# Alzheimer's disease

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**Abstract**

Alzheimer's disease, the commonest cause of dementia, is a growing global health concern with huge implications for individuals and society. In this review, we outline the current understanding of the epidemiology, genetics, pathology and pathogenesis of Alzheimer's disease, before discussing its clinical presentation, and current treatment strategies. Finally, we discuss how our enhanced understanding of Alzheimer pathogenesis and the recognition of a protracted preclinical phase is informing new therapeutic strategies with the aim of moving from treatment to prevention.

## Introduction

Alzheimer's disease (AD) is recognised by the World Health Organisation as a global public health priority. Despite large gains in our understanding of AD pathogenesis and how we conceptualise the disease since Alois Alzheimer reported the first case in 1907 [1] there are still no disease-modifying treatments. Here we provide an overview of current thinking in AD, with respect to epidemiology, genetics, pathology and pathogenesis, before considering its clinical presentation, current treatment options and future therapeutic strategies.

## Epidemiology

Dementia – acquired progressive cognitive impairment sufficient to impact on activities of daily living – is a major cause of dependence, disability and mortality. Current estimates suggest that 44 million people live with dementia worldwide presently. This is predicted to more than triple by 2050 as the population ages, when the annual cost of dementia in the US alone may exceed US$600billion [2]. In

England and Wales, dementia is the leading cause of death overall, accounting for 11.6% of all deaths registered in 2015 [3]. Recent studies suggest the incidence of dementia, particularly in men, may be declining in Western countries; it is unclear which causes of dementia are declining, and this may be underpinned by better management of vascular risk [4,5]. In coming years, the largest increase in dementia prevalence is expected in low and middle-income countries, which show patterns of increasing cardiovascular disease, hypertension and diabetes [2]. AD is the single biggest cause of dementia – accounting for 50-75%, and is primarily a condition of later life, roughly doubling in prevalence every five years after age 65 [2].

**Aetiology**

Whilst the vast majority of AD occurs on an apparently sporadic basis, mutations in three genes – amyloid precursor protein (APP), presenilin 1 (PSEN1) and presenilin 2 (PSEN2) – cause a rare (<0.5%) familial form of AD (fAD). Symptoms develop earlier than in sporadic AD, typically between 30 and 50 years of age [6].

“Typical” late onset AD is likely to be driven by a complex interplay between genetic and environmental factors. It is now thought that ~70% of AD risk is attributable to genetic factors. The APOE gene, which has three variants, ε2, ε3 and ε4, is the single biggest risk for sporadic AD: compared to non-ε4 carriers, ε4 heterozygotes have an odds ratio (OR) for AD ~3, rising to ~12 in homozygotes [7]. Genome-wide association studies (GWAS) using many thousands of samples have identified more than 20 genetic risk factors, implicating inflammatory, cholesterol metabolism and endosomal-vesicle recycling pathways [8]. In particular, microglial activation in response to amyloid deposition is now recognised to play a key role in AD

pathogenesis. These relatively common risk genes each confers only a very small increased risk, but when combined in a polygenic risk score, can almost double case prediction from chance [9]. Focussed genetic approaches and studies using next generation sequencing have also revealed a number of other low frequency genes conferring relatively high risk for AD, which in turn are providing insights into pathogenesis (Figure 1).

Epidemiological evidence suggests education and physical exercise may protect against AD, whereas mid-life hypertension and diabetes adversely influence risk [10]. Obesity has long been considered a risk for dementia and AD, but this has recently been questioned [11]. The mechanisms by which vascular risk factors might influence AD remain unclear, not least as few epidemiological studies have pathological confirmation of diagnosis. Vascular risk factors may increase the risk of clinical AD through a ‘double-hit’ with superimposed cerebrovascular damage, or vascular damage might influence the development of AD pathology directly.

**Pathology**

The cardinal features of Alzheimer pathology are amyloid plaques and neurofibrillary tangles (NFTs) (see Figure 2). In addition, neuropil threads, dystrophic neurites, associated astrogliosis, and microglial activation are seen, and cerebral amyloid angiopathy frequently co-exists [12]. The downstream consequences of these pathologic processes include neurodegeneration with synaptic and neuronal loss leading to macroscopic atrophy. Mixed pathology frequently occurs particularly in older individuals, and includes vascular disease and Lewy bodies [13]. Indeed, even in familial AD cases Lewy body pathology often co-exists, the mechanism for which

remains uncertain [14]. TDP-43 pathology is increasingly recognised as an important co-pathology [15].

