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The probabilistic model of Alzheimer disease: the amyloid hypothesis revised

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Abstract

The current conceptualization of Alzheimer disease (AD) is driven by the amyloid hypothesis, in which a deterministic chain of events leads from amyloid deposition and then tau deposition to neurodegeneration and progressive cognitive impairment. This model fits autosomal dominant AD but is less applicable to sporadic AD. Owing to emerging information regarding the complex biology of AD and the challenges of developing amyloid- targeting drugs, the amyloid hypothesis needs to be reconsidered. Here we propose a probabilistic model of AD in which three variants of AD (autosomal dominant AD, *APOE* ε4-related sporadic AD and *APOE* ε4-unrelated sporadic AD) feature decreasing penetrance and decreasing weight of the amyloid pathophysiological cascade, and increasing weight of stochastic factors (environmental exposures and lower-risk genes). Together, these variants account for a large share of the neuropathological and clinical variability observed in people with AD. The implementation of this model in research might lead to a better understanding of disease pathophysiology, a revision of the current clinical taxonomy and accelerated development of strategies to prevent and treat AD.

Alzheimer disease (AD) is the most common cause of dementia in elderly people and is becoming increasingly prevalent worldwide. The incidence of dementia doubles with every six years of age, from 3.9 per 1,000 person-years at the age of 60–64 years up to 104.8 per 1,000 person-years at the age of 90 years or older[1]. Thus, with an ever-ageing population, the number of people with dementia worldwide is predicted to climb to 131.5 million in 2050 (REF.[1]). In 2015, the global societal economic cost of dementia was estimated as US $818 billion, a sum similar in magnitude to the gross domestic products of countries such as the Netherlands, and this cost is forecast to steadily increase in the coming years (up to US $2 trillion by 2030)[1].

According to its original pathological definition, AD is defined by extracellular amyloid plaques and intracellular neurofibrillary tangles[2]. The recent 'ATN' research framework of AD defines the disease on the basis of its underlying molecular pathology (plaques = amyloid ('A'), neurofibrillary tangles = hyperphosphorylated tau ('T')) and the ensuing neurodegeneration ('N'), irrespective of the clinical phenotype or underlying genetics[3]. Hence, the presence of both amyloid-β (Aβ) and tau deposits in the brain (A^+T^+) defines AD, whereas the presence of Aβ only (A^+T^-) defines a so-called Alzheimer pathological change[3]. Even though this framework is intended to be agnostic (that is, no direct assumptions regarding the causal role or order of biomarker abnormalities are made), it is strongly influenced by the amyloid hypothesis, which posits that Aβ is the earliest molecular driver of the disease[4,5].

The amyloid hypothesis states that the peptide Aβ causes a cascade of downstream events that finally lead to cognitive impairment and dementia[4,5]. It has been the dominant

model of AD pathogenesis for more than 30 years and the guiding influence for drug development, which to a large degree has aimed to produce compounds that either reduce Aβ production (secretase inhibitors) or increase Aβ clearance (immunotherapies). The hypothesis implicitly assumes a deterministic cause–effect model (that is, a chain of events that will invariably produce the same output from a given starting condition or state), in which the extracellular deposition of fibrillar Aβ (that is, amyloid) is the causative event and is followed by intracellular aggregation of hyperphosphorylated tau, synaptic dysfunction, neurodegeneration, cognitive dysfunction and, finally, loss of autonomy (that is, dementia)[4,5]. Some other diseases fit a deterministic model, such as certain cancers, in which a cancerogenic event always entails uncontrolled cell proliferation that is invariably followed by clinical cancer with final organ failure. For example, in chronic myeloid leukaemia, one single genetic event (that is, a fusion gene, *BCR–ABL1*, formed by a translocation between chromosomes 9 and 22) is necessary and sufficient (that is, conferring a 100% lifetime risk) to induce neoplastic proliferation. Interfering with the signalling pathway activated by *BCR–ABL1* using tyrosine kinase inhibitors is an extremely effective therapeutic strategy at almost any disease stage[6].

While the cornerstones of the amyloid hypothesis are supported by substantial evidence derived largely from autosomal dominant AD, Down syndrome, and cellular and animal models based on autosomal dominant mutations, its current formulation fails to account for a number of clinical and preclinical observations. The amyloid hypothesis has been heavily criticized[7,8], as has the linear causal dynamics it implies[9]. Alternative models have been based largely on neurobiological arguments, and have failed to gain widespread acceptance in the community[10]. A revision of the amyloid hypothesis that fits the current clinical evidence more closely may help to redirect research and drug development towards more diverse pathways. In this Perspective, we consider supporting evidence for and inconsistencies in the current conceptualization of the amyloid hypothesis, and present an alternative model. We primarily leverage evidence from clinical studies and use preclinical findings as secondary evidence.

The amyloid hypothesis

Supporting evidence

The amyloid hypothesis of AD originated from evidence in Down syndrome[11] and autosomal dominant AD, in which the proteins encoded by genes whose mutations are causative of familial AD — that is, mutations in *PSEN1* (encoding presenilin 1 (PSEN1)), *PSEN2* (encoding presenilin 2 (PSEN2)), or *APP* (encoding amyloid precursor protein (APP) — are unambiguously involved in the metabolism of brain Aβ[2]. These pathogenic mutations increase the production of $A\beta_{42}$ — the form of Aβ most associated with AD — from APP or alter the $A\beta_{42}/A\beta_{40}$ ratios, both of which are thought to cause the deposition of $A\beta_{42}$ into cortical plaques. *PSEN1*, *PSEN2* and *APP* mutations have nearly 100% penetrance, and cognitive impairment almost invariably develops in people who carry these mutations[12]. Conversely, a protective mutation in *APP* (A673T, the Icelandic mutation) can reduce the risk of AD by decreasing the production of Aβ[13].

The estimated prevalence of autosomal dominant AD is less than 1%[14,15], with the vast majority of AD cases being sporadic; that is, determined by the effects of many genes (of which the apolipoprotein E (APOE) gene (*APOE*) is the most important[16]), environmental exposures and unknown factors. Nevertheless, it has been assumed that the amyloid hypothesis, as formulated on the basis of evidence from autosomal dominant AD and Down syndrome, is also applicable to sporadic AD. In the following sections we report some of the supporting evidence for the amyloid hypothesis.

The neuropathologies of autosomal dominant and sporadic AD are similar.— Autosomal dominant AD and sporadic AD cases with comparable disease duration are similar in terms of their Consortium to Establish a Registry for Alzheimer's Disease (CERAD) scores and their diffuse plaque scores[17]. Even Lewy body pathology, the pathognomonic lesion in Parkinson disease and a common pathological co- morbidity in AD, is similar between autosomal dominant AD and sporadic AD (being present in 27% of autosomal dominant cases and 31% of sporadic cases)[17], even though the metabolism of α-synuclein (the major component of Lewy bodies) is not affected by PSEN1, PSEN2 or APP.

