saharan Africa, West	969	181 803	0.11	0.04	0.02	0.18	0.06%	0.02%
World Bank classification								
Low income	868	5 036 979	2.52	1.23	0.62	4.37	0.24%	0.10%
Lower middle income	3 109	9 395 204	18.90	6.74	3.57	29.21	0.35%	0.12%
Upper middle income	6 827	4 759 025	13.70	10.44	8.35	32.49	0.50%	0.29%
High income	32 865	16 367 508	216.77	78.00	243.14	537.91	1.24%	0.74%
Total	16 986	35 558 717	251.89	96.41	255.69	603.99	1.01%	0.59%

Source: *Dementia: a public health priority.* WHO, 2012.

The major limitation was the sparse data on health and social care from LMIC, with cost models relying largely on extrapolation of economic conditions from higher-income to lower-income countries, adjusted for per capita GDP. Also, it was not possible to distinguish between direct medical costs (within the health care sector) and direct social care costs (within the community and care-home

sector). The cost of illness analysis conducted for ADI's World Alzheimer Report 2010 addressed many of these limitations.[75]

The global costs of dementia (base case option)

The total global societal costs of dementia were US$ 604 billion in 2010 (Annex6.11.5). This corresponds to 1.0% of the aggregated worldwide GDP, or 0.6% if only direct costs are considered. The total cost as a proportion of GDP varied from 0.24% in low-income countries to 1.24% in high-income countries, with the highest proportions in North America (1.30%) and Western Europe (1.29%). The per capita costs of dementia varied considerably by World Bank income classification, from US$ 868 in low-income countries, to US$ 3 109 in lower-middle-income countries, to US$ 6 827 in upper-middle-income countries, to US$ 32 865 in high-income countries. When multiplied by the estimated numbers of people with dementia, this generated aggregated costs of US$ 4.37 billion in low-income countries, US$ 29.21 billion in lower-middle-income countries, US$ 32.39 billion in upper-middle-income countries, and US$ 537.91 billion in high-income countries. Therefore, the costs of dementia are unevenly distributed. About 70% of the global societal costs of dementia occur in just two WHO GBD regions (North America and Western Europe) and 89% of the total costs are incurred in high-income countries. However, the minority (46%) of people with dementia live in high-income countries, 39% of people with dementia live in middle-income countries (where 10% of costs are incurred) and 14% in low-income countries (accounting for less than 1% of the total costs).

The distribution of total costs between sectors also varies markedly by country income level. In high-income countries, the costs of informal care (45%) and the direct costs of social care (40%) contribute similar proportions to total costs, while the proportionate contribution of direct medical costs (15%) are much lower (Figure 6.11.7). However, in low-income countries and lower-middle-income countries direct social care costs are small and informal care costs predominate. Thus, while the total cost per person with dementia is 38 times higher in high-income countries than in low-income countries, the direct costs of social care are 120 times higher. In the ADI worldwide survey of care home utilization, the proportion of people with dementia living in care homes was significantly higher in high-income countries (30%, 95% CI 23–37%) than in LMIC (11%, 95% CI 5–17%).

Sensitivity analyses

If only basic ADLs are used for the costs of informal care instead of combining basic ADLs and IADLs, the total costs are 22% lower. They are 30% higher if combined ADLs/IADLs and supervision are included. Compared with US$ 604 billion in the base case, these sensitivity analyses provide a lower bound of US$ 470 billion (only basic ADLs) and an upper bound of US$ 783 billion (all informal care including assistance with basic ADL and IADL and supervision).

Since a substantial proportion of caregivers are spouses and most, but not all, could be assumed to be beyond the usual working age, the informal care and total costs were recalculated by applying a reduced wage to the estimated proportion of caregivers in each country who were spouses. This leads to a 9% reduction in the total worldwide cost estimate from US$ 604 billion to US$ 548 billion when costed at 50% of the average wage and a 14% reduction to US$ 520 billion when costed at 25% of the average wage. With the replacement costs approach, based on the average wage of a social care professional in that country, the total costs were slightly higher.

Under the base case option, low-income countries accounted for just 0.7% of total worldwide costs, middle-income countries for 10.2% and high-income countries for 89.1%. Using PPP rather than

exchange rates to translate costs in local currencies to the common US dollar metric, the proportions increased for low-income countries (2.1%) and middle-income countries (20.0%) and fell for high-income countries (77.9%).

Discussion - the economic cost of dementia

The estimated annual worldwide cost to society of dementia, US$ 604 billion, highlights the enormous impact that dementia has on socioeconomic conditions worldwide. If dementia care were a country, it would be the world's twenty-first largest economy, ranking between Poland and Saudi Arabia. The scale of these costs is understandable given that:

- *the 35.6 million people worldwide comprise 0.5% of the world's total population;*
- *a high proportion of people with dementia need some care, ranging from support with IADL, to full personal care and round-the-clock supervision;*
- *in some high-income countries, one third to one half of people with dementia live in resource- and cost-intensive residential or nursing homes.*[23,76]

The marked imbalance in the global distribution of prevalence and costs arises, in part, because of the imbalance of costs between sectors. In LMIC, the formal social care sector (accounting for the direct costs of care in the community by paid social care professionals, and of care homes) is practically non-existent. Therefore, responsibility falls largely on unpaid informal carers, and informal care costs predominate. In high-income countries the direct costs of social care account for nearly half of all costs. Since average wages (used to estimate informal care costs) are much lower in LMIC, this has an important impact on comparative total costs.

It is difficult to compare our estimates of the global societal costs for dementia with those for other conditions because few such estimates exist and there are problems with comparability. In the United Kingdom, a recent report commissioned by the Alzheimer Research Trust focused on the economic burden of dementia and other chronic diseases, and sought to compare like-for-like disease costs with national expenditure on research.[77] *The societal costs of dementia (£23 billion) almost matched those of cancer (£12 billion), heart disease (£8 billion) and stroke (£5 billion) combined. However, for every £1 million in costs arising from the disease, £129 269 was spent on cancer research, £73 153 on heart disease research and £4 882 on dementia research. In a paper from Sweden the costs of dementia were compared with other estimates for chronic disorders.*[78] *The annual costs of dementia (50 billion SEK) was higher than for depression (32.5 billion SEK), stroke (12.5 billion SEK), alcohol abuse (21–30 billion SEK) and osteoporosis (4.6 billion SEK).*

Future trends

The reported projections for future growth in numbers of people with dementia should be treated with caution. First, these rely on demographic projections which may not be accurate for many parts of the world, especially for older age groups. Second, it was assumed that age-specific prevalence in each region would remain constant over time. However, changes in risk exposure may increase or decrease incidence. Conversely specific therapies and better social and medical care may reduce case mortality and increase prevalence. Disease-modifying therapies that delay onset, even to a modest extent, would have considerable potential for reducing age-specific prevalence.

It is particularly difficult to make confident projections of future economic costs. If we assume that all potential background factors remain unchanged, and we factor in only the forecast increases in the number of people with dementia, then by 2030 worldwide societal costs will have increased by 85%.

The reality is more complicated. Future costs could be influenced by macroeconomic factors (e.g. the pace of economic development) and by dementia-specific factors. These would include changes in the prevalence of dementia, in patterns of help-seeking and trends towards earlier diagnosis, in the availability of health and social care services, changes in care systems and care conditions and the availability of new and more effective treatments. There are very few estimates of the extent of the "treatment gap" for dementia in LMIC, but it is likely to be much greater than in better-resourced settings.[79] The current inequitable distribution in dementia costs between world regions will also have implications for future trends, which are likely to tend towards more rapidly increasing per capita and population costs in LMIC, with the result that the global distribution of costs will come to resemble that of morbidity. These cost increases will be driven by several underlying factors. First, increases in numbers of people with dementia will occur much more rapidly in LMIC because of the more rapid demographic ageing in those regions. Second, with economic development, wages will rise rather rapidly in LMIC. Third, resources for dementia care, particularly formal medical and social care, are unequally distributed worldwide. With increased awareness will come increased demand for care. Residential and community social care systems are well developed in many high-income countries but are scarce in LMIC where there is a reliance on traditional, informal family care arrangements. In many LMIC the traditional family and kinship structures are under threat from the demographic, social and economic changes that accompany economic development and globalization. Therefore, the need for community and residential care is likely to grow in LMIC, and with it direct costs.

3. Control Strategy

Dementia is a complex disease and its management is often challenging. Personality and behavioural changes, and the eventual inability to perform activities of daily living lead to dependence. As functional impairment deteriorates, health care utilization increases until patients are forced to become institutionalized. Patients can remain in severe stages of AD for several years.[80,81,82]

From The WHO dementia Report 5:

3.1 Etiology and potential for prevention

The US National Institutes of Health (NIH) conducted a state-of-the-science conference review in 2010 to provide health-care providers, patients and the public with an assessment of currently available data on prevention of Alzheimer disease and cognitive decline.[83] Their report states that "firm conclusions cannot be drawn about the association of any modifiable risk factor with cognitive decline or Alzheimer disease". However, the evidence base is still incomplete and further research is required. Very few primary prevention randomized controlled trials have been conducted, and the results do not support potential for risk reduction. Nevertheless, many of these trials recruited older people, and follow-up periods were relatively short. Given that neurodegeneration may precede the onset of dementia by several decades, this may have been a case of too little too late. There is, however, a strong evidence base from population-based cohort studies attesting to the potential risk reduction benefits of better cardiovascular health, more education, and higher levels of physical activity.

Dementia, cardiovascular risk factors and cardiovascular disease

Research suggests that vascular disease predisposes to Alzheimer disease as well as to vascular dementia.[84] In short and longer latency incidence studies, smoking increases the risk for Alzheimer disease.[85,86,87,88,89] Diabetes is also a risk factor and, in longer-term cohort studies, midlife hypertension and raised cholesterol are associated with the onset of Alzheimer disease in later life.[90,91,92] Aggregated cardiovascular risk indices incorporating hypertension, diabetes, hypercholesterolemia and smoking increase risk for dementia incidence incrementally whether exposure is measured in midlife or a few years before onset of dementia.[87,89]

Despite occasional negative findings from large prospective studies, the accumulated evidence for a causal role for cardiovascular risk factors and cardiovascular disease in the etiology of dementia and Alzheimer disease is very strong.[93,94] This has led to speculation that atherosclerosis and Alzheimer disease are linked disease processes, with common pathophysiological and etiologic underpinnings (ApoE ε4 polymorphism, hypercholesterolemia, hypertension, hyperhomocysteinemia, diabetes, metabolic syndrome, smoking, systemic inflammation, increased fat intake and obesity).[95]

One of the complicating factors for interventions in this area is that evidence suggests that while hypertension, raised cholesterol and obesity in midlife increase the risk for later onset of dementia, blood pressure levels, cholesterol and body mass index fall progressively before the onset of the disease.[91,96,97] Hence people with dementia have lower blood pressure levels, cholesterol and body mass than others. Therefore, early primary prevention may be the most effective intervention. Preventive trials indicate that statins and antihypertensive treatment do not seem to lower the incidence of dementia when initiated in older people, but there have been no long-term trials from midlife onwards.[98,99]

3.2 Diagnosis of Alzheimer disease

Alzheimer disease is usually diagnosed on physical and neurological exams, and checking for signs of intellectual impairment through standard tests of mental function. For a diagnosis of AD, new criteria were published in 2011.[100]

McKhan et al. define the initial and most prominent cognitive deficits based on history and examination in one of the following categories:[100]

- Amnestic presentation: It is the most common syndromic presentation of AD dementia. The deficits should include impairment in learning and recall of recently learned information. There should also be evidence of cognitive dysfunction in at least one other cognitive domain, as defined earlier in the text.
- Nonamnestic presentations: Language presentation: The most prominent deficits are in word-finding, but deficits in othercognitive domains should be present. Visuospatial presentation: The most prominentdeficits are in spatial cognition, including object agnosia, impaired face recognition, simultanagnosia, and alexia. Deficits in other cognitive domains should be present.
- Executive dysfunction: The most prominent deficits are impaired reasoning, judgment, and problem solving. Deficits in other cognitive domains should be present.