Amyloid plaques are extracellular accumulations principally composed of abnormally folded Aβ with 40 or 42 amino acids (Aβ40 and Aβ42), two by-products of amyloid precursor protein (APP) metabolism. Aβ42 is more abundant than Aβ40 within plaques due to its higher rate of fibrillisation and insolubility. Amyloid deposition does not always follow a stereotyped pattern of progression, but broadly speaking develops in the isocortex, and only latterly affects subcortical structures. Unlike NFTs, amyloid plaques involve the entorhinal cortex and hippocampal formations to a lesser extent [12]. Different staging systems for Aβ including those from Braak and Braak [16], Thal criteria [17] and Consortium to Establish a Registry for Alzheimer Disease (CERAD) [18].

NFTs are primarily composed of paired helical filaments (PHF) consisting of hyperphosphorylated tau. Tau pathology typically begins in the allocortex of the medial temporal lobe (entorhinal cortex and hippocampus) before spreading to the associative isocortex. Primary sensory, motor and visual areas tend to be relatively spared. Neuronal and synapse loss typically parallel tangle formation, and as such the clinical features and severity of AD are better correlated with NFT pathology [12], whilst β-amyloid pathology reaches a plateau early in the symptomatic phase of the disease [19].

Several criteria have been proposed for the pathological diagnosis of AD. Early attempts using either amyloid plaques or NFT were limited by low specificity or

sensitivity [20]. Previous pathological criteria for AD from the National Institute of Aging and Reagan Institute combined the CERAD neuritic plaque score with the Braak and Braak NFT staging, deriving three diagnostic categories: high, intermediate and low likelihood. An AD diagnosis could only be made if criteria for high or intermediate likelihood of AD were met in conjunction with a dementia diagnosis [21]. A limitation of this system is that it did not address individuals dying with a high burden of AD pathology but without clinical symptoms. Updated NIA-AA neuropathological guidelines attempt to address this, acknowledging the potential for disconnect between the clinical picture and neuropathological changes [22].

**Pathogenesis**

The amyloid hypothesis, the prevalent theory of AD pathogenesis, suggests that accumulation of pathological forms of Aβ, produced by sequential cleavage of the amyloid precursor protein (APP) by the β- and γ-secretase enzymes in the brain is the primary pathological process, driven through an imbalance between Aβ production and Aβ clearance. The formation of NFTs and subsequent neuronal dysfunction and neurodegeneration, perhaps mediated via inflammation, are thought to be downstream processes [23] (see Figure 3). Strong support for a central role for Aβ comes from genetics: all fAD mutations are involved either in Aβ generation or processing and result in relative overproduction of toxic forms of β-amyloid. Conversely, an APP missense mutation (A673T) results in a lifelong decrease in APP cleavage by β-secretase conferring a reduced clinical risk of AD [24]. In sporadic disease, ApoE is involved in amyloid clearance, as are many other risk genes (Figure 1).

Whilst fibrillar amyloid within dense-core plaques was originally thought to be critical to the development of AD, it is now thought that soluble Aβ oligomers may be the most pathological forms: oligomers purified from AD brains and applied to neurons *in vitro* inhibit long-term potentiation, cause synaptic dysfunction, damage dendritic spines and cause neuronal death [25,26]. Human oligomers also induce hyperphosphorylation of tau at AD-relevant epitopes and cause neuritic dystrophy in cultured neurons [27]. Plaques may therefore act as a 'reservoir' from which amyloid oligomers diffuse, or may even act as a protective mechanism, sequestering toxic Aβ series until they reach a physiologic saturation point [28].

Whilst accumulation of Aβ is *necessary* for a diagnosis of AD, the fact that a significant proportion of elderly individuals die with evidence for significant β-amyloid deposition without symptoms shows that it is *not sufficient* for AD-dementia. The Aβ soluble oligomer:plaque ratio may be lower in patients with asymptomatic amyloidosis than patients with AD-dementia, supporting the concept that plaques may act as a protective reservoir [29]. Tau is clearly a vital part of the process that leads to AD, as evidenced by the requirement for both Aβ and tau pathology for a diagnosis for AD, and the close association between neurodegeneration and tau load. However, whilst mutations in the tau gene lead to accumulation of tau and a variety of neurodegenerative dementias within the frontotemporal dementia spectrum [30], unlike mutations in β-amyloid genes, tau mutations alone do not cause AD.