Evidence of a temporal sequence of events.—A large body of evidence supports the notion of a chronological ordering of the major pathophysiological events, starting with deposition of Aβ in plaques and followed by aggregation of hyperphosphorylated tau into tangles, leading to neurodegenerative changes and, finally, cognitive impairment[18].

AD-related tau pathology spreads extensively from the medial temporal lobe to neocortical areas in the presence of Aβ, suggesting a facilitating role for Aβ in the development of tau pathology[19]. In animal models, evidence has been found that overexpression of APP accelerates the development[20,21] and propagation[22] of AD pathology. Human induced pluripotent stem cells develop tau pathology following the introduction of *APP* and *PSEN1* mutations found in familial AD, suggesting that Aβ can lead to tau pathology in this model[23]. Conversely, Aβ immunotherapy reduces tau load in one mouse model[24].

Individuals with detectable amyloid pathology but no detectable tau pathology (A^+T^- individuals), according to established cut-offs, are relatively frequent in the population (that is, they constitute 25% of cognitively unimpaired individuals and 28% of people with mild cognitive impairment (MCI)), whereas A^-T^+ individuals are exceedingly rare, accounting for 1% of cognitively unimpaired people and 3% of individuals with MCI[25]. This supports the hypothesis that extensive neocortical tau spread starts when Aβ has already been deposited.

There is evidence that tau pathology leads to neurodegeneration. The intensity and topography of tau deposition as revealed by positron emission tomography predicts future atrophy[26]. Tau accumulation in neurons leads to neurofibrillary tangle formation, and such neurofibrillary tangle- bearing neurons die in the course of the disease as indicated by ghost tangles[27]. Recently, it was shown that tau aggregates drive granulovacuolar degeneration, an AD- related pathological lesion associated with neuronal loss and expressing markers of the

activated necrosome[28,29]. Necrosome activation is indicative of necroptosis, a programmed form of necrosis[30,31].

The effect of tau on cognition seems to be mediated by neurodegeneration. Several studies have shown associations between tau pathology and cognition. In cognitively unimpaired elderly people, AD-like memory decline is associated with Aβ and tau deposition, and is predicted by hypometabolism in AD-specific cortical regions[32]. When neurodegeneration is taken into account in a formal mediation analyses, the association between tau and cognition disappears for some cognitive functions (semantic memory and visuospatial functions)[33]. This suggests that the effect of tau deposition is largely mediated by neurodegeneration, and supports the causal chain of tau deposition leading to neurodegeneration, which in turn leads to cognitive impairment[33].

Evidence of anti-Aβ and anti-tau drug effects.—In people with sporadic AD, aducanumab (an anti-Aβ monoclonal antibody) strongly reduced brain amyloid plaque load[34]. Two twin phase III clinical trials, EMERGE and ENGAGE, were designed to evaluate the efficacy and safety of aducanumab in patients with either MCI owing to AD or mild AD dementia[35,36]. Interestingly, a decrease in the level of phosphorylated tau (p-tau) in the cerebrospinal fluid (CSF) and temporal tau tracer retention on positron emission tomography was observed in patients taking aducanumab[37]. Decreases in CSF p-tau and total-tau levels were also observed in patients taking the anti-Aβ monoclonal antibody gantenerumab[38] or the anti- tau vaccine AADvac1 (REF.[39]). In addition, gantenerumab attenuated increases in the levels of neurofilament light polypeptide (a marker of neurodegeneration) in the CSF[38], and AADvac1 reduced CSF levels of neurofilament light polypeptide and brain atrophy[39]. Even though full datasets for the trials involving these drugs have not been published yet, these results suggest that it is possible to reduce tau pathology and, potentially, neurodegeneration by targeting amyloid pathology, supporting a causal relationship between Aβ deposition and tau deposition.

For the first time in the history of phase III AD clinical trials of disease-modifying drugs, the EMERGE trial showed that patents taking the drug under study — a high dose of aducanumab for 78 weeks — exhibited a reduction in clinical decline (that is, −22% on the Clinical Dementia Rating Scale Sum of Boxes (CDR-SB)) compared with those taking placebo[37]. Even though the magnitude of the effect was minor (-0.39 CDR-SB points at 78 weeks[37]), it was achieved in a clinically symptomatic population in which individuals had probably been exposed to Aβ for an extended period[40,41]. The reduction of amyloid load and slowing of disease progression associated with an Aβ-clearing treatment were confirmed in phase II trials of the anti-Aβ monoclonal antibodies lecanemab and donanemab[42,43]. Clinical trials with similar drugs are ongoing in asymptomatic individuals with AD pathology, but the results will not be available for a few years[44,45].

A^+T^+ individuals show relatively stereotypical features of disease—Decades of research have demonstrated a relatively consistent transition from preclinical to clinical stages in individuals with Aβ and tau pathology. Compared with A^-T^- individuals, A^+T^+ individuals exhibit a higher prevalence of *APOE* ε4 (REFS[46–48]; the strongest genetic risk factor for AD), older age[46–49], a more frequent concurrent clinical diagnosis of MCI

or prodromal AD[46], poorer global cognition[46,47,49,50], a predominantly amnestic cognitive profile[46,49,50], increased posterior temporoparietal atrophy[51] and elevated risk of future cognitive decline[46–49] and dementia[48,52].

Evidence of amyloid toxicity in other forms of amyloidosis.—Aβ is not the only amyloidogenic peptide or protein that causes a disease. In transthyretin (TTR) amyloidosis, TTR accumulates in cerebral blood vessels, in a similar way to Aβ, and in other organs, owing to a mutation in *TTR* that destabilizes the physiological TTR tetramer, leading to misfolded monomers that aggregate into amyloid fibrils. Treatment with protein stabilizers has been successful in patients with TTR amyloidosis. The TTR amyloid shows aggregation properties similar to those of Aβ and other amyloidogenic proteins. Thus, TTR amyloidosis is the proof- of- principle that amyloid formation can cause a clinical disorder that can be successfully treated by inhibiting the formation of amyloid aggregates[53]. A similar rationale could be translated to AD- related Aβ-amyloidosis.

Evidence against

Although there is evidence supporting the amyloid hypothesis, there is equally compelling evidence that does not support it, at least in the way that it is currently articulated.
The amyloid hypothesis predicts that tau deposition will not happen in the absence of amyloid, A^-T^+ individuals should be, at most, rare, tau should colocalize with amyloid, A^+T^+ individuals should invariably develop neurodegenerative changes and cognitive impairment, and anti-Aβ and anti-tau treatments should halt or greatly slow the progression of neurodegeneration and cognitive impairment. The following sections provide evidence against these predictions and, in consequence, falsify the current articulation of the amyloid hypothesis.