Diagnostics tests such as MRI and CT and laboratory testing are also done to rule out medical causes of decreased brain function. Definitive changes found in the brain of affected

AD patients are microscopic and can be seen only when a sample of brain tissue is removed and examined, usually on autopsy.[11,13]

To appropriately diagnose for AD, other forms of dementia or diseases need to be ruled out. This includes the following:

- **Medication-induced dementia.** Medication-induced dementia is the most frequent cause of "reversible" dementia. To rule out a medication-induced dementia, a thorough drug history and a review of all current medication (both prescription and over-the-counter) needs be undertaken.
- **Metabolic/endocrine/nutritional/systemic disorders. Metabolic/endocrine/nutritional/** systemic disorders (e.g., hypothyroidism, B12 deficiency, and systemic diseases and heavy metal metal poising) are additional causes of "reversible" dementias and can be diagnosed with routine laboratory tests. Tests recommended include blood count, sedimentation rate (if indicated), electrolytes (including calcium), liver and renal function tests, urinalysis, syphilis serology, B12 levels, thyroid function tests, and a toxicity screen (if medical history and the physical exam so indicate).
- **Vascular dementia/hydrocephalus/tumors/hematoma.** Vascular dementia (VaD) may result as a sequel to any form of cerebrovascular disease and blood hyperviscosity. VaD is responsible for approximately 20 per cent of dementia cases including Alzheimer disease.
- **Normal pressure hydrocephalus, brain tumors, and subdural hematoma**, the most common of the structural brain lesions, and stroke can also present with dementia. Confirmation or exclusion of their presence usually requires a CT or MRI scan.
- **Depression** is another common cause of dementia in the elderly population. The following symptoms cognitive impairment symptoms may be present: confusion, memory disturbance, and attention deficits, all of which can be mistaken for dementia. Depression may also coexist with dementia and exacerbate the problem, causing; "excess disability." A good history and thorough mental-status is required as part of the treatment plan. The DSM-IV criterion for diagnosis of depression is often referred to confirm or rule out depression. As the patients affected by Alzheimer disease are advanced in age they are likely to have other chronic illnesses. Most patients with chronic illnesses do not have a single, predominant condition. Rather, most have comorbidity, the simultaneous presence of multiple chronic conditions.

The clinical criteria and diagnosis of dementias, including AD, has not changed since the 1990's. Given the advantages of early diagnosis and early intervention, there is an urgent need to revise the criteria for diagnosis so that the disease may be identified in the earlier stages. There is much research in identifying the shift between **EARLY** cognitive changes associated with dementia and that associated with normal aging, an area known as mild cognitive impairment (MCI). The current consensus is that mild cognitive impairment is not synonymous with early dementia, one in three regress, one in three stay the same and one in three progress to dementia.[14] This remains a challenge for both clinicians and researchers since the Mini Mental State Examination (MMSE), Dementia Rating Scale and other evaluating tools are relatively insensitive to early cognitive symptoms.[13]

3.3 Management of Alzheimer disease

The primary goals of treatment are to maximize the patient's ability to function in daily life, maintain quality of life, slow the progression of symptoms, and treat depression or disruptive behaviors.

Treatment of AD takes on a systematic approach. First, if there are medical conditions that make Alzheimer symptoms worse that illness needs to be managed. There are several medications such as alcohol, sedatives and antihistamines, that can also aggravate AD, and these must be identified and removed, or switched to alternative medicines.[17] If non pharmacological methods fail, medications may also be administered to treat depression, while antipsychotics medicines can be used to treat aggressive or violent behavior. Finally, "caring for the caregiver" is another vital part of any treatment strategy for AD. Experts within this field recognize that caregivers are at a high risk for depression and medical illness. As a result, recommendations and guidance about community resources and support is integrated into the overall management of the disease.

3.3.1 Pharmacological therapy review for AD

The current pharmacologic therapy for AD only provides short-term improvement for a short period of time, six to eighteen months.[21] The only medicines approved in the US and several parts of Europe for short term alleviation of symptoms are cholinesterase inhibitors and memantine. These drugs do not affect the pathology of AD, but allows the brain to compensate for the loss of neurones that communicate via acetylcholine, a neurotransmitter. This section reviews the clinical efficacy of approved and possible pharmacological therapies for AD.

Cholinesterase inhibitors

Cholinesterase inhibitors are a class of medicines that block cholinesterase-an enzyme that breaks down the neurotransmitter acetylcholine. AD is linked with low levels of acetylcholine, hence inhibiting or blocking the breakdown of acetylcholine through cholinesterase inhibitors may help to improve brain function.[101]

Treatment effects have been demonstrated with several different cholinesterase inhibitors, indicating that the class of agents is consistently better than placebo. However, the disease eventually continues to progress despite treatment and the average effect is often modest. However, global changes in cognition, behavior and functioning have been detected by both physicians and caregivers, indicating that even small measurable differences may be clinically significant. These drugs are similar yet have distinct pharmacology profiles such as onset of action, side effect profile, potential drug interactions, ease of administration (e.g. twice a day versus three times a day), and route of metabolism. Donepezil is indicated for treatment of AD in the USA. However, no published results are available for severe dementia, though open-label follow up from trials suggests that these drugs continue working as the cholinergic deficit increases.[102] Benefits reported for these medications tend to occur at higher doses. However, the higher the dose, the more likely the side effects.[102]

Given the increase in AD prevalence, more studies are needed to determine the role of cholinergic medicines in patients with severe AD and to provide comparative data on therapeutic options for this subset of patients.[103] Efficacy is always likely to be limited by the nature of the stage of the disease. The more severe the dementia, the more neuronal damage and the less the number of surviving cholinergic neurons hence the limitation of the effectiveness of an AChEI – once all receptors are saturated there is no more effect that can be produced – there is a ceiling.

Cochrane Reviews of the cholinesterase inhibitors suggest that treatment effects have been demonstrated with several agents, and that this class is generally more efficacious than placebo. Positive changes in cognition, behavior and function were demonstrated, however, the disease continues to progress and the treatment effect is modest and short lived.[102]

While none of these (cholinesterase inhibitors and NMDA) are FDA approved for vascular dementia (VaD); the growing body of evidence indicates that these may be equally effective in VaD. The implication is that for clinical trials of these therapies may be less susceptible to misclassification (AD v VaD) than putative therapies that intervene is AD specific pathology.

The cholinesterase inhibitors (donepezil and rivastigime) may not be cost effective for the management of AD but the study that reached this conclusion has been challenged by the industry which has asserted that it was under powered. Results of this study were asserted to " … *incompatible with many drug company-sponsored observational studies and advertisements claiming remarkable effects of cholinesterase inhibitors*".[104] In addition, previous claims that donepezil can stabilize cognitive deterioration and delay nursing home placement by two to three years have not been validated by this study. The study also showed that the long-term use of donepezil cost the UK National Health Service more than placebo.[104] The more general understanding is that these drugs do not work in the more severe states of the disease.

Improvements in cognitive functions for the first two years were significantly better than placebo. However, no benefits were seen in the long term endpoints of institutionalization, and the experts state that improvements in cognition does not reduce institutionalization as reported by pharmaceutical companies.[105]

The National Institute of Health and Clinical Excellence recommend donepezil and rivastigmine as options for managing mild as well as moderate Alzheimer disease. Guidance from NICE technology appraisal guidance 111 issued in November 2006 was amended on September 2007, August 2009).[105] The criteria is based on QALYs (quality adjusted life years) in the UK. Also, a therapy that is beneficial but results in longer life expectancy may actually increase health care costs compared to not treating due to the longer life expectancy.

Glutamatergic agents

One of the pathological hypotheses suggested to cause AD is neurotoxic mechanisms resulting is excessive amounts of amino acids being released. AD patients have a loss of glutamatergic pyramidal neurons, while the glutamatergic receptors NMDA (N-methyl-D-aspartate) are preserved. An over stimulation of these receptors could lead to neuronal loss which could affect the pathophysiology of Alzheimer disease. A glutamatergic NMDA receptor blocker, called memantine is effective in treating severe AD. The drug has been approved in Germany since 1970's, but clinical trial data to support its use have been limited. Data from recent clinical trials investigating the safety and clinical efficacy of memantine show that it is effective for moderate to severe AD. The medication is still being studied and is approved in the United States and several European countries.[106]

3.3.2 Psychiatric management of non-cognitive symptoms

While an important aspect of AD, there a numerous therapies many with issues and challenges in the AD patient.

Non-cognitive symptoms of dementia tend to evolve over time, so regular monitoring allows adaptation of treatment strategies to current individual needs. For example, among the behavioural disturbances common in Alzheimer disease, depression is more common early in the illness, while delusions and hallucinations are more common in the middle and later stages. Behavioural issues to be addressed include major depression and other depressive syndromes, suicidal ideation or behaviour, hallucinations, delusions, agitation, aggressive behaviour, disinhibition, anxiety, apathy, and sleep disturbances.[107]

Early intervention is important since psychiatric symptoms can respond to treatment more readily than cognitive and functional deficits.[107] Table 6.11.5 shows the behavioural clusters manifested in AD and relevant classes of medications for intervention. [107]

Table 6.11.5: Behavioural Clusters Matched with Potentially Relevant Classes of Medications.

Behaviour	Agent
Agitation/aggression	Antipsychotics,anticonvulsants, antidepressants, anxiolytics
Anxiety	Antidepressants, anxiolytics, anticonvulsants
Apathy	Antidepressants, stimulants
Disturbed effect/mood	Antidepressants, anticonvulsants
Altered ideation/perception	Antispsychotics
Vegetative features	Antidepressants, anxiolytics, stimulants

Source: American Psychiatric Association. Practice guidelines for the Treatment of Alzheimer Disease and Other Dementias of Late Life.

- There is sufficient evidence from randomized controlled trials to support the use of both traditional and atypical antipsychotics for the management of agitation and psychosis in dementia. Of the two classes atypical antipsychotics appear to be better tolerated compared to traditional antipsychotics.[107]
- There is evidence that SSRIs (selective serotonin reuptake inhibitors) antidepressants may be administered and are better tolerated than other antidepressants.

The American Academy of Neurology practice guidelines conducted an in-depth review of pharmacological therapies for non-cognitive symptoms in dementia. The expert panel conclude that most studies in this area focus on mixed populations with dementia. Therefore, it is not entirely possible to assess the efficacy of specific medications for patients with specific form of dementias such as AD.

4. Major Problem and Challenges for Disease Control: Why Does the Disease Burden Persist?

While a cure is desirable, the likely first step may be an intervention that reduces the risk of future disease, similar to the approach to cardiovascular disease. Clinicians and caregivers are challenged with caring for an increasing aging population affected by dementia. Increased life expectancy has seen a rise in chronic medical disease and associated illnesses, including dementia. For example, there will be an estimated 400% increase in population of North Americans aged 85 and older by 2050, 40% of whom will develop dementia. Clinicians providing care for patients with dementia are confronted with numerous challenges in managing AD and other dementias. Psychiatric and behavioural problems are present in up to 90% of patients with dementia.[13]

Behavioral issues tends to wax and wane, peaking during the middle stages of AD. Aggression, is significant predictor of nursing home admission in the USA. Some of these treatment options include employing unique social and environmental interventions; knowledge and use of increasingly sophisticated medications, and providing individualized therapy to patients, working with care givers or varying systems providing care. The burden for the general practitioner is the lack of specific medicines for AD and other dementias - the physician has a limited range of therapeutic options. Management of dementia is also complex since it requires differentiating and managing various changing neuropsychiatric and behavioural problems. A balance also has to be reached between aggressive intervention and palliative care continued treatment versus withdrawal of medicines, and patient benefit versus caregiver burden. Managing dementia is complex and presents a major public health concern for the today and the future.

4.1 Country preparedness for dementia

From the WHO dementia Report 5:
The challenges to governments to respond to the growing numbers of people with dementia are substantial. A broad public health approach is needed to improve the care and quality of life of people with dementia and family caregivers. The aims and objectives of the approach should either be articulated in a stand-alone dementia policy or plan or be integrated into existing health, mental health or old-age policies and plans. Some high-income countries have launched policies, plans, strategies or frameworks to respond to the impact of dementia.

There are several key issues that are common to many national dementia policies and plans, and these may be necessary to ensure that needs are addressed in an effective and sustainable manner. These include: scoping the problem; involving all the relevant stakeholders, including civil society groups; identifying priority areas for action; implementing the policy and plan; committing resources; having intersectoral collaboration; developing a time frame and monitoring and evaluation.

The priority areas of action that need to be addressed within the policy and plan include raising awareness, timely diagnosis, commitment to good quality continuing care and services, caregiver support, workforce training, prevention and research.

People with dementia and their families face significant financial impact from the cost of providing health and social care and from reduction or loss of income. Universal social support through pensions and insurance schemes could provide protection to this vulnerable group.

Formal recognition of the rights of people with dementia and their caregivers through legislation and regulatory processes will help reduce discriminatory practices. Fundamental to upholding a person's rights is the recognition of capacity in persons with dementia. Where capacity is impaired due to dementia, legal provisions should recognize and protect the right to appropriate autonomy and self-determination including substitute or supported decision-making and procedures for implementing advance directives. Education and support relating to ethical decision-making and human rights should be an essential part of capacity-building for all involved in providing dementia care, including policy-makers, professionals and families.

4.2 Health and social systems development

The health and social care needs of the large and rapidly growing numbers of frail dependent older persons should be a matter of great concern for policy-makers in all countries. This is particularly so for LMIC which will experience the greatest increase in ageing in the coming decades.

This challenges governments to develop and improve services for people with dementia, focusing on earlier diagnosis, provision of support in the community, and a responsive health and social care sector. Integrated and coordinated health and social pathways and services will be needed to cater for the changing needs of people with dementia and their caregivers. Such pathways should ensure that the needs of specific or minority population groups are taken into account.

Improved community support will assist families to provide care for longer and to delay or reduce reliance on high-cost residential care. Where resources are finite, especially in LMIC, a focus on community outreach could be an efficient use of scarce resources to improve the quality of life of people with dementia and their caregivers. The effectiveness of task shifting (with appropriate guidelines and training) in LMIC should be further evaluated as a solution to the under-supply of a professional workforce.