The advent of cerebrospinal fluid (CSF) and positron-emission tomography (PET) biomarkers of Aβ and tau pathology has led to numerous studies exploring the progression and interaction between these pathologies *in vivo*. Such studies in

healthy elderly individuals and patients with both sporadic [31] and familial AD [32] provide further evidence that amyloid pathology develops many year before clinical symptoms, and precede changes in CSF tau and tau PET which in turn are proposed to predate MRI changes and finally clinical symptoms [31]. These models – which as discussed below have led to new criteria for AD – continue to evolve as more data become available; and whilst there are considerable data to suggest that β-amyloid is upstream of tau pathology in AD, some healthy elderly individuals have evidence for tau-pathology without β-amyloid which may be part of the normal ageing process, or reflect a non-AD neurodegenerative pathway [33].

There is much interest in both the mechanisms by which AD proteins targets certain brain regions but not others, and how they spread through the brain. Abnormally folded Aβ and tau has been shown to induce conformational change in structurally normal peptides, much as occurs in prion disease. These may be transferred trans-synaptically from one neuron to another [34]. The site of the original pathological event might then determine which cortical networks are affected, and, through differential network breakdown, explain the phenotypic diversity seen in AD.

Whilst amyloid and tau pathology are clearly critical in the pathogenesis of AD, how the two are mechanistically linked is unclear. A number of lines of evidence suggest that the innate immune system play a critical role in AD pathogenesis, and may provide this link. Activated microglia co-localise with amyloid plaques at post mortem [35]. A number of AD-risk genes, including CR1, CD33, and TREM2 are involved in immune system pathways, [36,37]. Clinical studies using PET ligands which bind to activated microglia provide further *in vivo* evidence for a role of neuroinflammation in

AD [38,39]. The question of whether (or when) neuroinflammation is protective, detrimental, or perhaps both, may well depend on disease stage and genotypes, and remains to be fully elucidated.

**Clinical features**

The commonest presentation of AD is of an elderly individual with insidious, progressive problems centred on episodic memory. At this stage, the patient may fulfil criteria for amnestic mild cognitive impairment (MCI). Topographical difficulties subsequently commonly emerge, alongside difficulties with multi-tasking, and loss of confidence. As the condition progresses, cognitive difficulties become more profound and widespread so as to interfere with activities of daily living; at this stage a patient can be diagnosed with AD dementia. Increasing dependence is the rule, and later in the disease behavioural change, impaired mobility, hallucinations and seizures may emerge. Death is on average 8.5 years from presentation [40].

A number of atypical (non-memory) clinical syndromes are also recognised, particularly in younger-onset cases. These include posterior cortical atrophy (PCA), logopenic aphasia (LPA) and the frontal variant of AD. In PCA, whilst amyloid is widely distributed, the burden of tau pathology and atrophy is at least initially focussed on the parieto-occipital lobes, and patients typically present with prominent visuospatial and visuoperceptual problems and dyspraxia with relatively preserved memory [41]. In LPA, patients present with prominent word finding pauses, anomia and impairments in working memory [42]. Frontal AD, which is rare, can closely resemble behavioural variant frontotemporal dementia [43]. fAD tends to have a typical amnestic presentation, albeit at a much younger age. Some PSEN1

mutations are associated with additional features including prominent myoclonus, seizures and spastic paraparesis [44].

*Diagnostic criteria*

With the recognition that the pathological changes occur years prior to symptoms, and the advent of biomarkers of β-amyloid and tau pathology and MRI measures of atrophy, diagnostic criteria have evolved both to allow for the diagnosis to be made earlier and with increased molecular specificity. The most recent diagnostic criteria from both the National Institute of Aging (NIAA) and the International Working Group (IWG-2) now incorporate one or more preclinical AD phases, where biomarker evidence of AD pathology exists in the absence of symptoms [45–47]. Whilst a definitive diagnosis of AD still requires pathological confirmation, the NIA-AA criteria allow dementia, or mild cognitive impairment, to be attributed to underlying Alzheimer pathology with high, intermediate or low likelihood by incorporating biomarker information. Both sets of criteria also recognise atypical, non-amnestic presentations [46,48] (see Table).