Reports of tau positivity in the absence of amyloid.—As previously mentioned, the observed prevalence of A^-T^+ individuals is low if the established stringent cut- offs for tau positivity are applied. However, with use of more liberal cut-offs, earlier regions of interest (for example, tau deposition limited to the transentorhinal region or Braak stage I/II) or more sensitive tau positron emission tomography tracers, the presenceof A^-T^+ has been found in up to 45% of individuals without dementia[50,54,55] This condition is referred to as ‘primary age- related tauopathy’[56] and is sometimes considered a variant of AD[57], undermining the initiating role of Aβ in the cascade.

At odds with the findings of imaging studies, which have generally been taken to indicate that Aβ deposition precedes tau deposition, neuropathology studies have supported the opposite sequence. Large cross- sectional autopsy studies have shown that tau pathology is found at young ages (that is, 21–40 years), when Aβ plaques are absent, in the brainstem and locus coeruleus; this pathology then expands into further subcortical nuclei and the entorhinal cortex. In these studies, individuals exhibiting only Aβ plaques in the absence of neurofibrillary tangle pathology were in a minority compared with individuals with tau pathology lacking Aβ deposition[58,59]. This finding argues against a deterministic model in which Aβ is the cause of tau pathology. Rather, this finding is consistent with the notion that pre-existing age-related tauopathy is a prerequisite for Aβ to act as driver for the spread

of tau to the neocortex[59]. This may also explain why even people with autosomal dominant AD, in which the overproduction and deposition of Aβ are substantial, do not develop symptoms before 30–60 years of age. Indeed, this is the age when a considerable proportion of individuals exhibit age-related tau deposition mainly in the transentorhinal and entorhinal cortex of the medial temporal lobe[58].

In mutant APP transgenic mice that overexpress Aβ, severe Aβ plaque pathology is not accompanied by significant tau or neurofibrillary tangle pathology[60–62]. Indeed to promote accelerated tau pathology by Aβ in transgenic mice, a minimum of pre- existing tau pathology, as present in double Aβ and tau transgenic animals, is required[20]. Recently, a molecular link between Aβ and tau was identified, namely the cellular prion protein (PrP^C). In animal and cellular models, binding of Aβ and p- tau to PrP^C is associated with accelerated spreading of tau pathology, which leads to toxic effects[22,63]. In humans, both Aβ and p- tau bind to PrP^C[22]. As PrP knockdown in APP transgenic mice leads to improved performance of the animals in cognitive tests[64], the critical involvement of proteins other than just Aβ argues against the pathogenesis of AD being driven solely by Aβ.

The ‘spatial paradox’ of the spread of amyloid and tau pathology.—If tau pathology. causally follows Aβ deposition, at least some degree of colocalization of tau deposition within amyloid- rich regions might be expected. The observations that Aβ and tau initially deposit in different brain regions (that is, Aβ in the neocortex and tau in the brainstem and (trans)entorhinal cortex) and that the topographical spreading patterns of Aβ and tau over time overlap only minimally[65,66] are inconsistent with the amyloid hypothesis[19,58]. No comprehensive and persuasive explanation has been offered so far for this discrepancy, but a role for APOE4 in the toxicity of both Aβ and p-tau has been suggested[67].

The rarity of A+T+ Braak stage V/VI cases without co-morbid pathology.—AD pathology is often contributory and less commonly the sole cause of dementia in autopsy series of patients with dementia. A recent pathology study of 375 brains showed that in individuals with dementia, the prevalence of isolated amyloidosis associated with tauopathy sufficiently extensive to justify the dementia (Braak stage V/VI) is below 20%[68]. Even when any severity of tauopathy is allowed (Braak stage I or higher) in association with plaques, the combination of plaques and tangles without other pathology accounts for barely 30% of dementia cases[68]. About two-thirds of patients with dementia show co-morbid molecular pathology in addition to plaques and tangles, namely Lewy bodies of α-synuclein aggregates, insoluble aggregates of TAR DNA-binding protein 43 (TDP43) or both[68]. Vascular pathology is also frequently co-morbid with neuropathological changes in AD[69]. Moreover, in people with AD, *APOE* ε4 carriers have 2.5 times greater odds of having quadruple brain pathologies (plaques, tangles, Lewy bodies and TDP43 aggregates) than non-carriers[68].

The lifetime risk of cognitive deterioration in A+T+ cases.—The amyloid hypothesis implies that cognitive deterioration is the invariable end point of Aβ accumulation if people live long enough to reach the final steps of the cascade. However, the cumulative incidence of dementia (corrected for age, sex, education and *APOE* genotype)

in cognitively unimpaired A^+T^+ individuals aged 74 years is less than 20% after 5 years of follow-up and less than 50% after 14 years of follow-up[49]. This observation indicates that being A^+T^+ is not a strong predictor of cognitive decline. Of course, it could be argued that the process of the Aβ cascade is slow, and that if follow-up were more extensive, the lifetime risk would approach 100%. However, data are currently not available to confirm or reject this hypothesis.

The extent of the clinical effects of anti-Aβ drugs is uncertain.—If AD fitted a deterministic model, treatment at the preclinical stage would interrupt the disease process and prevent clinical manifestations, whereas treatment at the symptomatic stage would be expected to at least halt clinical deterioration. This would hold true especially in the presence of good target engagement; that is, the clear reduction in Aβ production and the significant reduction in plaque load that follows treatment with β-site APP-cleaving enzyme 1 (BACE1; also known as β-secretase 1) inhibitors and anti-Aβ immunotherapies[34,70]. Halting clinical deterioration is indeed the effect of imatinib in chronic myeloid leukaemia, a drug that works as a specific inhibitor of tyrosine kinases, targeting oncogenic signalling cascades. Treatment with imatinib is necessary and sufficient to treat chronic myeloid leukaemia at any disease stage[71].

By contrast, the many trials with anti-Aβ drugs conducted so far in AD have almost invariably failed to even slow, never mind halt, cognitive deterioration. In the DIAN-TU trial in autosomal dominant AD[72], the monoclonal antibodies gantenerumab and solanezumab reduced amyloid load, indicating target engagement[38,73], but they had no effect on cognitive decline[74].

In sporadic AD, the 22% reduction in clinical decline associated with aducanumab treatment that was observed in the EMERGE trial was a barely significant effect, despite the agent's drastic effect on amyloid load, consisting of almost normalization of amyloid load[37]. Moreover, the top-line results of the ENGAGE trial did not show any effect on clinical decline even in patients taking high-dose aducanumab (that is, +2% of CDR-SB, corresponding to +0.03 CDR-SB points, as compared with placebo after 78 weeks)[37]. In a phase II trial with the anti-Aβ monoclonal antibody lecanemab, cognitive decline was slowed by as much as 47%, as assessed on the cognitive scale ADAS-Cog14, although this was a secondary outcome of the study[75]. The anti-Aβ monoclonal antibody donanemab hit its primary outcome in a phase II trial by delaying clinical progression by 32%, although results on secondary outcomes were mixed[43].