Capacity-building of the workforce is essential to improve knowledge and awareness of the benefits of a coordinated response to care. Dementia care, long-term care and chronic disease management incorporating a multidisciplinary team should form part of professional education and should be supported by the development of appropriate practice guidelines. The effectiveness of task shifting (with appropriate guidelines and training) in LMIC should be further evaluated as a solution to the under-supply of a professional workforce. In a world with an increasingly mobile population, the migrant workforce brings its own set of challenges that need to be understood and addressed.

4.3 Support for informal care and caregivers

Dementia has an immense impact on the lives of the family, and particularly the person who takes the primary role in providing care. Most care is provided by family and other informal support systems in the community and most caregivers are women. However, changing population demographics may reduce the availability of informal caregivers in the future.

The provision of care to a person with dementia can result in significant strain for those who provide most of that care. The stressors are physical, emotional and economic. A range of programmes and

services have been developed in high-income countries to assist family carers and to reduce strain. The beneficial effects of caregiver interventions in decreasing the institutionalization of the care recipient have been clearly demonstrated.

Evidence from LMIC also suggests that home-based support for caregivers of persons with dementia, emphasizing the use of locally-available low-cost human resources, is feasible, acceptable and leads to significant improvements in caregiver mental health and in the burden of caring. Despite evidence of effectiveness, there have been no successful examples of scale-up in any of the health systems in which the evaluative research has been conducted. Further research should focus on implementation in order to inform the process of scale-up.

Despite the availability of services in some countries or parts of countries, there are barriers to uptake. Lack of understanding of services, lack of understanding or stigma attached to the syndrome, previous poor experience with services, and cultural, language and financial barriers creates obstacles to service utilization. Information and education campaigns for the public - including people with dementia, their caregivers and families – can improve service utilization by raising awareness, improving understanding and decreasing stigmatizing attitudes.

Support is needed to enable informal caregivers to be able to continue in their role for as long as possible. Support includes information to aid understanding, skills to assist in caring, respite to enable engagement in other activities, and financial support.

4.4 Awareness-raising and advocacy

Despite the growing impact globally, a lack of understanding of dementia contributes to fears and to stigmatization. For those who are living with dementia (both the person and their family), the stigma contributes to social isolation and to delays in seeking diagnosis and help. There is an urgent need to improve the awareness and understanding of dementia across all levels of society as a step towards improving the quality of life of people with dementia and their caregivers. Governments have a role to play in resourcing public awareness campaigns and in ensuring that key stakeholders are involved in such campaigns. Awareness-raising campaigns should be relevant to the context and audience. They should be accurate, effective and informative and should be developed in consultation with people with dementia, their families and other stakeholders, including civil society.

4.5 The way forward

The findings of this report demonstrate that dementia is a global public health challenge. A range of actions is required to improve care and services for people with dementia and their caregivers. These actions include advocacy and awareness-raising, developing and implementing dementia policies and plans, health system strengthening, capacity-building, supporting caregivers and research. The actions need to be context-specific and culturally relevant.

5. Current Pharmaceutical Product "Pipeline" for AD Treatment

Currently there are numerous medicines under investigation in the pharmaceutical pipeline using different approaches than the currently approved medicines. According experts from industry more than 100 compounds are in development. On Alzheimer disease these proposed therapies target a variety of proteins such as circulating Aβ protein, Aβ plaques, protein tau, P-tau. More detailed information on clinical trials can be obtained on the Evaluation of Medicinal Products (EMEA) and the US Food and Drug Administration (FDA) websites. Table 6.11.6 mentions some of the new compounds currently under development for Alzheimer disease.

Table 6.11.6: New Medicines in Development for Alzheimer disease

Drug name	Indication	Company	Development Status
ABT-126 acetylcholinesterase inhibitors	Alzheimer disease	Abbott	Phase 2
ABT-126	Alzheimer disease	Abbott	Phase 2
LY2886721	Alzheimer disease	Eli Lilly and Company	Phase 1
AZD3480	Alzheimer disease	Targacept Inc.	Phase 2
AVP-923 (dextromethorphan/quinidine)	Alzheimer disease, mild cognitive impairment	Avanir Pharmaceuticals	Phase 2
MABT5102A	Alzheimer disease	Genentech	Phase 2
AZD5213	Alzheimer disease	AstraZeneca	Phase 2
gantenerumab	Alzheimer disease	Hoffmann-La Roche	Phase 3
AAB-003 (PF-05236812)	Alzheimer disease	Pfizer	Phase 1
BMS-241027	Alzheimer disease	Bristol-Myers Squibb	Phase 1
MABT5102A	Alzheimer disease	Genentech	Phase 2
BIIB037	Alzheimer disease prodromal or mild AD	Biogen Idec	Phase 1
GSK2647544	Alzheimer disease,	GlaxoSmithKline	Phase 1

Sources: Evaluation of Medicinal Products (EMEA) http://www.ema.europa.eu/ema/ [108] and the US Food and Drug Administration (FDA) http://www.fda.gov/ [109]

6. Past/Current Research into New Therapeutic for AD

There are a lot of clinical trials going on at present, research into possible interventions is moving fast. This section provides some information on some of the areas of ongoing research for AD. The past five years has seen a growth in the number of drugs being developed for AD. Future compounds under research are aimed at delaying progression of the illness.[110]

6.1 Immunotherapy

The exact mechanisms leading to Alzheimer disease (AD) are largely unknown which limits possible sources of target for effective immunization. During the last decade, much efforts have been done from pharma industries on targeting clearance of Aβ from the brain of AD patients via the administration of Aβ antigens (active vaccination) or anti-Aβ antibodies (passive vaccination).[111]

Active immunotherapy

Based on promising results from animal models, the first phase I human clinical trial using active vaccine with multiple doses of Aβ42 in adjuvant (AN1792 and QS-21) was performed on 80 patients with mild to moderate dementia. A significant percentage of patients developed antibodies to Aβ, although at different titers, and no adverse events were reported.[112]

Following the success of this trial, a phase II trial was designed and performed in 2001 with a cohort of 372 patients to evaluate vaccine efficacy. This trial was stopped after the report of serious adverse events from 18/298 patients (6%), who developed meningoencephalitis.[112] Although the trial was stopped prematurely, results from post mortem biopsies of AD patients enrolled in the trial showed promising results. Indeed, there was a marked reduction in Aβ deposition in some patients, as well as significant reduction of plaques deposition in different cortical regions. Residual plaques showed a particular appearance suggesting phagocytosis from microglia.[113] Long term follow-up of immunized patients showed no signs of cognitive improvement or survival although Aβ42 immunization titers lasted for years in several immunized patients.[114] They also showed greater reductions in brain volume which has never been explained.

Passive immunotherapy

Passive immunization has also been investigated ultimately, in two major clinical trials. [72, 73] The first two trials were performed in individuals with mild to moderate Alzheimer dementia. In this large phase III trial, patients were administered intravenously a humanized recombinant Aβ monoclonal antibody directed against the N terminus of Aβ (AAB-001 or Bapineuzumab).[115]

The AAB-001 antibody is a humanized version of mouse monoclonal antibody m3D6 directed against the first 8 amino acids at the N-terminus of Aβ that has been shown to be able to decrease amyloid plaques in mouse models of AD.[116]

The clinical results with bapineuzumab were equivocal in terms of cognitive benefit. The occurrence of ARIA-E (amyloid-related imaging abnormalities)-effusion or edema after bapineuzumab, and more rarely ARIA-H (hemosiderin deposits), which may not actually be hemorrhages (especially in *ApoE* ε4 carriers), has raised concerns on the safety of these antibodies directed against the N-terminus of the Aβ peptide. The North American studies 301 and 302 completed as planned; the two complementary studies in Europe were early terminated in August 2012.[115]

One possible explanation for the ARIA-E or ARIA-H induced by bapineuzumab is that it targets the non.soluble forms of the Aβ protein. Other trials, targeting the midregion of the Aβ◎ peptide have been performed sequentially. Solanezumab, a humanized anti-Aβ monoclonal antibody directed against the midregion of the Aβ peptide, was shown to neutralize soluble Aβ species, prone to be toxic. Solanezumab Phase II study showed a good safety profile as well as indications of a possible clearance of the Aβ peptides in brain of AD patients. Antibody administration was well tolerated with doses up to 400 mg weekly.

These promising results gave rise to two Phase III trials on AD patients with solanezumab.[117] This study, led by Eli Lilly & Co.'s recently provided its results. Although it missed its primary outcome, the trials showed some signs of slowing cognitive decline perhaps more evident in milder subjects. Statistics found a 34% less mental decline in mild Alzheimer patients compared to those on a placebo treatment for 18 months according the Eli Lilly & Co.'s analyses.[71] According experts in the field, the results are not as clear as stated by Eli Lilly & Co.'s in particular results on the cognitive endpoints.

Further studies need to be performed. Researchers and medical doctors have suggested that treatment must be given earlier on, at the prodromal stage, or even earlier.

A clinical trial, targeting healthy asymptomatic individuals with a genetic mutation leading to early onset (generally aged less than 50 years) AD dementia is now being launched by Genentech & Co.'s.[72] Subjects will be injected with crenezumab, a humanized Aβ◎ monoclonal antibody. The study will involve about 300 participants from Colombia and the United States. The participants come from the same family in Medellin and can be traced. They all share a rare genetic dominant mutation that typically triggers Alzheimer symptoms around the age of 45. This trial is unique and has great expectations from the scientific and medical communities as it will help determine if the amyloid hypothesis is correct. Results are expected by 2015.[118] The generalizability of the results of this particular study for sporadic or late onset cases of Alzheimer disease will have to be investigated further.

6.2 Drugs for Disease Modification and Disease Prevention

6.2.1 Drugs for Disease Modification

Therapies targeting tau protein. Clinical trials of medicines targeting tau protein are in their initial phases. By targeting tau, the medicine aims to stabilize microtubules, which help support and transport of essential nutrients and information between cells. When tau malfunctions, microtubules break and tau accumulates into tangles. The medicine, identified through Penn's Center for Neurodegenerative Disease Research (CNDR) Drug Discovery Program, was previously shown to prevent further neurological damage and improve cognitive performance in animal models. Bristol-Myers Squibb, who developed and owns

the rights to the drug, has started enrolling patients into a phase I clinical trial in people with mild Alzheimer disease.

Secretase inhibitors. One of the features of AD pathophysiology is the accumulation of senile plaques at the end of degenerating brain neurons. β amyloid, a major constituent of these plaques, is toxic to neurons in vitro and is considered to be responsible for the neuronal cell loss in AD. β and γ secretases are the two enzymes critically responsible for forming β amyloid. This discovery has prompted new therapies directed at blocking these enzymes, thus preventing or slowing the progression of the disease. Result of significant clinical trial data demonstrated that the use of secretase inhibitors is non-specific, worsens cognitive decline and is associated with serious safety issues.

Metal chelation. As mentioned above, brain damage in Alzheimer disease is caused by β amyloid, but metal ions, such as zinc and copper, both of which accumulate in the brain with old age, are also neurotoxic. Research has shown that these metals cause β amyloid aggregation, and the mixture of the two (i.e. β amyloid and metal ions) results in the production of hydrogen peroxide, which in turn causes oxidative damage. Clioquinol, an antibiotic, which acts as a chelating agent, facilitates the removal of metal ions, and has the potential to slow progression of AD and modify disease pathology.[40]

Neurotransmitter targets. Cholinesterase inhibitors, are currently the only widely approved class for the treatment of AD and other dementias (See *Role of Acetylcholinesterase inhibitors and antidepressants in people with dementia).*[119] This therapeutic class inhibits the enzyme acetylcholinesterase, which breaks down acetylcholine in the synaptic cleft and therefore they increase acetylcholine levels in the brain. These drugs, do not attack the underlying disease pathology, instead they compensate for the loss of neurons that communicate via this enzyme. Cholinesterase inhibitors appear to slow down cognitive decline, however the improvements are very modest. Memantine, which works to inhibit the action of neurotransmitter glutamate, has been launched in the US and some European countries.

6.2.2 Drugs for Prevention and Disease Modification

AD is an insidious disease; sometime years go by before symptoms become noticeable. Disease prevention, therefore may be beneficial, and may decrease the prevalence of AD. Studies assessing prevention are underway.

- *NSAIDS:* One such prevention study is evaluating the use of NSAIDS (non steroidal anti-inflammatory drugs) on AD. Preliminary results were promising, however AD researchers are reluctant to recommend NSAIDS given the toxicities (gastrointestinal ulcers, renal toxicity, hypertension) associated with taking these medicines.