**Important differential diagnoses**

In patients presenting to clinic with memory complaints, the differential diagnosis is broad. Causes other than AD include individuals anxious about perceived memory loss in the absence of objective evidence for impairment, the so-called “worried well”; individuals with affective disorders; and the effects of drugs and alcohol. Other mimics of AD include other neurodegenerative disorders including Lewy body dementia and frontotemporal dementia; vascular cognitive impairment; infectious, inflammatory and metabolic conditions; and a range of miscellaneous causes

including transient epileptiform amnesia and obstructive sleep apnoea.

**Diagnostic approach**

The mainstay of the diagnosis of AD remains the clinical assessment, and in particular the clinical interview with the patient and an informant, and a cognitive and focussed physical examination. Neuropsychology allows for the quantification of both the pattern and severity of cognitive deficits against age-related norms.

Blood tests are performed routinely to exclude conditions which may cause, or more commonly contribute, to cognitive symptoms, and typically include full blood count, renal function, thyroid function, vitamin B12 and folate. Depending on the clinical scenario, it may be appropriate to exclude a range of inflammatory, metabolic, and infective causes with specific serological tests (e.g anti-nuclear, anti-neuronal, Lgi1 antibodies, syphilis and HIV serology).

Structural imaging, using computed tomography or ideally magnetic resonance imaging (MRI) is recommended for all patients investigated for cognitive impairment to exclude structural abnormalities and provide positive diagnostic information [49]. The presence of focal symmetrical medial temporal atrophy has predictive value for AD [50]. In PCA-AD, there is typically parieto-occipital atrophy with relative sparing of the hippocampi, at least early in the disease [41]. MR imaging allows for the other neurodegenerative diseases to be excluded, and for the presence and extent of cerebrovascular disease (e.g. white matter hyperintensities and lacunar infarcts) which can mimic, or very commonly co-occur with, AD to be evaluated. Cerebral microbleeds may be evaluated using iron-sensitive sequences: deep microbleeds

are more likely to be due to hypertension, whilst lobar microbleeds are more likely to be caused by cerebral amyloid angiopathy [51] and, in the correct clinical context, to have positive predictive value for AD. Figure 4 shows representative MR images. 18F-fluorodeoxyglucose (FDG) PET hypometabolism in the parieto-temporal association areas, posterior cingulate and precuneus is supportive of an AD diagnosis [52].

Amyloid PET imaging (Figure 5) is now available clinically, with three agents approved by the European Medicines Agency and the US Food and Drug Administration. Florbetapir, flutemetamol and florbetaben all bind fibrillary β-amyloid, and closely correlate with β-amyloid burden at post-mortem [53–55]. To date, amyloid PET is not routinely reimbursed in most countries; a number of ongoing studies are currently evaluating its clinical utility and cost-effectiveness [56]. Tau PET imaging, using tracers such as AV1451, is a recent development which is currently only used for research purposes [57].

Cerebrospinal fluid (CSF) examination can be used both to exclude rare, reversible causes of cognitive impairment, but also to aid in a positive, molecular diagnosis of AD. The typical CSF pattern in AD is low Aβ1-42 and elevated levels of both tau and phospho-tau (p-tau); this pattern also has value in predicting which individuals with MCI will develop AD [58] and as a result are included in diagnostic criteria [59]. There are to date no AD-specific blood based biomarkers in routine clinical use [60].

Genetic testing, with appropriate consents, can be used to identify autosomal dominant causes of AD where these are suspected. The increasing availability of

genetic panels using next generation sequencing allows for large numbers of genes to be tested concurrently at reasonable costs. Routine testing of genetic risk factors (e.g. ApoE status) is not currently recommended.

**Treatment/management**

Disease-modifying treatments, i.e. those proven to alter the underlying disease pathology or disease course, are not yet available. Optimal management needs to be tailored to the individual patient and their specific circumstances, and to adapt as the disease progresses. Both the patient and carers should be involved in decision-making, with all reasonable steps taken to allow for patient involvement even as cognition declines; a multi-disciplinary approach including medical professionals, nurses, social services and charities/support services is vital. Important issue to consider include driving, noting that a diagnosis of AD does not necessarily preclude driving if symptoms are mild and executive and parietal functions are relatively preserved; support at home; finances; and future planning especially while the individual has capacity to make decisions. Referral to palliative care to discuss end-of-life planning can be particularly valuable, ideally in advance of end-stage dementia.