These observations suggest that, even assuming the best-case scenario for lecanemab in terms of its beneficial effect on cognitive decline, more than 50% of the clinical progression is independent of Aβ deposition, and sets the stage for alternative explanations and understanding the role of non-anti-Aβ therapies.

Topographically atypical cases.—Approximately 25% of AD cases deviate from typical AD in terms of the localization of neurodegeneration and the associated cognitive profile[76]. Atypical clinical presentations include posterior cortical atrophy (the 'visual' variant), logopenic primary progressive aphasia (the 'language' variant), the behavioural/

dysexecutive variant (or the 'frontal' variant) and the corticobasal variant. These atypical presentations might be due to genetic[77,78], neurodevelopmental[79,80] or unknown factors affecting the cascade before or after Aβ deposition, supporting the notion that the outcome of the amyloid cascade can be heavily modulated. Among the genetic factors, *APOE* stands out as a powerful modifier of the amount and topography of Aβ and tau deposition, as well as of clinical presentation, as discussed later. The topography of pathology is even more atypical in autosomal dominant AD, in which deposition of Aβ in the basal ganglia happens as early as 10 years before expected symptom onset[81]. In people with sporadic AD, Aβ deposition in the striatum follows Aβ deposition in the cortex by many years[82].

Cascade the other way around: head injury.—An alternative to Aβ aggregation causing neuronal damage might be that neuronal damage is upstream of Aβ deposition. Results from animal models of AD show that axonal defects can precede Aβ deposition and promote the amyloidogenic process[83]. Animal experimental studies on head injury, in which axonal damage is the main lesion, show accumulation of APP, BACE1 and PSEN1 in damaged axons, followed by an increase in Aβ aggregation and plaque formation[84]. Furthermore, autopsy and biopsy studies in patients with severe traumatic brain injury show extensive cortical Aβ deposition in the subacute phase after trauma, including in individuals as young as 35 years[85,86].

The probabilistic model of AD

The current amyloid hypothesis considers Aβ deposition to be the causative agent of AD pathophysiology, being necessary and sufficient to initiate the cascade, and predicts that clinical symptoms invariably develop as the final stage. Here we propose an alternative model in which Aβ is still a key factor in AD pathophysiology, but that stipulates that the penetrance of the amyloid cascade is directly proportional to the penetrance of genetic risk factors (FIG. 1). This probabilistic model identifies three variants of the disease in which stochastic factors play an increasingly relevant role: autosomal dominant AD, *APOE* ε4-related sporadic AD and *APOE* ε4-unrelated sporadic AD. The model allows stochastic factors to account for the variability among variants of molecular pathology, onset and progression of neurodegeneration, age at clinical onset, biomarker and clinical features, and lifetime risk (FIGS 1,2). It should be acknowledged that although the proposed variants feature specific characteristics, a certain degree of overlap exists in their pathological and clinical features. The following sections outline the major arguments in favour of the probabilistic model.

Autosomal dominant AD

The deterministic view of the amyloid hypothesis fits reasonably well autosomal dominant AD, albeit imperfectly. Indeed, *PSEN1*, *PSEN2* and *APP* mutations have nearly 100% penetrance as cognitive impairment develops almost invariably in individuals with these mutations[12] (FIG. 1). The typical age of dementia onset is 35–55 years for *PSEN1* mutations, 45–65 years for *PSEN2* mutations and 45–60 years for *APP* mutations[87]; the duration of symptoms (before death) is around 10 years for all of these mutations[88] (FIG. 2). Individuals with a *PSEN1*, *PSEN2* or *APP* mutation feature the following characteristics:

deposition of Aβ in the caudate nucleus[81,89] and large parts of the frontal, parietal, temporal and occipital neocortex, sparing the superior frontal, medial temporal and medial occipital regions[90]; deposition of tau that largely overlaps with deposition of Aβ in the lateral frontal, temporal, parietal and occipital cortices but spares the mesial frontal and sensorimotor cortices and, rather, involves the medial temporal cortex[91]; neurodegeneration in the lateral temporal, parietal and occipital cortices, medial parietal and medial temporal cortices and medial occipitotemporal gyrus[81,90,92]; and amnesic-predominant cognitive impairment[12,81] (FIG. 1; TABLE 1). Moreover, such individuals also feature variable TDP43 burden[93,94] in the hippocampus and amygdala[93], α-synuclein pathology[94–96] in the amygdala[96], cerebral amyloid angiopathy (CAA)[97,98] with capillary involvement (CAA type 1) or without capillary involvement (CAA type 2)[17], and neuroinflammation associated with tau and Aβ[99] (TABLE 1).

Even among cases of autosomal dominant AD there is marked variability in the age of onset, neuropathology and clinical phenotype, suggesting that unknown stochastic factors are at play (FIG. 1). Indeed, in individuals with *PSEN1* mutations, only 72% of the variance in dementia onset is explained by the mutations[100], and around 16% of symptomatic *PSEN1* mutation carriers have atypical presentations, including behavioural changes, language impairment, dyscalculia and dysexecutive syndrome[100]. Moreover, a recent description of a *PSEN1*-mutation carrier who did not develop cognitive impairment until she was in her 70s (nearly three decades after the typical age of onset) confirms the role of *PSEN1*-independent factors in influencing the course of disease even in autosomal dominant AD[101]. Imaging investigations in this patient showed a high Aβ burden but limited brain tau deposition and neurodegeneration as well as relatively preserved cognition. A protective effect has been proposed for the two copies of the *APOE* ε3 Christchurch (R136S) mutation that this patient was carrying[101], but other genes are likely to be at play[102]. There is evidence that physical activity may delay symptom onset by 15 years even in autosomal dominant AD[103].

Taken together, these observations indicate that despite the high penetrance, stochastic factors markedly affect the clinical phenotype in autosomal dominant AD (FIG. 1).

APOE ε4-related sporadic AD

The prevalence of the *APOE* ε4 allelic variant is 14% in cognitively unimpaired individuals and 38% in people with AD[104], and increases to 64% in patients with amyloid- positive MCI and 66% in patients with AD dementia[105]. Different studies set the average age of dementia onset as 73–74 years in individuals with *APOE* ε4/ε4, 75–81 years in individuals with *APOE* ε3/ε4, and 76–82 years in individuals with *APOE* ε2/ε4 (REFS[106,107]) (FIG. 2). In general, it is widely accepted that carrying the *APOE* ε4 allele reduces the age of onset by about 12 years[108–110]. Although the *APOE* ε4 allele is strongly associated with a family history of dementia[111], inheritance does not follow an autosomal dominant pattern, as is the case for *APP*, *PSEN1* and *PSEN2* mutations, in which the disease is transmitted from generation to generation with a probability of 50% in the offspring of mutation carriers. Since its identification, *APOE* has been regarded as a risk factor for sporadic forms of AD dementia[112].

Several clinical and epidemiological observations suggest that *APOE* ε4 identifies a relatively distinct clinicopathological entity, as summarized next.