- *Antioxidants*. Pathological data indicates that oxidative stress and the accumulation of free radicals results in neuronal damage in AD. There are several studies evaluating the effects of antioxidative compounds on AD. Vitamin E and selegeline appear to delay progression. Research continues on the use of antioxidative vitamins and large studies in the USA are underway to clarify the role of vitamin E in AD prevention.[120] A number of studies have evaluated selegeline for the treatment of AD. Most of these studies show some improvement in cognition, however there is very little evidence to support global improvements in cognition, functional ability and behavior. In a metanalysis of 15

selegiline trials, authors concluded that there was insufficient evidence to recommend its use for AD. A cochrane review of selegeline for AD concluded that there may be some benefit in cognition and its use may be promising. However, at present there is insufficient evidence to recommend its use in practice.[120]

- *Hormones.* The attention and potential uses of hormone replacement therapy to treat AD is derived from epidemiological, clinical, and neuropathological observations and are still ongoing. Women are at a higher risk of developing AD than men since women are estrogen deficient post menopause whereas men benefit from estrogen as testosterone undergoes aromatization to estradiol. Estrogen is considered to have numerous beneficial properties some of which were thought to be antioxidant and anti-inflammatory properties, interactions with neurotransmitters such as acetylcholine and its ability to alter apolipoprotein which could lower the risk of developing AD. Unfortunately, no studies to date have demonstrated a positive impact on improving the biological course of AD. Studies are still ongoing and need to assess the type of HRT administered, timing of HRT in AD, effect of HRT with cholinergics. Currently, there is insufficient evidence for HRT in AD management.[121] The largest study to date, Women's Health Initiative Memory Study did not demonstrate any benefit of HRT on AD, and actually had a slightly increased risk among those actively treated.

- *Other Agents*. Various other pharmacological agents to treat AD are being studied. *Gingko biloba*, a plant extract that contains numerous pharmacological properties, some of which are thought to be antioxidative, anti-inflammatory or neurotransmitter modulators. Current research suggests that the use of gingko biloba provides smaller effects that that of cholinergics. Also, it is currently unknown which of the active components of this alternative compound contributes to cognitive enhancing effects. Furthermore, the compound is a non-regulated supplement in several countries and standardized preparations are not available.[122]

6.3 Biomarkers

A Biomarker is a biological signature that can be used as an indicator of a pathological situation. According to the 1998 Consensus Report of the Working Group on Molecular and Biochemical Markers of Alzheimer Disease, ideal biomarkers for AD should be: 1) reflective or indicative of AD pathology; 2) reliable; 3) easy to perform/analyze; and 4) relatively inexpensive.

Biomarker may have different roles, which have different standards. One is a surrogate for the disease, which demands nearly perfect sensitivity and specificity. The other is a supporting measure in the diagnosis, which again, requires a fairly high sensitivity and specificity. Another is as risk factor for future event, cardiovascular disease has many examples, such as the ratio of LDL to HDL, while not deterministic of a MI, predictive and used to intervene, at least to lower one marker (LDL), while there are essentially no effective pharmacological therapies that substantially raise HDL. (Sensitivity & specific require a standard on which to validate, which is another problem in AD).

There is currently a lack of specific and non-invasive biomarkers for Alzheimer disease. Still, as of 2013 a definite diagnostic is only possible after death of the patient with brain histopathology.

AD is a challenging disease for the development of biomarkers because a clinical diagnosis has substantial misclassification and a standard does not exist.

Identification of AD specific biomarkers is complicated because it can take 10 to 20 years between disease onset and symptomatic stage, difficulty of accurate clinical diagnostic, and complex genetic polymorphism. Identification of specific biomarkers for AD will have a considerable impact in the understanding of the disease itself. New biomarkers will allow the identification of individuals at risks and help in characterizing subpopulations for disease onset, progression and outcome. These specific markers could potentially facilitate the development of personalized treatments for each stage of the disease. Again most promising expectations of these new biomarkers would be to target molecules that researchers will use to develop medicines vaccines for individuals at risks. Biomarkers are also important monitoring tools for high throughput screening of candidate molecules such as active compounds, antibodies or genes which can modulate a particular biomolecular pathway involved in Alzheimer disease. However, recent data suggest extremely limited utility of biomarkers for Go/NoGo decisions in early stages of clinical development as there are still have no evidence linking them to clinical outcome.

6.3.1 Imaging and radiological markers

Magnetic resonance imaging (MRI) and computer aided tomography (CAT) scans can be used to visualize brain structure and help in AD diagnostic. In AD patients, a considerable reduction of hippocampus region, involved in memory processes, is observed. This anatomical measurement is useful in predicting the transition from normal to MCI and from MCI to AD.[123] However, there are concerns that this approach may lack the specificity needed to clearly diagnose AD. While some individuals have hippocampal atrophy without substantial AD pathology, one of the challenges to volumetric measures, particularly sub-regions, is the accuracy, i.e. variability around the measure.

Brain metabolism is another important neurological parameter measured in AD diagnostic. As a result of brain atrophy and neuronal loss, patients in early stages of AD demonstrate reduced levels of brain metabolism.[124] Functional magnetic resonance imaging (fMRI) and PET scans with flurodeoxy glucose (FDGPET) as secondary measures of metabolic activity in various parts of the brain are key markers of brain metabolism.[125, 126] (fMRI) measures changes in oxygen concentrations related to regional cortical blood flow, while FDGPET measures glucose metabolism in neuronal populations.

Development of positron emission tomography (PET) imaging and compounds such as 11C labeled Pittsburgh compound B (11C-PIB) ligand has revolutionized imaging in dementia and opened new avenues for advanced diagnostic tools in AD. 11C-PIB binds with high affinity and high specificity to neuritic Aβ plaques.[127]

Studies from Klunk et al. have shown that 11C-PIB binds in several brain regions in cases of AD, with a significant 1.5–2 fold increase of 11C-PIB binding compared to controls.[128] Other studies have suggested that 11C-PIB load is indicative of disease progression in the next 2

years.[129,130] Since amyloid is known to start accumulating several years before clinical signs of disease, imaging techniques may allow detection at the prodromal stage of AD. There are numerous technical issues and challenges to measuring brain amyloid: 1) limit of detection, 2) not possible to distinguish vascular deposition from cerebral deposition, 3) the measure is continuous but often treated as a binary, positive or negative, 4) the amyloid burden is reported relative to a reference region, the cerebellum.

Further research that will identify new imaging markers and tracers will definitely help making a more accurate diagnostic for AD and monitor therapeutic effects. These imaging techniques remain extremely costly and therefore cannot be used in routine in all countries to monitor disease progression. Moreover as has happened in other areas of imaging and diagnostics modified and cheaper could potentially be developed and may be worth researching.

6.3.2 Biomarkers in cerebrospinal fluid

Cerebrospinal fluid (CSF) is a fluid surrounding the brain and the spinal cord. It is produced by the choroid plexus and serves as a protection for shocks and transport waste from the central nervous system. Because AD is a neurodegenerative disease, cerebrospinal fluid (CSF) has evolved as prime target for biomarker investigation. Samples of CSF can be obtained after lumbar puncture, which is invasive and potentially painful and stressful for elderly patients.

Several biomarkers in CSF have been identified so far for AD disorders such as such as decreased Aβ42, increased total tau (T-tau), and increased phosphorylated tau (P-tau).

The identification and characterization of amyloid-β (Aβ) and tau as the main pathological components of Alzheimer disease (AD) has driven many efforts in search for suitable biomarkers for AD. While these two proteins represent the two key pathological mediators of disease, other aspects of this multifaceted disease such as oxidative stress, calcium-mediated toxicity, and neuroinflammation are being unraveled, giving rise to possible new biomarkers for diagnostic or disease progression.[131, 132, 133] As with amyloid imaging, measuring Aβ in the CSF has technical challenges, as to what is being measure, total versus free Aβ.

There are different assays that provide different results, which while correlated, are not directly interpretable. Also, the techniques and materials are a particular issue. The key issue is that a clinical standard has yet to be developed, which make comparison of results across studies a challenge. Also, the ability to identify what is an optimal cutpoint is a challenge given the variation in assays and assay results.

CSF markers and conversion from MCI to AD

Combinations of P-tau and Aβ42 protein levels in CSF were successful in discriminating AD patients from normal cases with a sensitivity of 86% and 80% sensitivity between AD individuals and other non-AD related dementias in a study reported by Maddalena et al.[134]

Further research is needed to clarify if the ratio of Aβ 42 to P-tau can be a diagnostic criteria for AD, in particular to discriminate patients with possible AD (NINCDA-ADRDA criteria) or the more recent NIA-AA criteria.

CSF markers and conversion from normal to MCI/AD

More interestingly, while dementia patients can be identified through neuropsychological tests and clinical evaluation, a gap remains in diagnosing asymptomatic patients at risk of developing AD. Moreover, MCI is a heterogeneous category of all prodromal dementia, some of which are AD some of which are not which makes the study difficult to interpret. Many studies have focused on identifying biomarkers of the prodromal stage, before MCI/AD onset. Results from Fagan et al. show that an increased ratio of tau/Aβ42 and P-tau/Aβ42 in asymptomatic individuals is associated with an increased risk for conversion to mild cognitive impairment and very mild dementia (CDR-0.5).[135]

In the Fagan et al. study about 70% of patients with a high tau/Aβ42 ratio converted from normal to very mild dementia over a 3 year period while only 10% of those with a normal ratio converted to very mild dementia. After a five year follow-up period, less than 10% patients with MCI with a normal tau/Aβ42 ratio progressed to AD whereas more than 90% progressed to mild to moderate AD if there was a high tau/Aβ42 ratio. These promising results should be replicated in larger cohort of patients, and could possibly be used to design clinical trials for immunization or preventive treatment of individuals at high risk to convert from normal to MCI/AD. CSF markers of amyloid beta 42, P-tau or a ratio appear predictive of individuals likely to progress to frank AD dementia and may provide a mechanism to improve the diagnosis of AD or prodromal AD.[136]

CSF Markers of inflammation

As a result of amyloid plaque deposition in the brain, markers of inflammation such as cytokine IL-6, C-reactive protein, interleukin (IL)-1β, tumor necrosis factor-α, IL-6, IL-6 receptor complex, α-antichymotrypsin and transforming growth factor- β, have been described in the CSF of patients with AD although levels of these CSF components were not able to discriminate between AD patients and other non-AD demented patients.[137]

Therefore experts question if they can be viable biomarker candidates. As CSF closely reflects the composition of the brain extracellular space it remains a target of choice for identifying new biomarkers for diagnostic and disease progression.[138] However, because of its invasive collection procedure, it is not routinely used for the evaluation of AD patients.

6.3.3 Biomarkers in blood and plasma

There are many challenges to blood & plasma markers, some technical, some relate to issues of the blood-brain barrier. Blood-based biomarkers represent a considerable challenge because blood is not in direct contact with brain. Therefore brain derived proteins and metabolites that passes through the blood-brain barrier become markedly diluted into blood and plasma which are other complex mediums. Also the size of the particles may affect the rate of exchange across the blood brain barrier. There are at the moment high expectations for the search of new biomarkers for AD in blood and plasma. The advantages of using markers in blood and plasma are obvious as they can easily be collected from patients at an

affordable price and would allow large screenings to identify trial participants for early interventions and monitoring the effectiveness of new therapies.

Blood is a complex fluid, composed of proteins, lipids and metabolites as well as different cell types eg red cells, platelets and lymphocytes, which composition can fluctuate depending on internal and external environment. This makes it more challenging to target specific assay for disease but also offers a large palette of possible targets.

Search for a protein assay

Measuring proteins in blood is complex due to the wide dynamic range of proteins, isoforms, complexes as well as activities, and post-translational modifications. Despite these challenges, developments in both bioinformatics and mass spectrometry have led to substantial advances in proteomic analysis in blood and plasma. So far, using several protein identification techniques such as MALDI-qTOF and ion-trap MS, 2D electrophoresis, researchers have identified several proteins which were significantly increased in AD patients serum versus controls. These include inflammatory response mediators, such as CFH, complement components C3 and C4 and A2M.[139]

Studies performed in transgenic mice overexpressing APP and PS1 mutations also allowed identification of eight proteins to be differentially expressed in AD relative to controls in the original cohort of subjects. These include clusterin, complement component C1r, α1-antitrypsin and EGF receptor. Moreover plasma concentrations of complement-related proteins were shown to be associated with brain atrophy in AD.[140] A two- to six fold increase in oxidative damage markers such as oxidized forms of fibrinogen and α1-antitrypsin have been identified using proteomics.[141,142,143]

Recent studies using samples of AD patients have identified a panel of 18 proteins that effectively discriminate individuals with high and low brain Aβ. Among these proteins are the apolipoprotein-E (ApoE) and several proteins with established roles in Aβ clearance. These promising results may to accelerate the development of new biomarkers for AD and AD drug monitoring.

Search for mRNA and miRNA signature

Search for RNA/DNA biomarkers in blood in currently underway. The difficulty lies in the complexity single nucleotide polymorphisms, copy number variants and other 'static' variation of epigenetic changes, which may be more responsive to the internal and external environment. Isolating RNA from blood is also technically challenging but feasible. There is at present relatively little evidence of a transcript signature in blood of AD that might act as a biomarker. Exciting results on this direction are coming from research on miRNA which act as regulators of gene expression with BACE1 as a possible AD marker.[144,145] With the help of genome-wide technologies and bioinformatic approaches it is possible that research in this area will come to findings of blood based transcripts disease assay.

