



Rising life expectancy in developing countries such as China will bring with it an increase in the number of people with dementias.

## DEMENTIA

# A problem for our age

*As the number of Alzheimer's cases rises rapidly in an ageing global population, the need to understand this puzzling disease is growing.*

BY ALISON ABBOTT

The world is getting richer. But wealth brings its own burdens. Prosperous people live longer and old age carries a high risk of dementia — a condition that is so far neither preventable nor curable.

In 2000, for example, 4.5% of the population of the United States was older than 65 years, and there were 411,000 new cases of Alzheimer's disease. Ten years on, those numbers had risen to 5.1% of the US population and 454,000 cases, according to the Alzheimer's Association in the United States.

This same trend is happening across the world. In fact, when Alzheimer's disease is conflated with other dementias with similar clinical profiles, it covers an estimated 35.6 million people — around 0.5% of the global population. And these figures are about to get worse: the number of people with dementia is set to double in the next 20 years, according

to the *World Alzheimer Report 2010*, a global assessment of the economic impact of dementia.

Commissioned by Alzheimer's Disease International (ADI) — a federation of Alzheimer's associations around the world — the report gathered numbers on a range of Alzheimer's-like dementia. Dozens of teams are working to find ways to predict, prevent, diagnose and treat the condition, but so far their efforts have achieved only limited success. As a result, the economic costs of dementias will likely be crippling, the report says.

In 2010, the global economic impact of dementias was US\$604 billion. This figure dwarfs the costs of cancer or heart disease. Based on demographics, the ADI report foresees an 85% increase in cost by 2030, with developing countries bearing an increasing share of the economic burden.

"We are seeing a linear increase in prevalence in rich countries, but an exponential increase in low-income countries," says report co-author

Anders Wimo, an epidemiologist at the Karolinska Institute in Stockholm. "The need for solutions is urgent."

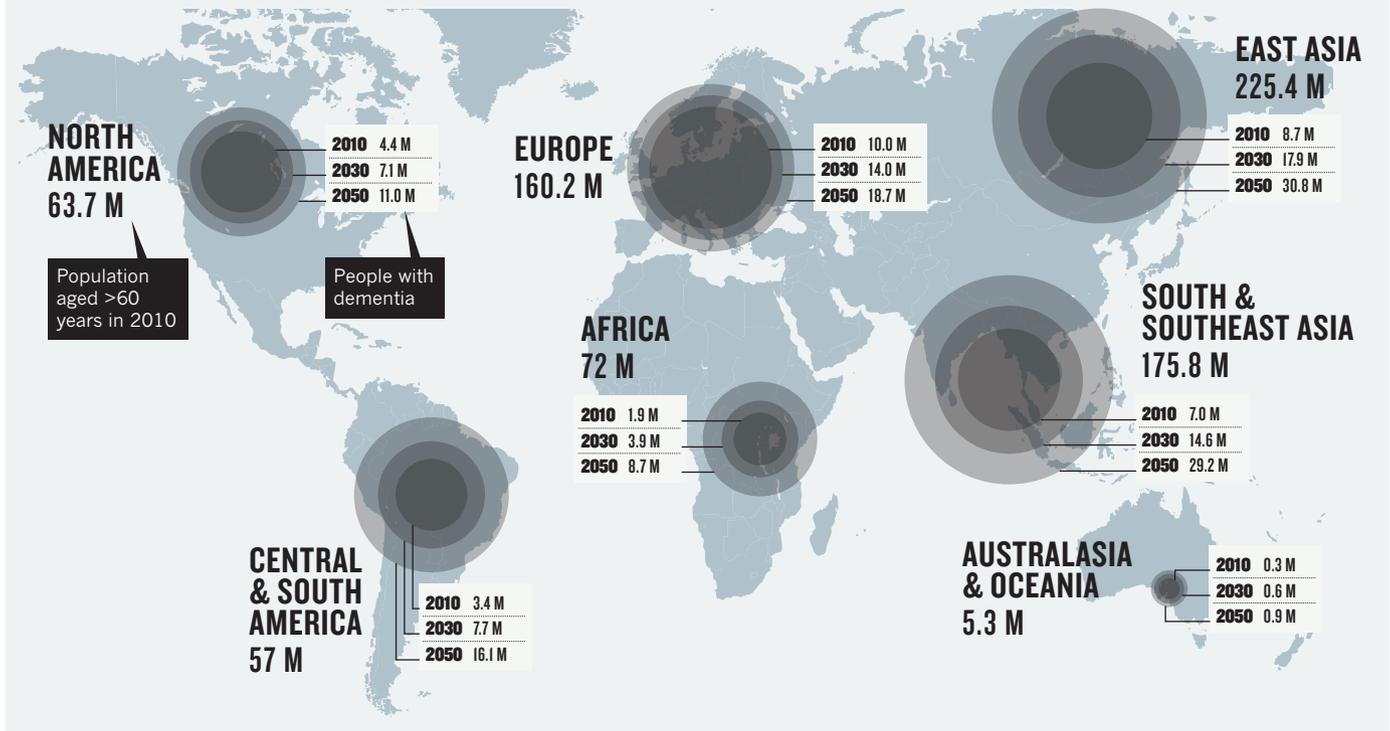
The ADI report used the best available data to determine the direct medical and social care costs, as well as the indirect costs, which mostly relate to family care and reduced productivity. Nearly 90% of the global costs in 2010, it says, are borne by rich countries — about 70% in Western Europe and North America — and less than 1% by low-income countries, where there is greater reliance on unpaid home care (see 'Global costs of dementia'). There is a fiftyfold difference in the cost of care per person between the richest countries and the poorest.