The burden and topography of pathology differs by APOE genotype.—In sporadic AD and irrespective of *APOE* genotype, Aβ deposition occurs first in the limbic cortex and extends posteriorly and dorsally into the precuneus and paracentral cortex and anteriorly and mesially to the orbitofrontal cortex[113]. Despite some inconsistent reports, possibly due to studies capturing different stages of the dynamic spread of Aβ deposition[114,115], most evidence indicates that *APOE* ε4 carriers show Aβ deposition at an earlier age than *APOE* ε4 non- carriers[116], and have a greater overall burden of Aβ pathology[117,118] located mainly in the anterior and mesial frontal cortex[117]. They also feature more severe CAA[119] with capillary involvement (CAA type 1)[120–123]. Conversely, APOE ε4 non-carriers feature preferential distribution of Aβ in lateral parietal regions[117], and CAA lacking capillary involvement (CAA type 2)[120–123] (FIG. 1; TABLE 1). Again irrespective of the *APOE* genotype, in people with AD, tau deposition is typically observed in large parts of the frontal, parietal, temporal and occipital neocortex, sparing the visual and sensorimotor regions[124], with neurodegeneration largely overlapping with tau deposition[125]. When *APOE* ε4 status is taken into account, carriers feature a lower overall burden[126] and less widespread[126,127] tau pathology and neurodegeneration than non-carriers, preferentially affecting the medial temporal structures[126–128]. Conversely, *APOE* ε4 non-carriers show greater tau deposition and atrophy in frontal[127,129] and parietal[126,127] cortices (FIG. 1; TABLE 1). Finally, *APOE* ε4 is also associated with increased risk of TDP43 proteinopathy in elderly individuals[130] and increased CSF α-synuclein levels[131] (TABLE 1).

The profile of cognitive impairment differs by APOE genotype.—*APOE* ε4 carriers show a disproportionately more severe impairment in memory than *APOE* ε4 non-carriers, who are relatively more impaired in executive function, visuospatial abilities and language[127] (FIG. 1; TABLE 1). In line with this, a recent study of patients with a pathologically confirmed diagnosis of AD found that individuals with an amnesic dementia phenotype were 2.5 times more likely to be *APOE* ε4 carriers than individuals with the primary progressive aphasia clinical phenotype[132]. These observations are consistent with the topography of tau pathology and neurodegeneration[127].

The lifetime risk of dementia differs by APOE genotype—Independent studies have reported variable lifetime estimates of AD dementia risk, but the gap between *APOE* ε4 carriers and *APOE* ε4 non-carriers is consistently large (FIG. 1). According to Reiman and colleagues, the lifetime risk of developing AD dementia at 85 years is approximatively 95% for *APOE* ε4/ε4, 90% for *APOE* ε3/ε4, 35% for *APOE* ε2/ε3 and 20% for *APOE* ε2/ε2 (REF.[133]). According to Genin and colleagues, the lifetime risks associated with *APOE* genotypes are 51–68% for ε4/ε4, 22–35% for ε3/ε4, 7–12% for ε3/ε3 and 4–7% for ε2/ε2 and ε2/ε3 combined[134].

Despite the high lifetime risk of the *APOE* ε3/ε4 and *APOE* ε4/ε4 genotypes, stochastic factors play a significant role. Indeed, although *APOE* ε4/ε4 carriers on average develop dementia about 10 years earlier than *APOE* ε2 carriers[107], there is still significant variation

in the age of onset for *APOE* ε4/ε4 carriers (standard deviation of 6 years)[133], consistent with the notion of stochastic protective and risk factors (see later).

The largest genome-wide association study, by the European Alzheimer Disease DNA Biobank, identified 75 loci from almost as many genes implicated in AD[135]. Most of these variants are common, and although individually they have a relatively small effect on disease risk, the additive effect is relatively large. Numerous studies have found that these non-*APOE* AD genes may also affect the age of onset[136–138]. According to the law of Mendelian segregation in populations, these genes will be transmitted independently from *APOE* ε4 in the population. This leads to a large number of combinations of genetic variants that co-occur with *APOE* ε4 in the population, leading to stochastic variation in the age of onset in *APOE* ε4 carriers. Moreover, some people with the *APOE* ε4/ε4 genotype may even escape AD dementia. For example, the Dutch 100-plus Study reported a centenarian who stayed cognitively healthy despite having an *APOE* ε4/ε4 genotype[139]. Similarly to the interaction of *PSEN1* with the *APOE* ε3 Christchurch mutation, the effect of *APOE* ε4/ε4 homozygosity may be modulated by both non-*APOE* genetic variants associated with AD and environmental exposures (see later). A similar phenomenon is known in the field of vascular diseases, in which individuals featuring supernormal vascular ageing (SUPERNOVA) have been described who do not show age-dependent increased arterial stiffness in spite of a heavy cardiovascular risk factor burden[140,141]. Epigenetic mechanisms have been invoked to explain the SUPERNOVA phenomenon[142].

Amyloid-associated risk for dementia differs by APOE genotype.—Amyloid positivity and *APOE* ε4 carriage individually increase the risk of progression to MCI or dementia in a similar way (hazard ratio of 2.0 and 2.1, respectively, after 8 years)[143]. However, their interaction shows that A^+ *APOE* ε4 carriers have the greatest risk of progression (hazard ratio 4.5), while the risk for amyloid-positive *APOE* ε4 non-carriers (hazard ratio 1.1) is similar to that for amyloid-negative *APOE* ε4 non-carriers[143]. This observation suggests the presence of a benign or a malign brain amyloidosis, according to its association with the *APOE* ε4 allele.

The influence of APOE ε4 on dementia risk declines after the age of 70 years.—The risk of dementia associated with the *APOE* ε4 allele is maximal between 55 and 70 years, and decreases afterwards[144,145]. This is consistent with the age of symptom onset of *APOE* ε4 carriers, and with the notion that the pathogenetic impact of non-AD co-morbidity increases at older ages[146], thus diluting the effect of *APOE* ε4.

Potential mechanisms—A number of neurobiological mechanisms have been proposed that might account for the specific effect of the *APOE* ε4 variant on the neurodegenerative process of AD. First, it has been proposed that APOE plays a major role in Aβ clearance. APOE binds Aβ[147] and transports it across the blood–brain barrier into the blood, facilitating its perivascular clearance[148,149]. Differences in the efficiency of this process among isoforms, the APOE4 isoform being the least efficient[149], may explain Aβ accumulation in the brains of *APOE* ε4 carriers over time and the consequent greater risk of AD pathology. Genetic studies of Aβ levels in blood showed that *APOE* genotype is the most significant determinant of $A\beta_{42}$ and the $A\beta_{42}/A\beta_{40}$ ratio, while mutations in

BACE, APP and *PSEN2* are significantly associated with higher $A\beta_{40}$ levels[150]. Of note, an association with Aβ levels in blood is found for other non-*APOE* genes[150].