The latest research have clearly shown that proteins, transcripts and probably other constituents in CSF and blood, are different in people with AD. Although at present progress is being made, there are no proteins, transcripts or metabolites in blood that have been sufficiently replicated to be established as AD biomarkers. If the progress that has been made

to date is to be sustained and even accelerated, efforts should be made in facilitating design and collection of larger cohort of patient samples from different regions of the world and facilitate collaborations between academic research, clinic and pharmaceuticals.

Public–private partnerships have established large longitudinal cohorts with extensive sample collection, neuroimaging and clinical data in the USA through the Alzheimer Disease Neuroimaging Initiative (ADNI) study and in Europe through the AddNeuroMed study joined by others in Europe and ADNI-like studies in Japan, Australia and China. These collaborations are essential as they provide larger and cross validation between studies.[146]

Considerable expectations are been made in finding biomarkers in blood that would definitively ease sample collection procedures. With technical improvements of the proteome analysis, it is very likely that specific and reproducible markers will become available in the near future. Most likely, several researchers are convinced that there will not be just one single marker for AD but rather different sets of markers to predict conversion to MCI and AD disease onset. These markers are essential for the design and monitoring of effects of new AD therapies. We can also envisage that these markers could be used to help differentiate different sets of patients with distinct disease progression rates and adapt treatment in consequence. Several EU funded projects are currently being developed to identify such markers. One example is PredictAD, a project partially funded under the seventh Framework Programme by the European Commission. This project aims at developing a standardised and objective approach to diagnose AD. [147] PredictAD is composed of a consortium of of top-level European research from VTT Technical Research Centre of Finland, GE Healthcare (UK), Nexstim Ltd. (Finland), University of Kuopio (Finland), Imperial College of London (UK), Karolinska Institutet (Sweden), University of Milan (Italy) and Copenhagen University Hospital, Rigshospitalet (Denmark).

The European Union is also involved to find new therapies for neurodegenerative diseases and enable early diagnosis for early targeted treatment. In this regard, a EU Joint Programmes - Neurodegenerative Disease Research (JPND) initiative, led by Philippe Amouyel, is working actively to promote translational and collaborative research for AD.[148] Funding calls for Centres of Excellence in Neurodegeneration (COEN) and harmonisation of the use of biomarkers were initiated under the umbrella of JPND.

Pharmacog for "Prediction of cognitive properties of new drug candidates for neurodegenerative diseases in early clinical development" is a partnership of 32 academic and industry actors from seven countries, coordinated by GlaxoSmithKline R&D and the Université de la Méditerranée. Pharmacog started its activities on January 1, 2010 thanks to significant funding (EUR 20.2 million) from the Innovative Medicines Initiative. This ambitious European project aims at providing the tools needed to define more precisely the potential of a drug candidate, reduce the development time of new medicines and thus accelerate the approvals of promising new medicines.[149]

7. Opportunities for Research into New Pharmaceutical Interventions

A great deal more is known about AD and other dementias than in 2004, but new found knowledge and new drugs currently being studied also pose new questions. The following sections describe some opportunities of research for AD.

Cholinergic therapies only bring about a temporary relief in AD symptoms, and it is not possible to predict who will respond. It is also unclear whether patients who do not respond to one anticholinesterase inhibitor will respond to another. Systematic clinical research is needed to answer these clinical questions. Furthermore, ways of measuring, determining response, and assessing when medications need to be stopped remain unclear and need to be addressed.

There may also be a need for more comparative clinical trials of these agents to determine which agent offers the greatest benefit and causes least resistance. The effective and appropriate administration of cholinergic and other medicines requires good baseline assessment with validated scales for objective measurement. Further work is required and practice guidelines are needed to assist clinicians in effectively diagnosing patients suspected with AD. There is also a need for better scales for the non-cognitive symptoms.

Cholinesterase inhibitors such as donepezil are licensed for use in mild to severe AD in the USA at present. More comparative trials evaluating multiple cholinergic medicines, as well as combination therapy with different classes for drugs, also remains unanswered and well-designed RCTs, with clear indications for appropriate doses for various stages of AD are needed.

AD is a complex disease overlaid with neuro-psychotic and behavioural symptoms, and management rarely responds to medicines alone. Important factors other than cognitive functions and activities of daily living need to be studied. Behavioural modification and education combined with drug therapies as well as caregiver's interventions require systematic clinical research with outcome variables related. These data are extremely difficult to capture as Alzheimer disease is also prone to external environmental and social factors.

Gaps Between Current Research and Potential Research Issues that Could Make a Difference

A review of currently available treatments suggests a number of areas for further study. Some of these recommendations are within the realm of improved evaluation and assessment.

- Improved detection and evaluation of Alzheimer disease, especially in the prodromal and early stages, when treatment that slows progression would be more likely to be beneficial. This implies the development of a reliable diagnostic tool.
- There is a clear need for validated biomarkers for measuring and monitoring disease progression – the lack of these means that trials of disease modifying therapies will not move ahead as rapidly as possible. The use of surrogate endpoints e.g. imaging also needs more investigation. Expert say what is needed is to characterize the relationship

between specific measure of cognitive function (such as episodic memory) and biomarkers to improve our understanding the progression of early cognitive of the AD type and how this predicts progression to a formal diagnosis of AD. To understand the relationship and timing of the various measures of pathology (CSF amyloid beta, tau, P-tau, amyloid burden), perhaps volume/atrophy, cognition and function. There are many hypotheses but limited data.

- Work on standardization of the current biomarkers into the research criteria for a diagnosis of either early disease or advanced AD dementia is necessary.
- Development of consensus on clinically meaningful outcome measures and further characterization of the cognitive measures for early cognitive impairment.
- Within the field of pharmacologic therapy, there is a critical need for medicines with greater ability to improve cognition or at least slow the progression of dementia. Despite the progression in the areas mentioned above, research and development needs to further identify and test new cognition-enhancing medicines based on the pathophysiology and information learned about the disease from neuroscience and molecular genetics. For example, pharmacologic agents that prevent or slow amyloid deposition or remove precipitated amyloid might serve to slow down disease progression.
- Other research directions that could affect management of AD, is the optimal pharmacologic treatment of non-cognitive symptoms, including psychosis, agitation, depressions and sleep disturbances. Many current recommendations are based on small-uncontrolled studies or agents no longer in common use and/or at doses well above those used in current practice. There is, therefore, a critical need for randomized controlled studies and guidelines on up-to-date treatments for non-cognitive symptoms present in AD.
- Clinical questions that need to be further evaluated and studied include what to treat? There is a problem surrounding the terminology, and diagnosis associated with dementia and AD. Confusion remains about when to initiate treatment; how to treat i.e. which agents to start, how to switch drugs in the case of decreased efficacy, intolerance, adverse effects or drug interactions and how long to treat AD.
- In addition to symptomatic or palliative options, increased knowledge of the anatomical, cellular and molecular basis of AD, together with the identification of new drug targets, which may prevent, slow or delay its onset are needed. These possibilities may be expedited by the further progress in research and development of improved animal models; introduction of more efficient and effective clinical trials, and the use of non-invasive imaging to monitor the progression of the disease. Combination therapies may to offer maximum benefit in longer term disease modification but their use would need to be evaluated particularly in regard to safety.

8. Barriers to Closing the Alzheimer Pharmaceutical Gap

- *Access to human tissue* and developing a large biobank that could allow the finding of novel pathways for Alzheimer disease from genetics to gene expression and methylation
- *Lack of validated targets.* AD requires a clinical diagnosis, and at present, there are no reliable tests to confirm a diagnosis. Definitive diagnosis can only be made postmortem from brain tissue. Despite years of research, there is still an unclear understanding on the pathogenesis of AD. **Further research is still needed at the basic neuroscientific level**. Companies are already investing large amounts of money in AD, but the high risk and cost coupled with long clinical trials in disease modification, mean that at most a company could only take one or two approaches forward in disease modification trials at present. The problem is the high risk and the lack of markers to increase confidence in moving from Phase II to large Phase III trials.
- *Lack of animal models.* There are no good animal models that reflect the disease state. Those models that do exist model only aspects of pathology e.g. amyloid over-expression. Equally as important is the issue of access to animal models and the need to couple to functional endpoints such as for behaviour, neuroimaging, electrophysiology. Current animal models are not readily accessible for research and drug screening at the preclinical level because of intellectual property and licensing issues. Many of these models belong to academia (not industry) and institutes and the costs of the models are prohibitive to academic scientists and small biotech companies. Public Private Partnerships such as Pharmacog, a partnership of 32 academic and industry actors from 7 countries exist and aim at reducing the development time of new medicines and thus accelerate the approvals of promising new medicines.
- *Barriers in the design and implementation of clinical trials*. Experts from industry say "*Adaptive clinical designs, along with 'adaptive development programs' use the concept of adaptive clinical trial design and apply that to program development. Using both will result in reaching the goal, earlier and with less resources, overall, although the upfront cost is higher than the 'traditional' approach."* Clinical trials are needed to determine the efficacy and safety of AD medicines. In an effort to control AD at the early stages, clinical studies are evaluating the effectiveness of therapies at mild cognitive impairment (MCI) stages, which is considered the prodromal stage to AD. Guideline's for MCI studies have not been established. Another area that requires further work is the design and outcomes measures to slow down AD progression. Scientific evidence has determined that neuropathology processes resulting in AD occurs several years prior to the onset of AD symptoms. However, conducting long-term clinical studies to monitor a patient's progression or decline in function is costly and requires substantial resources. Morever the earlier a patient moves into disease course the less exact the diagnosis is going to be. As well, the more patients are included in a clinical trial, the larger the study is, the more it costs, the harder it is to detect a change of parameter and the higher risk of safety issues will occur.
- *Lack of biomarkers for therapeutic endpoints* remains a major barrier in the clinical development of efficacious AD drugs. The availability of such markers would benefit and hasten AD drug development. Any reliable predictor of clinical outcome will accelerate the development of effective AD medicines. Much work in this area is already ongoing, however continued efforts are still required. Commonly accepted markers in cerebrospinal fluid (CSF) or blood such as alpha -amyloid and tau are still not adequately validated and may not be sensitive for longitudinal progression and treatment effects on

AD. Additionally, neuroimaging markers, as determined by MRI are reasonably validated and sensitive for use in long-term trials but are not suitable for short-term duration, proof-of-concept trials. Recent evidence suggests the CSF biomarkers may also not change much over a short timeframe. There is also a need to develop an infrastructure to speed up validation studies, such as large-scale biologic sample collection from ongoing aging populations. The availability and development of specific imaging technology such as positron emission tomography (PET) is also needed to determine whether changes in the brain or its function can be identified before the person develops symptoms of the disease.

- *Barriers in academia.* Academic drug discovery and development programs are usually underfunded and lack infrastructure, in terms of staff and equipment especially at the preclinical level. Furthermore, the lack of communication, interaction and collaboration between necessary research groups can limit drug discovery and research. Today, science and medicine requires an interdisciplinary approach to solving medical conditions. Several partnerships of public-private partnerships (PPP) launched by EU and have been discussed previously.
- *Barriers in biotechnology.* AD drug discovery and development is considered high risk and attracting capital for early high-risk projects is very difficult, especially when the return on investment is questionable or long-term. The cost of conducting clinical trials is also another major barrier to small companies: risks are high and the probabilities of scientific success low. Therefore, external funding is important. Experts from industry say risk sharing plays an important role as well (discussed in chapter 8.4). EUROPA, the European commission group to improve innovation proposes that a small business innovation research programme (SBIR) mechanism like that employed in public funding in the USA, be introduced into the FP7-through integrated projects.[150] This programme will speed up the creation of new companies and provide capital for small-to-medium sized enterprises. In the United States, SBIR mechanisms amounts to 1.3 billion US dollars.[14]
- *Regulatory barriers.* Another barrier that affects both the pharmaceutical and biotech industry is the lack of international harmonization of clinical trials and regulatory requirements. Designing trials that meet individual requirements is costly and timely. A further barrier to drug development is the definition of therapeutic effectiveness of AD medicines. The FDA requires that medicines show superiority to placebo on a performance-based test and a measure of global clinical function. Outcome measures are still nonspecific and need to be established by the medical community. Other outcome efficacy measures that affect AD function are needed to guide drug development, and registration. Biotech industry is the lack of international harmonization of clinical trials and regulatory requirements. Designing trials that meet individual requirements is costly and timely. A further barrier to drug development is the definition of therapeutic effectiveness of AD medicines. The FDA and EMEA require that medicines show superiority to placebo on a performance-based test and a measure of global clinical function. Outcome measures are still nonspecific and need to be established by the medical community. Other outcome efficacy measures that affect AD function are needed to guide drug development, novel delivery methods, and registration.

