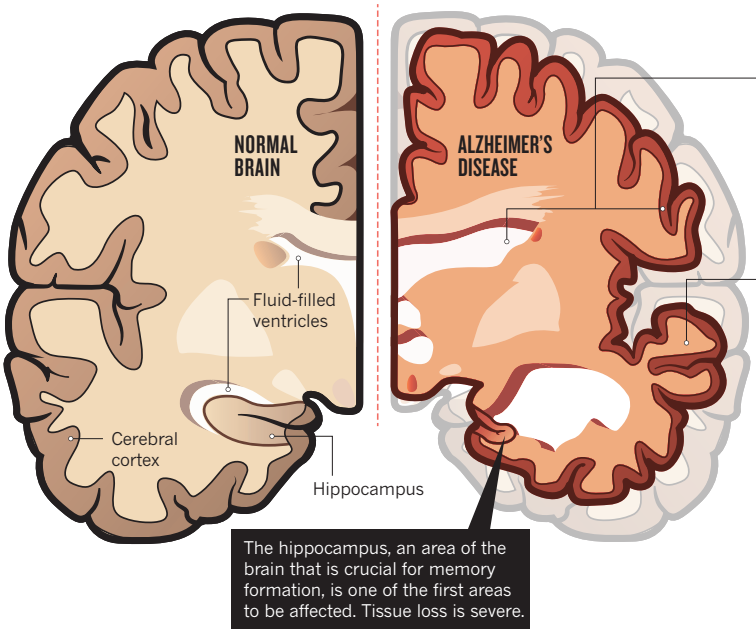
AN AGE-OLD STORY

Alzheimer's disease is a progressive neurodegenerative condition of the brain that is responsible for around two-thirds of dementia cases. Despite much effort, the condition's cause remains uncertain and no effective treatment yet exists.

By **Liam Drew**; *infographic by* **Mohamed Ashour**.

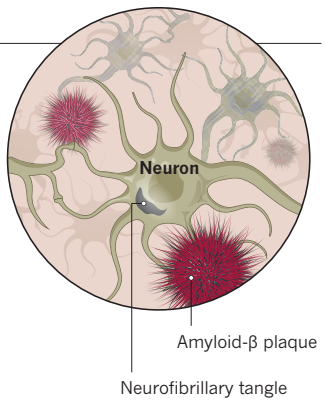
DISEASE OF DECLINE

Subtle losses of memory or changes in behaviour are the first outward signs of Alzheimer's disease. Slowly but relentlessly, cognition declines, language is disrupted and behavioural changes accumulate, diminishing a person's independence. These changes are underpinned by both structural and microscopic changes in the brain.



STRUCTURAL CHANGES

Alzheimer's disease spreads through the brain, causing a progressive loss of the connections between neurons (synapses), and then neurons themselves. In the later stages of the condition, the brain is noticeably shrunken — the cerebral cortex appears shrivelled and the fluid-filled ventricles are expanded.



MICROSCOPIC CHANGES

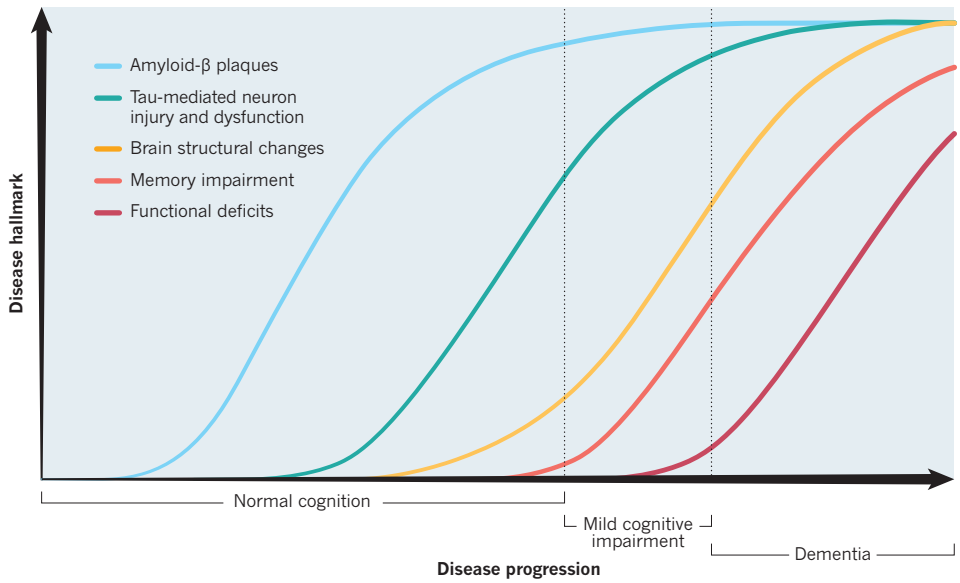
Two hallmarks of Alzheimer's disease are visible only under the microscope.