Second, it has been proposed that *APOE* ε4 drives multiple AD-associated proteinopathies. In addition to its role as a regulator of Aβ deposition[14], recent studies indicate that the *APOE* ε4 genotype is associated with the deposition of tau[67,151], α-synuclein[152,153] and TDP43 (REF.[154]), independently of Aβ deposition (FIG. 1; TABLE 1). When hybridized with tau transgenic mice, *APOE* ε4 mice develop more tangles than *APOE* ε3 mice[67,151]. Similarly, when crossed with A53T α-synuclein transgenic mice, *APOE* ε4 mice develop more α-synuclein pathology[152]. In both the tau model[67] and the α-synuclein model[153], neurodegeneration was accelerated by *APOE* ε4. In humans, *APOE* ε4 is associated with increased TDP43 burden, and with higher odds of hippocampal sclerosis and late-life cognitive impairment independent of Aβ pathology[154]. These data indicate that multiple proteinopathies might be an integral component of *APOE*-related neurodegeneration, and that, differently from *PSEN1*, *PSEN2* and *APP* mutations, *APOE* ε4 has effects on pathologies other than AD.

Third, *APOE* ε4 may drive vascular deficits and blood–brain barrier dysfunction. *APOE* ε4 carriers exhibit an increase in blood–brain barrier breakdown in the hippocampus and medial temporal lobe, independent of tau and cortical Aβ burden[155], and APOE4 impairs pericyte function[155,156]. *APOE* ε4 carriers have more severe CAA in the subiculum and entorhinal cortex and more frequent hippocampal microinfarcts than *APOE* ε4 non-carriers[157]. It is unknown to what extent these vascular changes contribute to cognitive impairment in *APOE* ε4 carriers.

Fourth, *APOE* ε4 is proposed to have adverse effects on brain structure and metabolism and cognition across the lifespan. There is consistent evidence that *APOE* ε4 adversely affects brain structure in infants[158], and brain metabolism[159] and cognition[160] in midlife, well before the onset of AD- type pathology. A similar impact on brain metabolism has also been observed in younger adults[161].

Last, *APOE* may have a role in the innate immune response in AD. *APOE* ε4 carriers show higher neuroinflammatory levels than non-carriers[14,162,163]. This observation might explain the proinflammatory state often reported in some patients with AD[164–166], and the direct association of neuroinflammation with tau and Aβ pathology in *APOE* ε4 carriers[99,167–170].

As is the case for *APOE* ε4, rare and relatively highly penetrant AD risk genes such as *TREM2* could identify other AD variants with specific clinical and biological characteristics, but the low prevalence of carriers in clinical series has so far prevented any meaningful clinicopathological characterization or classification of AD subtypes driven by these genetic variants.

APOE ε4-unrelated sporadic AD

About 30–40% of individuals with amyloid-positive AD do not carry *APOE* ε4 (REF.[105]), and their average age of dementia onset ranges between 80 and 82 years in *APOE* ε3/ε3 cases to between 82 and 85 years in *APOE* ε2/ε2 and *APOE* ε2/ε3 cases[106,107] (FIG. 2). In

these patients, the amyloid cascade as described earlier herein does not differ significantly from that of autosomal dominant AD or *APOE* ε4-related sporadic AD, but a number of known and unknown modulating factors heavily influence the chain of events at all steps of the cascade (FIG. 1), making the disease process and clinical manifestations less predictable. Indeed, various lines of evidence from epidemiology, genetics, neuropsychology and biomarker studies support this view.

Non-APOE genes account for relatively few AD cases.—The genetic landscape of AD includes more than 60 genes other than APOE[171]. Twin studies have allowed estimation of the proportion of AD cases attributable to genetic factors as about 60–80%, while about 20–40% can be attributed to environmental factors[172,173]. *APOE* ε4 accounts for the largest share of the genetically attributable proportion, while non-*APOE* ε4 genes account for a minor share[174]. Indeed, a polygenic risk score, which takes into account a combination of risk loci, can discriminate individuals with AD and controls with an area under the curve of 75–84% (the remaining part being environmental risk factors or undiscovered genetics such as de novo mutations and/or rare variants), while *APOE* alone is able to discriminate them with an area under the curve of ~70%[174].

It must be acknowledged, however, that knowledge of the effect of non-*APOE* genetic variants has increased just recently as a result of large multicohort studies. Indeed, a recent study of 13,959 patients with AD and 35,600 controls found that the dementia risk of individuals in the top decile of a full polygenic risk score (including *APOE*) is 57%, while the risk associated with *APOE* ε4 alone is 44%[175]. Interestingly, when *APOE* is removed from the polygenic risk score, the disease risk of individuals in the top decile drops to 36%[175], a still substantial risk. Future studies of even larger cohorts may lead to a larger share of the attributable proportion of AD dementias being assigned to non-*APOE* genetic variants.

Genes other than APOE modulate APOE ε4-related risk.—Population-based studies have found that non-*APOE* genetic variants interact with *APOE*, for example, modifying the risk[136–138] and age of onset of dementia[136,137]. In the Rotterdam Study and International Genomics of Alzheimer's Project cohorts, non-*APOE* genetic variants account for 7–10 years of the variability of the age of onset in *APOE* ε4 homozygotes[136]. This suggests that non-*APOE* gene pathways may biologically interact with the *APOE* pathway.

Non-Aβ pathways are involved in AD pathophysiology.—The non-*APOE* genes described so far encompass multiple biochemical pathways, some of which are associated with neuroinflammation and cholesterol metabolism (for example, *TREM2*)[176,177], *ABCA7* (REF.[178]), *PLCG2* (REF.[179]) and *CLU*[180]. Other described non-*APOE* genes, such as *CR1* and *CD33*, are associated specifically with the innate immune system. Together, these data suggest that all the pathophysiological pathways mentioned earlier herein may, under certain conditions, contribute substantially to AD risk[181].

A formal pathway analysis was conducted in a genome-wide association study of the International Genomics of Alzheimer's Project for the common and rare variants separately (frequency 0.01 or greater and less than 0.01, respectively)[182]. Four function clusters were

seen for the common variants, including APP metabolism and Aβ formation; tau protein binding; lipid metabolism (four pathways including protein–lipid complex assembly); and immune response. In line with the interaction of non-*APOE* genes with *APOE*, enrichment of the four clusters remained after removal of genes in the *APOE* region. Interestingly, when genes in the neighbourhood of *APOE* and other highly significant non-*APOE* genes were removed, tau protein binding, lipid metabolism and immune-related pathways remained significantly associated, suggesting that non-*APOE* genes are involved in these pathways[182].

The more recent European Alzheimer's Disease DNA BioBank consortium found very similar pathways (Aβ and hyperphosphorylated tau deposition, lipid metabolism and innate immunity, including macrophage and microglial cell activation)[135]. Its pathway analysis showed that genes in the Aβ pathways with the highest microglial expression show the strongest association with AD, suggesting a functional relationship between microglia and Aβ pathways[135].