Acetyl-cholinesterase inhibitors (AChEI) (donepezil, galantamine and rivastigmine) are the mainstay of symptomatic treatment, increasing acetylcholine availability by inhibiting its breakdown in the synapse. Peripheral cholinergic side effects such as leg cramps and gastro-intestinal upset are common but usually well tolerated, especially when the drugs are introduced at low dose and titrated slowly. AChEI should be avoided or used with caution in individuals with heart conduction defects

due to the risk of brady-arrhythmias. AChEI have proven beneficial effects in mild to severe AD, with most evidence at the mild-to-moderate stage [61]. There are fewer data on measures of behavioural disturbance and activities of daily living, but some evidence of benefit. In all domains, however the benefit observed in clinical trials is modest at best. There is no evidence that one drug in the class is more efficacious than another [61]; differences in the frequency of dosing, dose variation, timing of escalation, and delivery (oral and transdermal) provide options that can be tailored to individual patients. The DOMINO-AD study demonstrated that withdrawal of donepezil in moderate-severe AD increased the risk of nursing home placement in the following 12 months of treatment, but not in the following three years. The authors suggested that withdrawal of treatment may have potential risks, even when the benefits of continuing are not clear [62].

Memantine is an alternative symptomatic treatment, licenced for moderate-severe AD. Memantine, a low affinity NMDA receptor antagonist, aims to reduce L-glutamate excitatory neurotoxicity without interfering with its physiological actions. Side effects include constipation and headache. Memantine has been shown to have a small but clinically appreciable benefit on cognition and functional decline in patients with moderate-severe AD, with some evidence it reduces the likelihood of patients developing agitation [63]. There is now some evidence for combination therapy using an AChEI and memantine. A recent meta-analysis found weak evidence for improved cognition with dual-therapy, but there was evidence of improved behavioural symptoms in moderate-severe AD [64].

Concurrent psychiatric disturbances are common and often difficult to treat. Depression and anxiety are frequently seen in AD and have significant impact on

quality of life, caregiver burden and risk of institutionalisation [65]. There is only limited evidence of benefit for antidepressant treatment for depression [66]. There is some evidence for benefit of psychological treatments in reducing depression and to a lesser extent, anxiety in patients with dementia [65]. Tricyclic antidepressants can worsen confusion and should be avoided.

Agitation, aggression and psychosis may develop in later-stage dementia. Atypical antipsychotics are usually favoured over typical agents but regardless of drug, benefits are moderate [67], and no treatments are licensed for behavioural symptoms in dementia. Serious adverse events include chest infection, stroke and death. Consequently, antipsychotics should be avoided if possible and limited to those with neuropsychiatric symptoms, particularly psychosis, that are severe, debilitating or posing safety risks [68]; ongoing use needs regular review. Where required, the best evidence is for low dose risperidone [69]. Non-pharmacological approaches are preferred and include communication skills training, music therapy and person-centred care training which have some evidence of benefit [70].

**Future prospects**

Although our understanding of AD has increased dramatically over recent years, it remains far from complete. Next generation genetic studies have implicated a number of pathways important to the pathogenesis of AD: these are currently being explored in cellular and animal models and are already leading to the identification of novel drug targets. A more nuanced model of the preclinical phase of AD, no longer viewing β-amyloid, tau and inflammation as steps along a sequential pathway but as part of a cellular phase of AD pathogenesis [71] will also lead to a more sophisticated approach to treatment and prevention.

The failure of a number of major Phase 3 clinical trials using monoclonal antibodies targeting cerebral β-amyloid has prompted scepticism about the amyloid hypothesis, but perhaps more worryingly about prospects for disease modification in AD more generally. It is important however to note that many of these studies have been complicated by concern over target engagement and patient selection [72]: not only did a proportion of individuals recruited for some of these trials not have evidence for AD pathology [28], but most studies have targeted patients with later stage AD, by which time β-amyloid may no longer be the most appropriate target. There are a number of ongoing clinical trials which will report over the next few years – with encouraging preliminary findings from a trial of Aducanumab, targeting AD at an earlier stage, and showing reduction in amyloid burden and delay in disease progression at one year in prodromal and mild AD patients [73]; a number of other studies in MCI and mild AD patients are ongoing [74]. There is a concerted effort to use strategies to either clear amyloid using immunotherapy or prevent the formation of pathological forms (either with β-site APP cleaving enzyme BACE or gamma-secretase inhibitors/modulators) in the preclinical phase. In fAD cohorts, the DIAN-TU and API-ADAD studies are identifying at-risk individuals with genetic screening [75,76]. The Generation study is recruiting ApoE4 individuals; and the A4 study is recruiting healthy elderly individuals with asymptomatic amyloidosis [77]. Alternate targets include tau pathology are attracting interest, with a number of clinical trials ongoing. Targeting neuroinflammation also has potential, although there have been no positive trials to-date [35].