9. European Union Funding Opportunities for AD

Europe and the Seventh Framework Program for Alzheimer disease

Alzheimer disease is an important topic of the key action on "the aging population and disabilities" of the European Union's Seventh Framework Programme. The European commission recognizes the impact of AD on individuals and society and the urgent need for treatments that can prevent, arrest and reverse degeneration and death of neurons. The multidisciplinary projects launched with EU support set a prerequisite in the understanding of the fundamental molecular and cellular mechanisms of AD and the development of diagnostic tools that may identify patients at an early pre-symptomatic stage. Furthermore a consortium of 21 of the most experienced AD laboratories from Europe and beyond are to conduct our research projects integrating data from studies with tissue cultures and genetically modified animals into a clinical investigations of demented patients. A broad array of bio-technological methods is also to be used. Results of these studies will lead to diagnostic screening strategies combing genetic, pathophysiological and biomarker information.

Giving advice on research

The European Research Advisory Board is a high-level independent advisory committee, made up of 45 top experts from EU countries, which provides advice on the design and implementation of EU research policy. It focuses on realizing the European Research Area, and on using policy instruments such as the Community Research and Development Framework Programme.

10. Conclusion

In 2012, dementia was declared a public health priority by the World Health Organization (WHO). Due to the ageing of the world population the number of patients with Alzheimer disease will rise significantly. If no treatment is available, this will be a major health issue with enormous financial burdens to health care systems.

Thus, there is an urgent need for both early diagnosis with specific markers as well as effective therapies that could be taken at the different stage of the disease. Currently only short term symptomatic treatment is available. While there is research and development already in this area, much work still is required. This includes:

- basic research in the pathophysiology of the disease and its risk factors;
- noninvasive and clinically effective diagnostics tools;
- wider scale outcome efficacy measures for the disease function;
- progress and developing medicines that slow progression, halt, or prevent AD from occurring;
- Additionally, challenges for clinical services include early diagnosis, and intervening early with the most appropriate and effective medicine.

There are several barriers to closing the obvious pharmaceutical "gaps" with regard to AD. Specific recommendations include the following:

The EU and EU-based philanthropic organizations need to recognize and help overcome the various scientific and systemic barriers to improving pharmaceutical R&D for Alzheimer disease and provide funding for making animal models more accessible and affordable. Also new grant agreements should be implemented that compensate investigators and institutions while making the models more widely available. There is a need for improved AD assessment tools, with increased sensitivity and efficiency for patient evaluation for AD primary prevention. More specifically, curtailing time requirements for clinical staff, data monitoring and data entry could decrease costs for trials.

An important research goal should also be the development and evaluation of new instruments in relevant domains that are sensitive, reliable, and valid for detecting changes in normal aging and early AD and before disease onset. Furthermore, it would be helpful if these can be self-administered and not require significant professional involvement. New uses of technology, such as computerized assessments and telephonic methods are some options and may be desirable in this field.

There needs to be more collaboration and a multidisciplinary approach in the areas of research and development for AD. Grant review should be by government and industry to facilitate bench to bedside Neurobiologists, clinicians, chemists need to work together. Funding resources and guidelines that can assist scientists in preclinical drug development is required.

New funding models should be explored which can support core research facilities and non-tenured staff in academic institutions, such as the creation of endowments for facilities and pharmaceutical and biotech consortia. Innovation is needed to encourage diversity of approaches to fight AD.

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Annexes

Annex 6.11.1: Meta-analysed estimates of dementia prevalence, generated from Poisson random effects models, by Global Burden of Disease region

GBD world region	Number of studies		Sex	Age group (years)							Standardized prevalence[1], for those aged 60 years and over (%)
	Potentially eligible studies	Used in meta-analysis (age-specific, age- and sex-specific)		60–64 (%)	65–69 (%)	70–74 (%)	75–79 (%)	80–84 (%)	85–89 (%)	90+ (%)	
ASIA											
Australasia	4	3, 0	All	1.8	2.8	4.5	7.5	12.5	20.3	38.3	6.91*
Asia Pacific, High Income	22	14, 10	M	1.4	2.3	3.8	6.4	10.9	18	34.9	6.30*
			F	0.9	1.7	3.1	6.0	11.7	21.7	49.2	
			All	1.0	1.7	2.9	5.5	10.3	18.5	40.1	5.57
Asia, East	34	34, 31	M	0.8	1.3	2.2	4.0	7.3	16.7	26.4	4.98*
			F	0.9	1.6	2.9	5.3	10.0	17.9	38.7	
			All	0.7	1.2	3.1	4.0	7.4	13.3	28.7	4.19
Asia, South	8	7, 6	M	1.0	1.7	2.9	5.3	9.4	16.4	33.7	5.65*
			F	1.5	2.3	3.8	6.5	11	18.1	35.1	
			All	1.3	2.1	3.5	6.1	10.6	17.8	35.4	5.78
Asia, South-East	6	5, 2	M	1.7	2.6	4.0	6.2	9.8	15	26.4	7.63
			F	1.8	3.0	5.1	9.0	15.9	27.2	54.9	
			All	1.6	2.6	4.2	6.9	11.6	18.7	35.4	6.38*
EUROPE											
Europe,	56	52, 46	M	1.4	2.3	3.7	6.3	10.6	17.4	33.4	7.29*

Western			F	1.9	3.0	5.0	8.6	14.8	24.7	48.3	
			All	1.6	2.6	4.3	7.4	12.9	21.7	43.1	6.92
THE AMERICAS											
North America (USA only)	11	8, 6	M	1.3	2.1	3.7	6.8	12.3	21.6	45.2	6.77*
			F	1.0	1.8	3.3	6.4	12.5	23.2	52.7	
			All	1.1	1.9	3.4	6.3	11.9	21.7	47.5	6.46
Latin America	11	11, 10	M	1.0	1.9	3.7	7.0	13.0	24.3	55.0	8.50*
			F	1.0	2.0	4.2	8.4	16.4	32.5	79.5	
			All	1.3	2.4	4.5	8.4	15.4	28.6	63.9	8.48

1. Standardized for age, or for age and sex (*)

Annex 6.11.2: Estimates of dementia prevalence (%) for Global Burden of Disease regions where it was not possible to carry out a quantitative meta-analysis

GBD world region	Sources of prevalence data used to calculate regional weighted average	60–64 years (%)	65–69 years (%)	70–74 years (%)	75–79 years (%)	80–84 years (%)	85+ years (%)	Age-standardized prevalence for those aged 60 years and over (%)
ASIA								
Asia, Central	EUR B, EUR C	0.9	1.3	3.2	5.8	12.1	24.7	5.75
Oceania	WPR B	0.6	1.8	3.7	7.0	14.4	26.2	6.46
EUROPE								
Europe, Central	EUR A, EUR B	0.9	1.3	3.3	5.8	12.2	24.7	5.78
Europe, Eastern	EUR C	0.9	1.3	3.2	5.8	11.8	24.5	5.70
THE AMERICAS								
Caribbean	AMR B, AMR D, Cuba (*40,119*) , Dominican Republic (*40*)	1.3	2.6	4.9	8.5	16.0	33.2	8.12
AFRICA								
North Africa/ Middle East	EMR B, AFR D, Egypt (*106*)	1.0	1.6	3.5	6.0	12.9	23.0	5.85
Sub-Saharan Africa, Central	AFR D, AFR E	0.5	0.9	1.8	3.5	6.4	13.8	3.25
Sub-Saharan Africa, East	AFR E, AFR D, EMR D	0.6	1.2	2.3	4.3	8.2	16.3	4.00
Sub-Saharan Africa, Southern		0.5	1.0	1.9	3.8	7.0	14.9	3.51
Sub-Saharan Africa, West	Nigeria (*16*)	0.3		0.86		2.72	9.59	2.07

Note: AFR D, WHO African Region with high child and high adult mortality; AFR E, WHO African Region with high child and very high adult mortality; AMR B, WHO Region of the Americas with low child and low adult mortality; AMR D, WHO Region of the Americas with high child and high adult mortality; EMR B, WHO Eastern Mediterranean Region with low child and low adult mortality; EMR D, WHO Eastern Mediterranean Region with high child and high adult mortality; EUR A, WHO European Region with very low child and very low adult mortality; EUR B, WHO European Region with low child and low adult mortality; EUR C, WHO European Region with low child and high adult mortality; WPR, WHO Western Pacific Region with low child and low adult mortality.

Annex 6.11.3: Total population over 60, crude estimated prevalence of dementia (2010), estimated number of people with dementia (2010, 2030 and 2050) and proportionate increases (2010–2030 and 2010–2050) by Global Burden of Disease -region

GBD world region	Population over 60 years (millions, 2010)	Crude estimated prevalence (%, 2010)	Number of people with dementia (millions)			Proportionate increases (%)	
			2010	2030	2050	2010–2030	2010–2050
ASIA	406.55	3.9	15.94	33.04	60.92	107	282
Australasia	4.82	6.4	0.31	0.53	0.79	71	157
Asia Pacific	46.63	6.1	2.83	5.36	7.03	89	148
Oceania	0.49	4.0	0.02	0.04	0.10	100	400
Asia, Central	7.16	4.6	0.33	0.56	1.19	70	261
Asia, East	171.61	3.2	5.49	11.93	22.54	117	311
Asia, South	124.61	3.6	4.48	9.31	18.12	108	304
Asia, South-East	51.22	4.8	2.48	5.30	11.13	114	349
EUROPE	160.18	6.2	9.95	13.95	18.65	40	87
Europe, Western	97.27	7.2	6.98	10.03	13.44	44	93
Europe, Central	23.61	4.7	1.10	1.57	2.10	43	91
Europe, Eastern	39.30	4.8	1.87	2.36	3.10	26	66
THE AMERICAS	120.74	6.5	7.82	14.78	27.08	89	246
North America	63.67	6.9	4.38	7.13	11.01	63	151
Caribbean	5.06	6.5	0.33	0.62	1.04	88	215
Latin America, Andean	4.51	5.6	0.25	0.59	1.29	136	416
Latin America, Central	19.54	6.1	1.19	2.79	6.37	134	435
Latin America, Southern	8.74	7.0	0.61	1.08	1.83	77	200
Latin America, Tropical	19.23	5.5	1.05	2.58	5.54	146	428
AFRICA	71.07	2.6	1.86	3.92	8.74	111	370
North Africa/ Middle East	31.11	3.7	1.15	2.59	6.19	125	438
Sub-Saharan Africa, Central	3.93	1.8	0.07	0.12	0.24	71	243
Sub-Saharan Africa, East	16.03	2.3	0.36	0.69	1.38	92	283
Sub-Saharan Africa, Southern	4.66	2.1	0.10	0.17	0.20	70	100

Sub-Saharan Africa, West	15.33	1.2	0.18	0.35	0.72	94	300
WORLD	758.54	4.7	35.56	65.69	115.38	85	225

Annex 6.11.4: Estimated annual numbers of incident cases of dementia, by age group and world region and Global Burden of Disease region

GBD world region	60–64 years	65–69 years	70–74 years	75–79 years	80–84 years	85–89 years	90+ years	Total
AUSTRALASIA	5 015	6 267	8 562	11 718	15 671	15 069	11 999	74 300
Asia Pacific, High Income	44 218	60 232	90 569	130 732	156 054	135 777	111 191	728 772
Oceania	689	768	953	922	747	420	275	4 774
Asia, Central	5 426	6 445	13 850	12 735	14 683	7 189	6 031	66 359
Asia, East	163 609	191 710	251 150	289 363	249 859	152 360	74 608	1 372 660
Asia, South	119 516	151 533	182 288	189 982	155 836	90 384	43 394	932 933
Asia, South-East	47 446	61 200	75 941	80 040	64 702	34 953	13 514	377 795
ASIA	**385 919**	**478 154**	**623 312**	**715 492**	**657 552**	**436 153**	**261 012**	**3 557 595**
Europe, Central	21 552	27 947	46 233	65 949	72 545	51 032	27 739	312 995
Europe, Eastern	33 771	40 091	95 946	99 652	137 457	79 242	58 657	544 817
Europe, Western	75 483	114 043	182 382	261 542	332 145	314 136	206 964	1 486 695
EUROPE	**130 807**	**182 081**	**324 561**	**427 143**	**542 147**	**444 410**	**293 360**	**2 344 507**
North America, High Income	52 406	70 167	94 281	130 578	174 934	173 137	147 305	842 808
Caribbean	3 979	5 197	6 475	7 178	7 348	4 968	4 405	39 551
Latin America, Andean	3 776	4 764	5 908	6 462	5 804	3 624	1 210	31 548
Latin America, Central	16 610	20 338	24 059	27 602	26 361	18 371	6392	139 732
Latin America, Southern	6 399	8 654	11 164	14 077	14 829	10 133	2958	68 215
Latin America, Tropical	16 786	20 071	25 269	26 023	24 696	14 745	4 303	131 892
THE AMERICAS	**99 956**	**12 9191**	**167 156**	**211 919**	**253 972**	**224 979**	**166 572**	**1 253 746**
North Africa/Middle East	30 328	35 742	45 605	50 307	41 393	19 764	9 488	232 627
Sub-Saharan Africa, Central	4 019	5 120	5814	5 602	4 173	2 052	926	27 706
Sub-Saharan Africa, East	16 318	20 287	23 222	23 251	17 922	9 318	4 636	114 953
Sub-Saharan Africa, Southern	4 461	5 839	6 838	7 150	6 092	3 656	2 429	36 465
Sub-Saharan Africa, West	15 252	19 618	23 002	22 915	18 614	9 902	4 762	114 067