Protective genes.—While *APOE* ε4 confers an elevated risk of AD, *APOE* ε2 has a protective effect[133,174]. Indeed, when compared with the *APOE* ε3/ε3 genotype, *APOE* ε2/ε2 and *APOE* ε2/ε3 have significantly lower AD odds ratios (0.13 and 0.39, respectively)[133]. Such odds ratios are much smaller when the reference is *APOE* ε4/ε4 (0.004 for *APOE* ε2/ε2 and 0.012 for *APOE* ε2/ε3)[133], consistent with high risk and high protection effects rather than an extreme effect of either of the genotypes. Other protective mutations and genes have been reported — for example, a mutation in *APP* (encoding A673T)[13], *PLCG2* (REFS[183,184]), *BDNF*[185], KL (which encodes klotho)[186], *TMEM106B*[187] and *POT1* (REF.[188]) — but the magnitude of the protection in each case has not yet been accurately estimated.

Lifestyles and vascular risk factors.—The Lancet Commission on Dementia Prevention, Intervention, and Care estimated that 40% of all cases of dementia are due to 12 modifiable risk factors. Of these, five are known to be general vascular disease risk factors (that is, hypertension and obesity in midlife, and smoking, physical inactivity and diabetes in later life) and seven are more specific to dementia (that is, lower education level in early life; hearing loss, traumatic brain injury and alcohol abuse in midlife; and depression, social isolation and air pollution in later life)[173]. As the *APOE* ε4 allele is the major genetic risk factor for sporadic AD, the influence of modifiable risk factors might be greater in the *APOE* ε4-unrelated variant than in the *APOE* ε4-related one, and this difference can be attributed to other modifiable or unknown genetic risk factors. Consistently, results from the population- based Rotterdam Study showed that favourable modifiable-risk profiles were associated with a lower risk of dementia only in *APOE* ε4 non-carriers, while no effect of modification was observed in *APOE* ε4 carriers[189]. Nevertheless, contrasting observational and intervention results have also been reported, indicating that lifestyle changes may be associated with decreased dementia risk also among people with a high baseline genetic risk[190] and identifying better cognitive outcomes of a multidomain intervention (diet, exercise, cognitive training and vascular risk monitoring) in *APOE* ε4 carriers[191].

Microbiota—Preliminary evidence suggests a role for the gut microbiota in AD pathogenesis[192–194]. Differences in the abundance of proinflammatory and antiinflammatory

taxa have been described in amyloid- positive and amyloid- negative patients with cognitive impairment[165], and they might be involved in the central and peripheral inflammatory state often reported in AD. It is not known whether there is an association between specific bacterial taxa and *APOE* genotype.

Resistance and resilience—Different combinations of the risk and protective factors described earlier herein can co-occur in the same individual, summing up to that person's ultimate risk of developing neurodegeneration and dementia. The complex interplay of risk and protective factors has been conceptualized into the notions of resistance, brain resilience and cognitive resilience. 'Resistance' refers to the brain processes underlying the ability to prevent pathology[195], despite the presence of risk factors. 'Brain resilience' refers to the neurobiological processes underlying the ability to better cope with pathology[195]. 'Cognitive resilience' refers to the functional process underlying the individual's ability to sustain a better-than-expected cognitive performance in relation to the degree of pathology[195]. Brain resilience and cognitive resilience can modulate the effect of molecular pathology on neurodegeneration, and can delay the onset of symptoms. Resistance and resilience are at play in all variants of AD, and resilience appears to be largely independent of *APOE* genotype and clinical AD[196], but their weight on the development of neurodegeneration and symptoms might be particularly relevant in the non-*APOE* ε4 sporadic AD variant. Unfortunately, resistance and resilience are theoretical constructs that have so far eluded direct observation. Future studies will need to operationalize them and test their effects in *APOE* ε4 and non-*APOE* ε4 AD variants.

Demographics.—Other variables play a role in the pathophysiology and clinical expression of AD. Indeed, increased age is one of the strongest risk factors for AD, and modulates the association between the *APOE* ε4 genotype and AD dementia, with the magnitude of the risk associated with *APOE* ε4 following an inverted U-shaped curve with a peak at 55–70 years of age[144,145] How age modulates *APOE*-associated risk is far from fully understood. Stochastic theories hypothesize that biological ageing occurs randomly and persistently with time, through random error, free radicals and wear and tear[197]. Others suggest an effect of age-related decline of the immune system[198] that is interwoven with telomere shortening, epigenetic alterations and insulin growth factor signalling. The effect of age comprises the joint effects of genetic and environmental factors discussed earlier herein, in line with studies in animal models that have shown that stochastic factors as well as genetic factors significantly contribute to ageing of nematodes[199]. Given that the late onset of AD dictates that patients have not died early in life, antagonistic pleiotropy has been suggested, implying that certain genes whose functions are beneficial during the reproductive age may exert adverse effects at a later age[200].

Other demographic variables, such as sex and ethnicity, influence the effect of *APOE* ε4. Indeed, women carrying the *APOE* ε4 allele are at greater risk of developing AD than men carrying the *APOE* ε4 allele[201,202], and they show a greater longitudinal reduction of hippocampal volume in the preclinical stage, denoting a stronger effect of *APOE* ε4 in women[203]. Moreover, *APOE* ε4 confers a greater risk of AD dementia in Japanese and white individuals than in African American and Hispanic individuals[144]. Consistently,

African American *APOE* ε4 carriers show lower levels of CSF p-tau and total tau than white *APOE* ε4 individuals[204], suggesting a differential effect of *APOE* ε4 as a function of ethnicity, which might be partially explained by environmental factors and non-*APOE* genetic variability.

Impact

The probabilistic amyloid hypothesis of AD has implications in the clinic and for research. Notably, *APOE* should be considered a major effect modifier in research and drug development. In all clinical and basic research studies, *APOE* should be considered a stratifying variable, not a mere covariate. When resistance to pathology and resilience to cognitive impairment are being investigated, *APOE* ε4-unrelated sporadic AD is the type for which effects are expected be most robust.

In drug development, *APOE* should be given more consideration as a drug target in AD[104]. According to the 2019 AD drug development pipeline, only one drug was targeting APOE-related mechanisms among the 132 under study in humans[44], and only two more APOE-targeting drugs were mentioned in a more recent review[205]. The vast majority of drugs are still targeting Aβ, tau or other disease mechanisms. Research into drugs that target APOE and APOE-related mechanisms should be greatly expanded, and initiatives aiming to repurpose drugs with a potentially APOE- mediated mechanism should be encouraged. A recent report encouragingly showed that APOE immunotherapy reduces amyloid-related pathology while improving cerebrovascular function in mice[206]. As *APOE* ε4-unrelated sporadic AD pathophysiology is driven largely by non-*APOE* factors, and analogous to the treatment of risk factors for vascular diseases, therapeutic interventions in *APOE* ε4 non-carriers should prioritize combined preventive interventions (drugs acting on multiple molecular targets, multiple lifestyle interventions, or combined drug and lifestyle interventions). The major hurdles are the paucity of data on the specificity of response to treatment by *APOE* genotype and the need for combining drugs with individually proven efficacy on cognitive outcomes — which are currently unavailable.