## AGEING IN ASIA

Just under half of people with dementia live in high-income countries, 39% live in middle-income countries, and only 14% live in low-income countries, the report says. But these

## ESTIMATED GROWTH OF DEMENTIA

The number of people with dementia will roughly double every 20 years, with the biggest increases in developing countries.



proportions are forecast to change dramatically in the coming decades, particularly in rapidly developing countries such as China and India, for two important reasons.

The first reason is demographic. In compiling the ADI report, Wimo and co-author Martin Prince of the Institute of Psychiatry at King's College London reviewed the available epidemiological studies. They found that the prevalence of dementias in people aged over 60 is fairly uniform across the world — between 5% and 7%.

As living standards increase in countries such as India and China, this will lead to increased life expectancy. Given that the biggest risk factor for dementia is age, a longer-living global population means there will be more people with dementia. The report predicts that the number of people with dementia will roughly double every 20 years, to 65.7 million in 2030 and 115.4 million in 2050 (see 'Estimated growth of dementia'). Most of this increase will be in developing countries.

Second, as wages rise, demand for more costly professional care will also increase — at least, that is what happened in wealthier countries where the Alzheimer's epidemic hit earlier. China has particular reason to worry: its one-child policy took effect in 1978, meaning that parents who reach old age in the next 20 years may not be able to rely on home care.

There are no comparable detailed global analyses for other chronic diseases. But *Dementia 2010*, a report commissioned by

the UK Alzheimer's Research Trust, estimated that the annual national cost of dementias was £23 billion (US\$38 billion), nearly twice that of cancer (£12 billion) and far more than the costs of heart disease (£8 billion) and stroke (£5 billion) (see 'Comparing costs').

The allocation of public research funds to these diseases does not reflect this hierarchy, however. In 2008, UK public spending on cancer research was 12 times higher than on dementia (see 'Comparing Investment'). In the United States, the National Institutes of Health spends 13 times more on cancer than on Alzheimer's-like dementias. "We can't fund all the good ideas we have in grant applications," says Neil Buckholtz, chief of dementia research at the US National Institute on Aging (NIA) in Bethesda, Maryland.