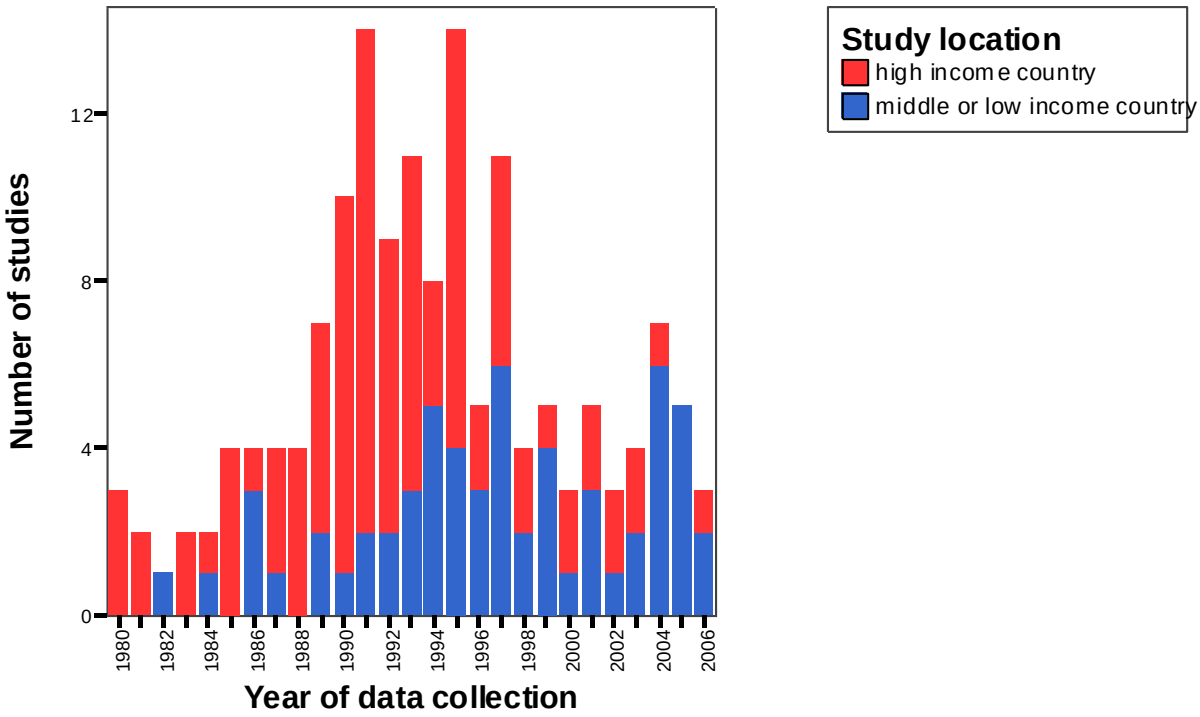
AFRICA	**70 378**	**86 606**	**104 481**	**109 225**	**88 194**	**44 692**	**22 247**	**525 818**
WORLD TOTAL	**687 060**	**876 031**	**1 219 510**	**1 463 780**	**1 541 864**	**1 150 234**	**743 185**	**7 681 665**

Annex 6.11.5: Per capita (US dollars) and aggregated costs (billions US dollars) by Global Burden of Disease region and World Bank income classification

GBD world region	Per capita costs (US$)	Number of people with dementia	Aggregated costs (US$ billion)				Total costs as % of GDP	Direct costs as % of GDP
			Informal care (all ADLs)	Direct medical costs	Direct social costs	Total costs		
Australasia	32 370	311 327	4.30	0.70	5.07	10.08	0.97%	0.56%
Asia Pacific, High Income	29 057	2 826 388	34.60	5.23	42.29	82.13	1.31%	0.76%
Oceania	6 059	16 553	0.07	0.02	0.01	0.10	0.46%	0.12%
Asia, Central	2 862	33 0125	0.43	0.28	0.24	0.94	0.36%	0.20%
Asia, East	4 078	5 494 387	15.24	4.33	2.84	22.41	0.40%	0.13%
Asia, South	903	4 475 324	2.31	1.16	0.57	4.04	0.25%	0.11%
Asia, South-East	1 601	2 482 076	1.77	1.48	0.73	3.97	0.28%	0.15%
Europe, Western	30 122	6 975 540	87.05	30.19	92.88	210.12	1.29%	0.75%
Europe, Central	12 891	1 100 759	8.59	2.67	2.94	14.19	1.10%	0.44%
Europe, Eastern	7 667	1 869 242	7.96	3.42	2.94	14.33	0.90%	0.40%
North America, High Income	48 605	4 383 057	78.76	36.83	97.45	213.04	1.30%	0.82%
Caribbean	9 092	327 825	1.50	0.78	0.71	2.98	1.06%	0.53%
Latin America, Andean	3 663	254 925	0.35	0.31	0.28	0.93	0.43%	0.27%
Latin America, Central	5 536	1 185 559	1.58	2.61	2.37	6.56	0.37%	0.28%
Latin America, Southern	8 243	61 4523	2.36	1.42	1.29	5.07	1.02%	0.54%
Latin America, Tropical	6 881	1 054 560	2.17	2.67	2.42	7.26	0.42%	0.29%
North Africa/ Middle East	3 296	1 145 633	1.90	2.05	0.54	4.50	0.16%	0.09%
Sub-Saharan Africa, Central	1 081	67 775	0.04	0.02	0.01	0.07	0.06%	0.02%
Sub-Saharan Africa, East	1 122	360 602	0.28	0.08	0.04	0.40	0.17%	0.05%
Sub-Saharan Africa, Southern	6 834	100 733	0.52	0.11	0.06	0.69	0.24%	0.06%
Sub-Saharan Africa, West	969	181 803	0.11	0.04	0.02	0.18	0.06%	0.02%
World Bank classification								
Low income	868	5 036 979	2.52	1.23	0.62	4.37	0.24%	0.10%
Lower middle income	3 109	9 395 204	18.90	6.74	3.57	29.21	0.35%	0.12%
Upper middle income	6 827	4 759 025	13.70	10.44	8.35	32.49	0.50%	0.29%
High income	32 865	16 367 508	216.77	78.00	243.14	537.91	1.24%	0.74%

Total	16 986	35 558 717	251.89	96.41	255.69	603.99	1.01%	0.59%

Annex 6.11.6: Numbers of prevalence studies, by year of data collection and income level of the country where the research was carried out

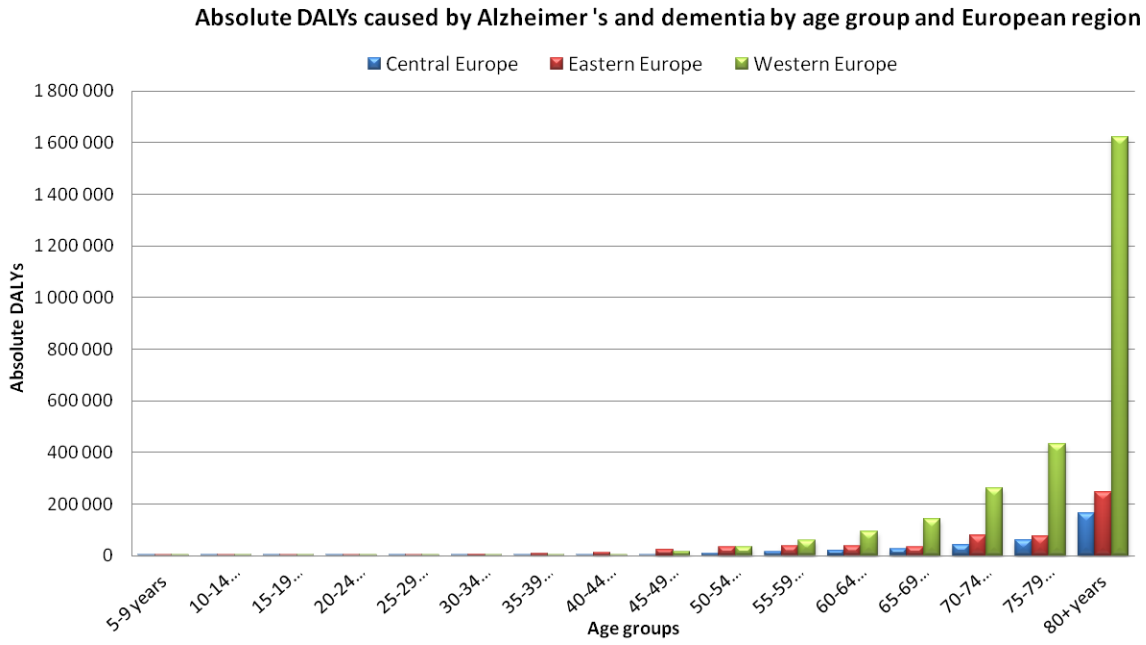


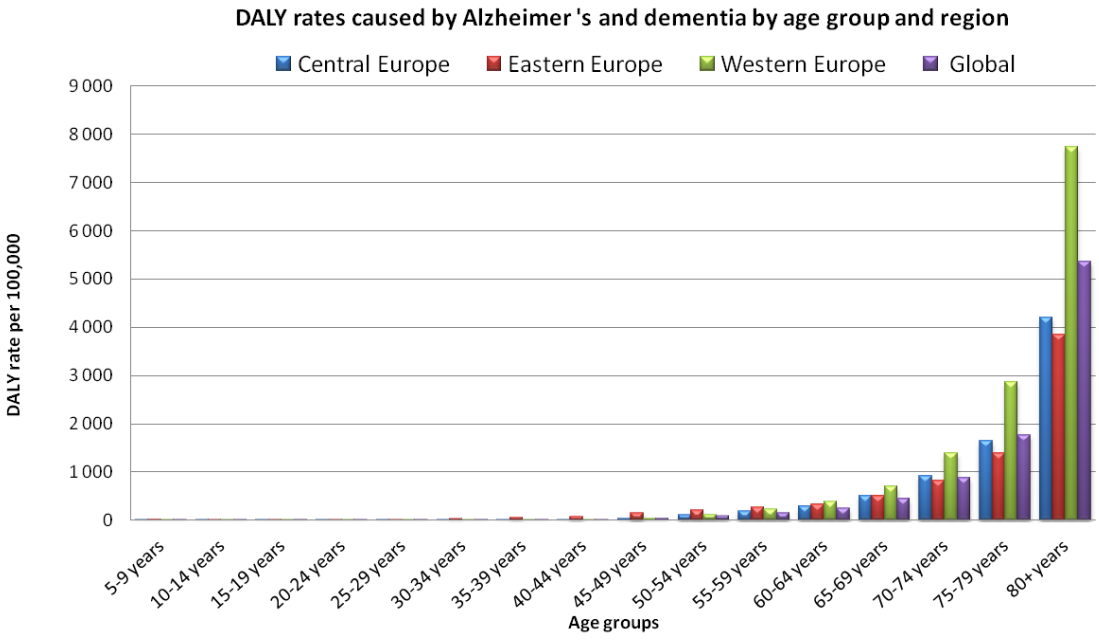
ANNEX 6.11.7: DALYs and death rates caused by Alzheimer disease and other dementia by age group and regions

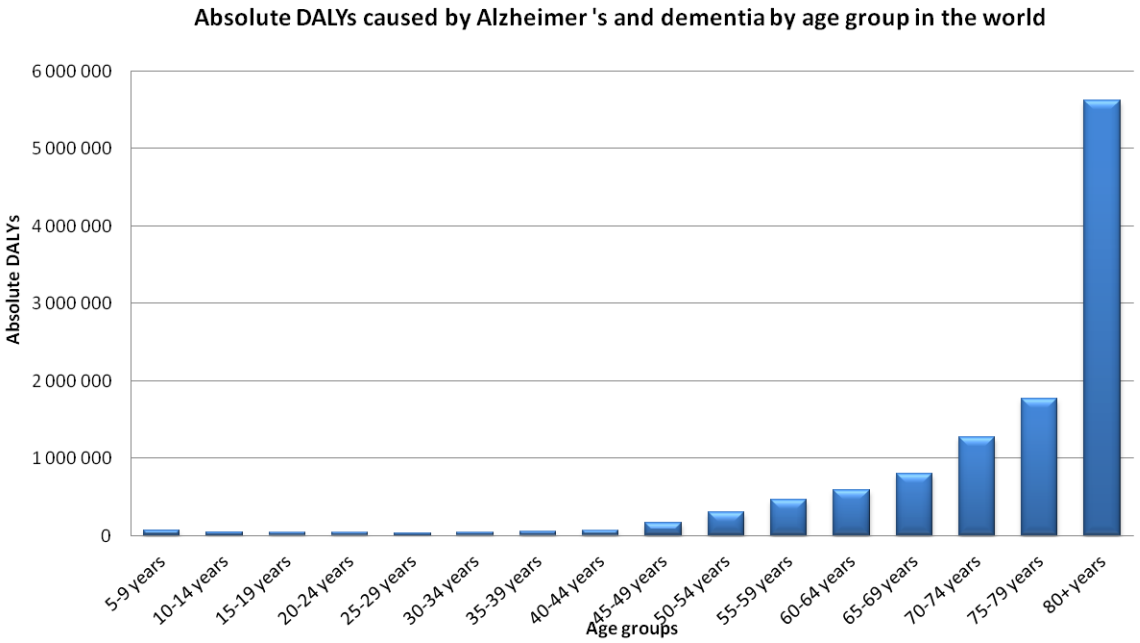
*By Faraz Chavoushi, World Health Organization, Department of Essential Medicines and Health Producnts, Geneva Switzerland.