Accumulations of the peptide amyloid-β, known as plaques, form between neurons. Microtubule-associated protein tau aggregates into neurofibrillary tangles inside neurons, and these structures persist after neurons have died.

ADAPTED FROM ILLUSTRATION BY STACY JANNIS/ALZHEIMER'S ASSOCIATION

A SLOW MARCH

By the time that a person begins to experience the symptoms of Alzheimer's disease, the condition is already well-established in the brain. The accumulation of amyloid-β, generally thought to be the first step in disease progression, could precede symptoms by 10–15 years. Tau accumulation occurs later, much closer to the onset of neurodegeneration.



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*Mild cognitive impairment is an abnormal decline in cognition that, unlike Alzheimer's disease, does not affect daily living. It is considered to be a precursor to the condition.

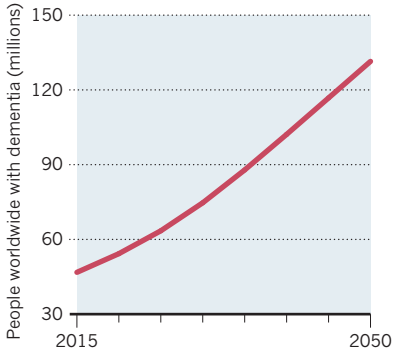
8–10 YEARS

The average time for which a person with Alzheimer's disease lives after diagnosis.

A GLOBAL PROBLEM

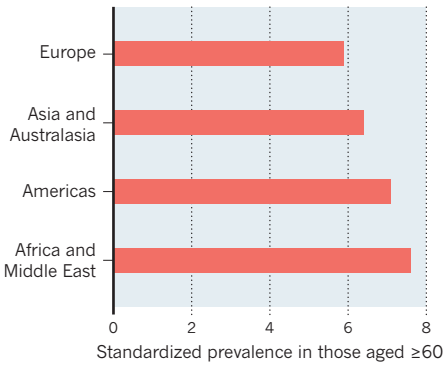
AGEING AND GROWING

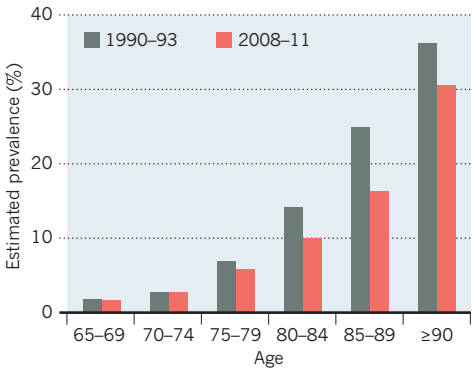
In 2015, almost 50 million people worldwide had dementia[2]. As the population grows and ages, the number affected is expected to surpass 130 million people by 2050.



LOCAL LESSONS

The prevalence of Alzheimer's disease (left) in people aged 60 or above is highest in north Africa and the Middle East, and the condition is least common in central Europe[2]. In affluent countries in the West, such as the United Kingdom, a decline in the prevalence of Alzheimer's disease in the elderly has been observed (right)[3]. This suggests that concurrent changes in lifestyle might have provided some protection from dementia (see page S18).





RISK FACTORS

GENETICS

Around 1% of cases of Alzheimer's disease are caused by mutations in the genes *APP*, *PSEN1* or *PSEN2*, which affect amyloid-β processing. Certain mutations in *APOE* and *TREM2* can increase the risk of developing the more common sporadic form of the condition.

SEX

The overall incidence of Alzheimer's disease in women is up to twice that of men[4]. This difference cannot be explained by women's greater life expectancy — but hormones and lifestyle might play a part.

LIFESTYLE

A raft of potentially modifiable risk factors for Alzheimer's disease have been identified. These include diabetes, obesity, depression, smoking and low educational attainment.