### TACKLING THE DISEASE

As the scale of the threat looms large, some countries are launching programmes to tackle dementia on several fronts. For example, in 2009, Germany opened the German Centre for Neurodegenerative Diseases (DZNE) in Bonn at a cost of €66 million (US\$95 million) per year. Developing treatment and preventive strategies will depend on clearly defining the disease and learning more about its clinical manifestations, says DZNE director Pierluigi Nicotera.

But these researchers will be aiming at a maddeningly elusive target. Fundamental questions about the disease — such as what its main cause is, and even what pathologies

define it — remain unanswered (see 'Common types of dementia'). The label 'Alzheimer's disease' was not widely used to describe dementia until 1976, when Robert Butler, the founding director of the NIA, coined the term, partly to make it easier to attract research funds to study the condition. At the time, the syndrome wherein some elderly people became forgetful and child-like was known as senile dementia. This was not viewed as a disease that might be prevented or cured, but as an intrinsic part of getting old.

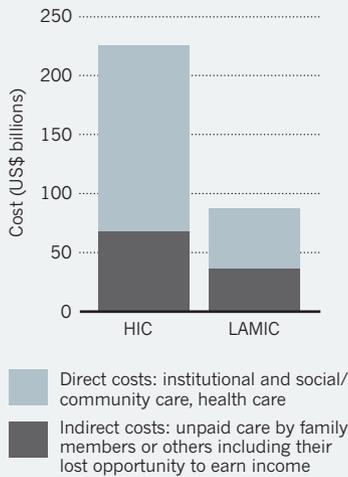
Alzheimer's disease is widely thought to be driven by amyloid pathology, in which peptides of amyloid- $\beta$  are generated in the brain and clump together into plaques. The plaques release toxic fragments of amyloid- $\beta$ , which wreak havoc by a mechanism that is not yet completely understood (see 'Little proteins, big clues', page S12).

Another form of dementia with similar symptoms is driven by vascular pathology. Leaking blood vessels deprive small areas of the brain of blood and oxygen, and these 'microstrokes' damage brain tissue and eventually result in cognitive defects. Scientists are still arguing about what proportions of dementias are driven by plaques and by vascular pathology. Post-mortem analyses of brains from people with dementia suggest that there is no simple answer: Alzheimer's-type pathology is more common, but it nearly always coexists with vascular pathology.

A 2011 investigation of more than 450 brains

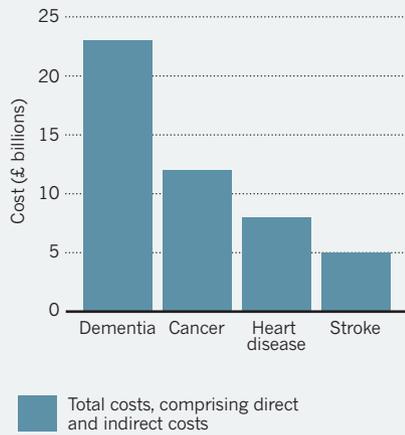
**GLOBAL COSTS OF DEMENTIA**

There is a vast difference in the cost of care per person between high-income countries (HIC) and low- and middle-income countries (LAMIC).



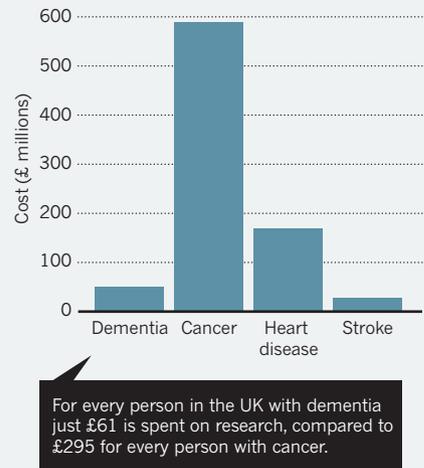
**COMPARING COSTS**

In the United Kingdom, the economic impact of dementias dwarfs the costs of other diseases.



**COMPARING INVESTMENT**

In the United Kingdom, annual government and charity spend on dementia research is 12 times lower than on cancer research.