If disease modifying therapies do provide a signal for efficacy in patients with established disease, it will be vital both to ensure they are affordable and can be rolled out quickly and equitably to all who will benefit, which will be a major challenge for existing healthcare systems. For disease prevention, it will be necessary to identify accurately which individuals are at risk. The development of new disease-specific biomarkers using PET, CSF and, in due course blood, has already provided important insights into the pathways leading to the development of AD. Application of these technologies to ever larger cohorts, particularly when combined with genetic data will improve our ability to detect individuals at risk of developing AD. Longer term follow-up will allow for the development of risk models and biomarkers that can predict not only if an individual is at risk of AD, but when – information vital both for clinical trials and eventually for personalised medicine. Combining this information with epidemiological approaches will provide a rational evidence base for the extent to which AD can and cannot be prevented by interventions in early or mid-life [78].

Ultimately, we foresee a time when polygenic risk score and other health measures proven to be risk factors can be combined to create an individualised risk score (much like the Framingham cardiovascular risk calculator). At an appropriate age, high risk individuals can then be referred for more invasive tests of AD pathology, e.g. amyloid imaging, and other, perhaps blood based biomarkers to predict proximity to disease, with bespoke treatments with a range of different agents being targeted to that individual's stage of disease. Whilst this model of personalised disease prevention may be some way off, advances on numerous fronts make this vision, if not yet a reality, at least in sight.

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Figure/table legends

**Figure 1:** An overview of genes which have been implicated in AD to date. The internal colour corresponds to their understood function. Where there are two

internal colours, the gene has been implicated in more than one pathway. Genes circled in yellow are also thought to influence APP metabolism; genes circled in red are thought to influence tau metabolism. The figure is minimally adapted from [8] with permission from Elsevier.

**Figure 2:** Pathology of Alzheimer's disease. Aβ immunohistochemistry highlights the plaques in the frontal cortex (A) and cerebral amyloid angiopathy (CAA) where Aβ accumulates within blood vessels (B, arrows). An Aβ cored plaque is shown at higher magnification in (C) showing a central core. In severe CAA Aβ accumulates within capillaries (D). Tau immunohistochemistry demonstrates both neurofibrillary tangles (E, arrows; H at higher magnification) and neuritic plaques (E, double arrow). Neuroinflammation is a prominent feature in Alzheimer's disease and this is evident by the number of reactive microglia (F; G at higher magnification). The bar in A represents 50µm in A and F; 100µm in B; 25µm in C and E and 15µm in D, G and H.

**Figure 3:** An overview of the major pathogenic events leading to AD as proposed by the amyloid hypothesis. The curved blue arrow indicates that Aβ oligomers may directly cause synaptic and neuritic damage and induce tau hyperphosphorylation, in addition to activating damaging inflammatory cascades. Figure reprinted from [28], available at http://onlinelibrary.wiley.com/wol1/doi/10.15252/emmm.201606210/full. Copyright under the Creative Commons Attribution License https://creativecommons.org/licenses/by/4.0/.

**Figure 4:** MRI images showing: A. characteristic hippocampal atrophy in a typical AD case best visualised in the coronal plane on T1; B. parieto-occipital atrophy in a posterior cortical atrophy case, here demonstrated in the sagittal plane on T1; C. microbleeds which are best visualised on SWI. The posterior distribution seen on this axial image is characteristic of CAA; D. extensive periventricular and subcortical white matter hyperintensities best visualised on FLAIR, seen here on a coronal image.

**Figure 5:** Florbetapir amyloid PET scan in healthy control (left) and AD patient (right). Warm colours indicate high amyloid accumulation. For clinical purposes florbetapir scans are read on a grey scale.

**Table**: **An overview of the different clinical and research diagnostic criteria for AD, and terminology used, from the preclinical through the symptomatic stages.** The IWG-2 criteria do not specifically differentiate between mild cognitive impairment and dementia, focusing on diagnosing the underlying disease process rather than the clinical syndrome.