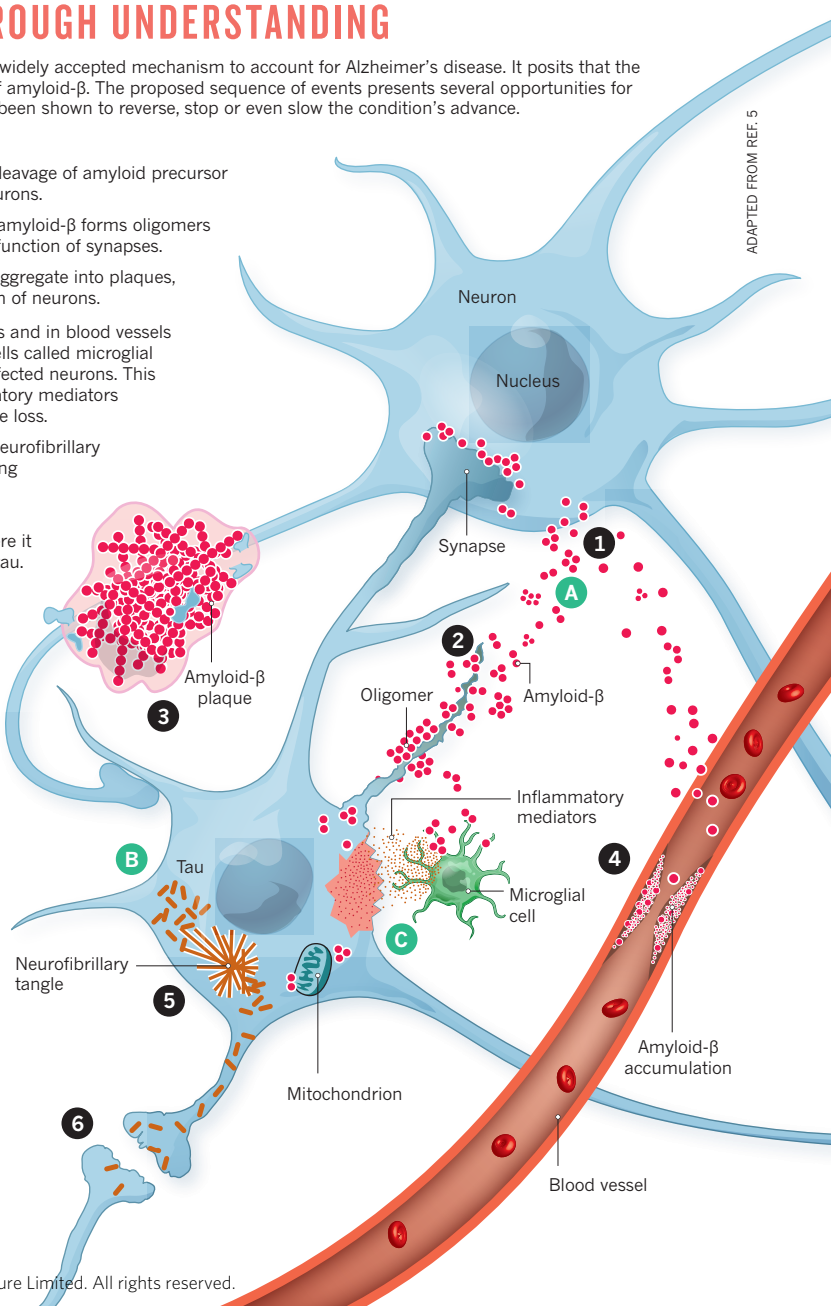
TREATMENTS THROUGH UNDERSTANDING

The amyloid hypothesis is the most widely accepted mechanism to account for Alzheimer's disease. It posits that the condition is driven by aggregation of amyloid-β. The proposed sequence of events presents several opportunities for intervention, but so far no drug has been shown to reverse, stop or even slow the condition's advance.

1. Amyloid-β is produced by the cleavage of amyloid precursor protein in the membrane of neurons.
2. In the space between neurons, amyloid-β forms oligomers that are thought to disrupt the function of synapses.
3. Fibrils of amyloid-β oligomers aggregate into plaques, which interfere with the function of neurons.
4. Amyloid-β deposits outside cells and in blood vessels of the brain activate immune cells called microglial cells that congregate around affected neurons. This triggers the release of inflammatory mediators and might contribute to synapse loss.
5. Misfolded tau aggregates into neurofibrillary tangles inside neurons, displacing intracellular organelles.
6. Misfolded tau can pass through synapses to other neurons, where it catalyses further misfolding of tau.

OPPORTUNITIES FOR INTERVENTION

- **A** Inhibitors of the enzymes that cut amyloid precursor protein and antibodies that bind to various forms of amyloid-β have been tested without success (see page S4).
- **B** Immunotherapies and small molecules that inhibit the aggregation and spread of tau are also under development.
- **C** If inflammation is shown to contribute to Alzheimer's disease, anti-inflammatory drugs could provide benefits to those affected.



Sources: 1. Jack. C. R. Jr *et al. Lancet Neurol.* **12**, 207–216 (2013); 2. Alzheimer's Disease International. *World Alzheimer Report 2015: The Global Impact of Dementia* (Alzheimer's Disease International, 2015); 3. Matthews, F. E. *et al. Lancet* **382**, 1405–1412 (2013); 4. Chêne, G. *et al. Alzheimers Dement.* **11**, 310–320 (2015); 5. L. Mucke. *Nature* **461**, 895–897 (2009).