For every person in the UK with dementia just £61 is spent on research, compared to £295 for every person with cancer.

from the UK Cognitive Function and Ageing Studies identified vascular damage in four-fifths of brains from individuals with dementia, and found plaques in nearly all of them (Wharton, S. B. *et al. J. Alzheimer's Disease*, in press). Scientists suspect that vascular pathology usually accelerates the damage driven by amyloid pathology. But the same study found that three-quarters of brains from individuals without dementia also had vascular pathology, and some of those from the oldest individuals showed a significant burden of plaques.

**AIMING AT AMYLOID**

Amid this confusion, companies interested in developing therapies have primarily been targeting amyloid pathology, encouraged by the fact that the heritable, early onset form of Alzheimer's disease is mostly caused by mutations in the genes responsible for the production and metabolism of amyloid-β. These familial cases account for fewer than 5% of total dementia (see 'Finding risk factors', page S20), but the companies hope that a significant proportion of later-onset dementia will be, one way or another, driven by amyloid-β. "There is a level of wishful thinking in this," says

Nicotera. But so far none of the amyloid-based strategies has been successful (see 'A tangled web of targets', page S9). Yet drug developers have not given up on the concept. More reliable biomarkers of Alzheimer's disease are being developed (see 'Warning signs', page S5), potentially making it possible to carry out trials on patients before symptoms, and irreversible damage, set in.

Some scientists are also wondering whether it might be valuable to target vascular pathology as well. In fact, drugs such as statins, which lower cholesterol levels in the blood, and drugs to reduce blood pressure are now routinely given long term to patients at high risk of heart attack or stroke. If vascular pathology drives a significant proportion of dementias, those who have benefited from the long-term cardiovascular treatment introduced in the past two or three decades might be protected from dementias as well.

Few epidemiological surveys have so far backed this up, but the authors of the most rigorous survey to date, the Rotterdam Study, announced at the Alzheimer's Disease International conference in Toronto in March 2011 that they have observed a slowing in

the number of people being diagnosed with dementia.

Launched in 1990, the Rotterdam Study is considered to be a model for epidemiology trials. Intended to pinpoint the factors that contribute to various diseases, including dementia, in the elderly, it has recruited nearly 15,000 middle-aged individuals from a local population in three cohorts — in 1990, 2000 and 2006 — and is following their progress. Preliminary results have shown a small decrease in the age-specific incidence of dementias, and fewer plaques and less vascular damage among undiagnosed individuals, says epidemiologist Monique Breteler, head of the neurological and imaging part of the survey.

If dementias were ever to come under control, other medical problems of the elderly would become more prominent, notes Rudi Westendorp, who studies healthy ageing at Leiden University Medical Centre in the Netherlands. Because people with dementia are either less aware of pain or are unable to express their distress, "painful illnesses like herpes zoster [shingles] are probably being masked by dementia", he says. "Sight and hearing fail distressingly when we get old — we need to invest more heavily in research aimed at circumventing this, like developing neural implants to bypass damaged retinas."

Westendorp is an optimist who believes that solutions will be found to these problems, including the dementias, in the foreseeable future if countries invest in research now. Most of the problems that come with old age, he says, will have a medical solution — so living to a grand old age need not carry such a social and economic burden. ■

**Alison Abbott** is Nature's senior European correspondent.

**COMMON TYPES OF DEMENTIA**

There is a great deal of overlap between the symptoms of various dementias.

Dementia type	Symptoms	Neuropathology	Proportion of dementia cases
Alzheimer's disease	Impaired memory, depression, poor judgement and confusion	Amyloid plaques and neurofibrillary tangles	50–80%
Vascular dementia	Similar to Alzheimer's disease, but memory less affected	Decreased blood flow to the brain owing to a series of small strokes	20–30%
Frontotemporal dementia	Changes in personality and mood, and difficulties with language	Damage limited to frontal and temporal lobes	5–10%
Dementia with Lewy bodies	Similar to Alzheimer's disease, also hallucinations, tremors	Cortical Lewy bodies (of the protein α-synuclein) inside neurons	<5%