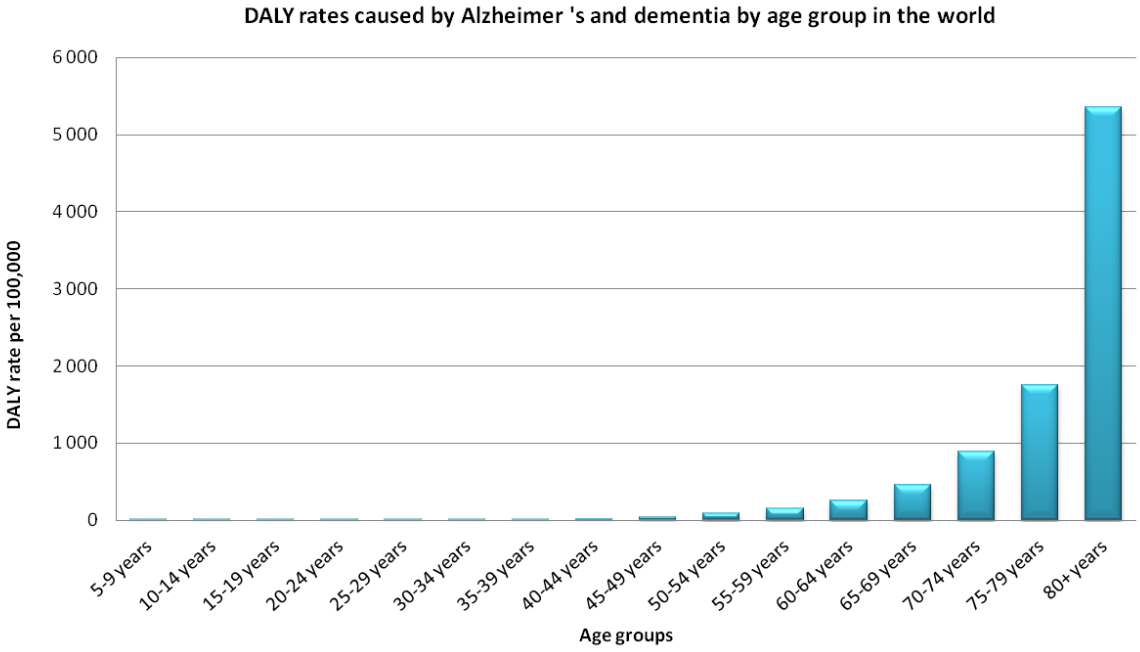
Data from the Global Burden of Disease 2010, Lancet Dec 2012.

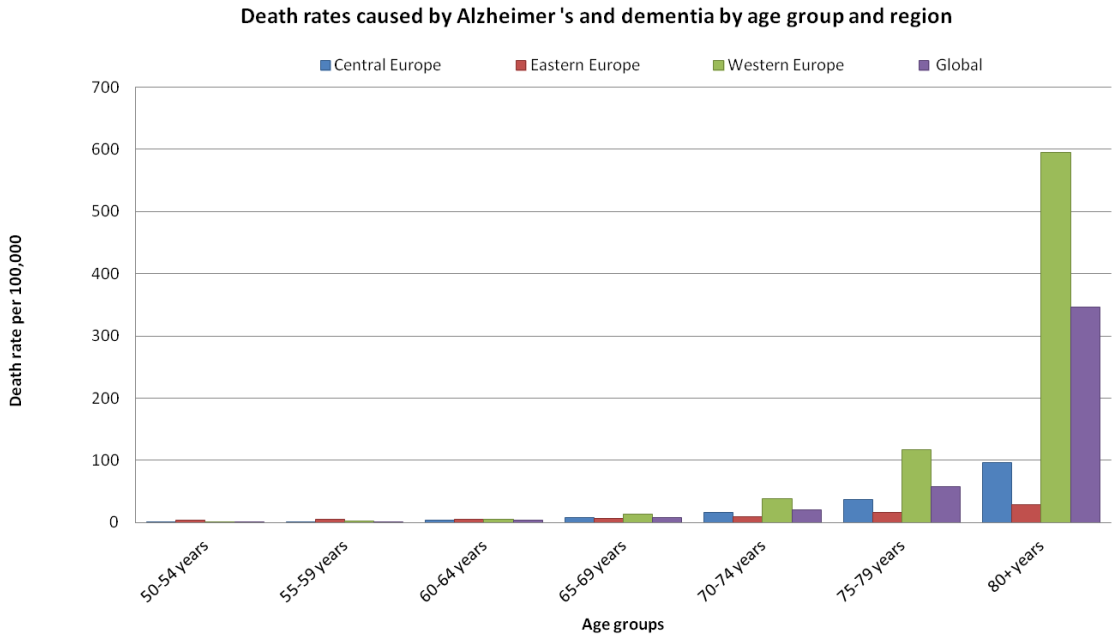
- Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012 Dec 15;380(9859):2163-96. doi: 10.1016/S0140-6736(12)61729-2.
- Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012 Dec 15;380(9859):2095-128. doi: 10.1016/S0140-6736(12)61728-0.






Absolute DALYs caused by Alzheimer 's and dementia by age group in the world
Absolute DALYs
6 000 000
5 000 000
4 000 000
3 000 000
2 000 000
1 000 000
0
5-9 years
10-14 years
15-19 years
20-24 years
25-29 years
30-34 years
35-39 years
40-44 years
45-49 years
50-54 years
55-59 years
60-64 years
65-69 years
70-74 years
75-79 years
80+ years
Age groups

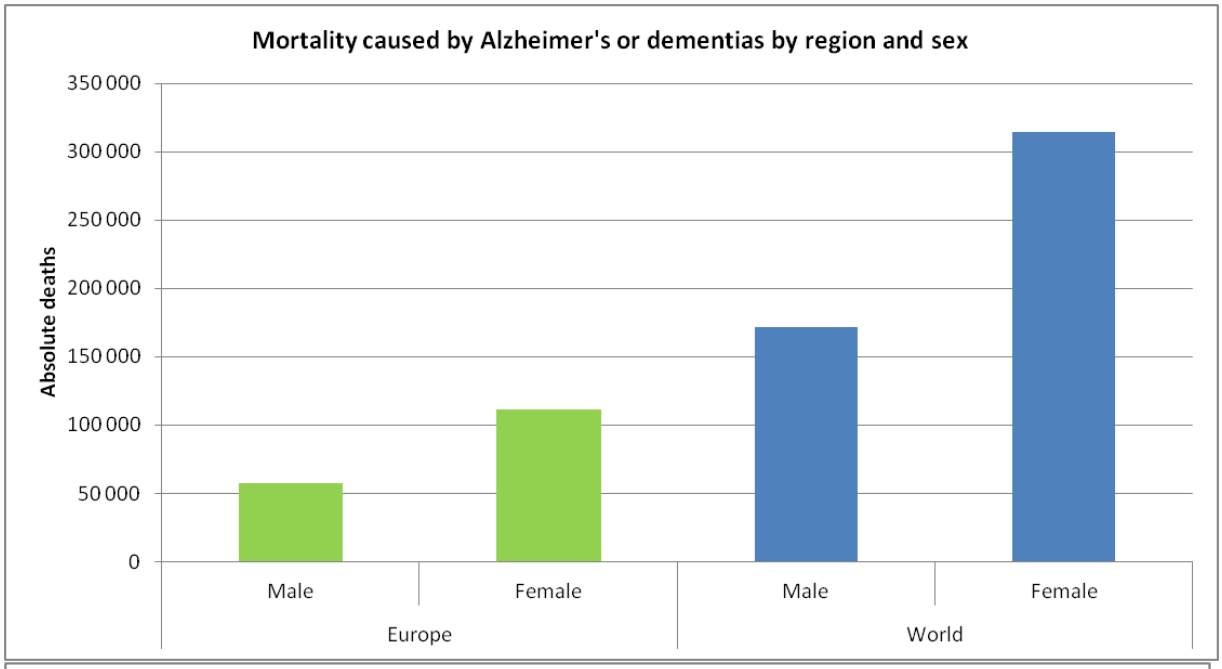

DALY rates caused by Alzheimer 's and dementia by age group in the world
DALY rate per 100,000
6 000
5 000
4 000
3 000
2 000
1 000
0
5-9 years
10-14 years
15-19 years
20-24 years
25-29 years
30-34 years
35-39 years
40-44 years
45-49 years
50-54 years
55-59 years
60-64 years
65-69 years
70-74 years
75-79 years
80+ years
Age groups

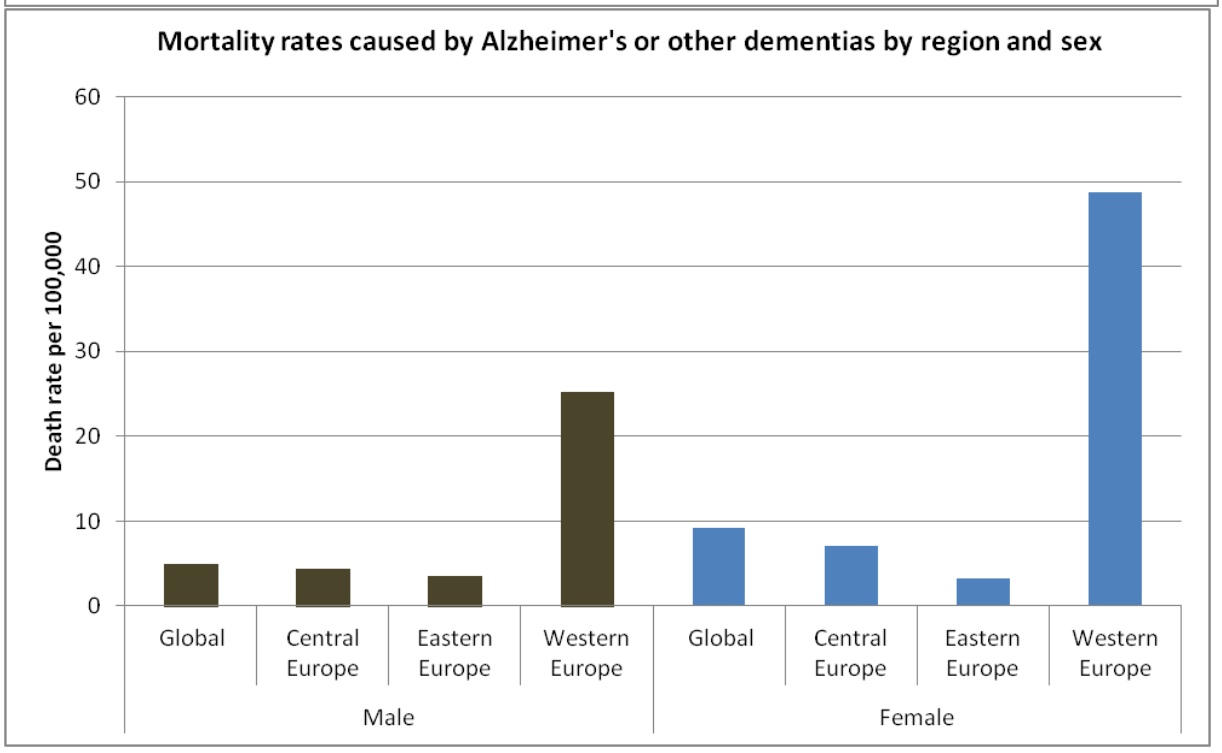

Death rates caused by Alzheimer 's and dementia by age group and region
Central Europe
Eastern Europe
Western Europe
Global
700
600
500
400
300
200
100
0
Death rate per 100,000
50-54 years
55-59 years
60-64 years
65-69 years
70-74 years
75-79 years
80+ years
Age groups

ANNEX 6.11.8: Mortality caused by Alzheimer disease and other dementias by region and sex

By Faraz Chavoushi, World Health Organization, Department of Essential Medicines and Health Products, Geneva Switzerland. Data from the Global Burden of Disease 2010, Lancet Dec 2012.

- Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012 Dec 15;380(9859):2163-96. doi: 10.1016/S0140-6736(12)61729-2.
- Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012 Dec 15;380(9859):2095-128. doi: 10.1016/S0140-6736(12)61728-0.





Appendices

Appendix 6.11.1: Role of antidepressants in people with dementia and associated depression. WHO, 2012.

Appendix 6.11.2: Conclusions on the future of information and communication technologies research, innovation and infrastructures. Council of European Union, 2009.

Appendix 6.11.3: Dementia The NICE-SCIE guideline on supporting people with dementia and their carers in health and social care. National Collaborating Centre for Mental Health, 2011.