The prevention of AD dementia should rely on reducing the risk rather than treating the disease. The amyloid hypothesis as a deterministic chain of events has understandably led to the unescapable conclusion that the clinical manifestations of AD (MCI and dementia) are but the last stage of a disease that starts much earlier (15–20 years) with Aβ deposition. The notion of preclinical diagnosis, in analogy to many malignant tumours, has been evoked, and criticized[207–209]. The probabilistic amyloid hypothesis does not necessarily imply disease starting before clinical manifestations. It views Aβ deposition and tau deposition as risk factors whence clinical manifestations do not necessarily follow, and ‘disease’ should be reserved for the clinical manifestations, in analogy to vascular diseases such as stroke and myocardial infarction. The clinical challenge is thus not accurate and early preclinical diagnosis, but accurate risk profiling. This will inform risk reduction interventions tailored on individual risk profiles[210].

Research should estimate the risk associated with molecular and lifestyle risk factors by *APOE* ε4 carrier status. Accurate estimates of risk factors will allow stratification into strata

of high, intermediate and low risk, and the devising of targeted interventions. Combined pharmacological (for example, anti-Aβ and anti-tau agents) and lifestyle interventions (for example, nutrition and physical activity) can be envisioned in specific patient populations to reduce both risk factors. Currently available risk estimates come from studies that have accurately investigated either modifiable lifestyle risk factors or molecular pathology, but seldom both, thus preventing accurate estimates of communality[210]. Future studies will need to estimate the risk of incident cognitive impairment and dementia in representative population samples with accurate assessment of both. Protocols for genetic counselling of people who carry one or two copies of the *APOE* ε4 allele and their relatives will need to be developed.

The molecular taxonomy of AD should stratify for *APOE*. The probabilistic amyloid hypothesis stresses the strong modulatory effect of APOE on amyloid-associated and tau-associated risk. The model implies that people should be classified as *APOE* ε4 carriers or non-carriers first, and then profiled according to the ATN framework. *APOE* ε4 carriers will be at greater risk than non-carriers at any ATN stage.

It may be argued that rare and relatively highly penetrant AD risk genes such as *TREM2*, *PLCG2* or *ABI3* could identify other relatively homogeneous high- risk groups with specific clinical and biological characteristics[179]. However, the low prevalence of carriers of the risk alleles in clinical series has so far prevented any meaningful clinicopathological characterization or classification of AD subtypes driven by these genetic variants[136].

AD research should focus on pathways of resilience to AD pathology. Acknowledging the relevance of stochastic factors in AD opens a window of opportunity to modulate mechanisms that might slow the progression of the cascade from pathology to neurodegeneration and from neurodegeneration to cognitive impairment. Interventions that target vesicular trafficking[211], neuroinflammation[212], cell differentiation[196], blood–brain barrier integrity[155] and the microbiota[194] are just a few of the potential strategies.

Developers of disease modifiers should prioritize people with no cognitive impairment. In the clinical trial space, the probabilistic model of AD means treating people with AD pathology when they are still in the preclinical phase. As of 2021, the overwhelming majority of new drugs were still being tested in people with cognitive impairment, with a few exceptions of trials in people without cognitive impairment at risk of AD dementia owing to AD pathology or genetic risk factors (GENERATION trial with the anti-Aβ vaccine CAD106; DIAN-TU-001 with the monoclonal antibodies gantenerumab and solanezumab; rrAD with amlodipine, losartan and atorvastatin; NCT02008357 with solanezumab; and NCT02719327 with omega-3 fatty acid icosapent ethyl)[213]. Individuals with cognitive impairment should be involved in trials only of symptomatic drugs, as supported by the recent success of pimavanserin in people with AD psychosis[214].

Conclusions

Although AD is a multifactorial and heterogeneous disease[215–217], much of the current drug development is driven by a deterministic model of the disease that concentrates

on a single pathway. Progress in drug development is more likely to happen if a less rigid framework for AD pathophysiology is adopted, in which AD is driven by genetic factors of decreasing penetrance (autosomal dominant AD, *APOE* ε4-related sporadic AD and *APOE* ε4-unrelated sporadic AD) and stochastic factors whose weight is inversely related to penetrance. We acknowledge that a probabilistic model may gradually convert into a deterministic one when more knowledge is accrued, and predictions become increasingly accurate. However, the adoption of a deterministic model when knowledge is insufficient can lead to overly simplistic approaches. Adoption of a probabilistic model when knowledge is insufficient for a deterministic one is a more complex, but more informative and conceivably more successful, approach. The adoption of the probabilistic amyloid hypothesis will have implications for drug development, clinical and basic research, and clinical taxonomy. Future research embracing this model might make sense of the many conflicting findings that are currently slowing progression towards the effective prevention and treatment of AD and other neurodegenerative diseases.

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Glossary

Alzheimer disease
(AD). The co-occurrence of brain Aβ and tau pathology. AD dementia is the final stage of AD, in which cognitive impairment and loss of daily function are also present.

Amyloid
In the brain, a 37–49-amino-acid polypeptide (amyloid-β (Aβ)) produced by the metabolism of the synaptic membrane protein amyloid precursor protein (APP). The amyloid fibrillar form is made mainly of the 42-amino-acid variant ($A\beta_{42}$) and is the primary component of amyloid plaques found in the brains of individuals with Alzheimer disease. Soluble $A\beta_{42}$ can be found in plasma and the cerebrospinal fluid and can give rise to soluble oligomers, thought to be the toxic form of Aβ.

Braak stage
Braak stage denotes the degree of tau pathology in Alzheimer disease and assumes progressive spread of such pathology from the transentorhinal region of the brain. Braak stages I and II denote neurofibrillary tangle involvement confined mainly to the transentorhinal region, stages III and IV when there is also involvement of limbic regions such as the hippocampus, and stages V and VI when there is extensive neocortical involvement.

Mild cognitive impairment
(MCI). A syndrome featuring cognitive impairment and no loss of daily function; Alzheimer disease is the underlying pathology in 60–80% of MCI cases. In these cases, the condition is also called prodromal Alzheimer disease or MCI due to Alzheimer disease.

Neurodegeneration
Progressive loss of the structure or function of neurons, which may ultimately involve cell death. The earliest detectable event is thought to be synaptic loss, followed by neuronal loss. Neurodegeneration can be detected in vivo with volumetric MRI and positron emission tomography with ^{18}F-labelled deoxyglucose.

Tau
A protein whose primary role is in maintaining the stability of microtubules in axons. In the course of Alzheimer disease, tau becomes hyperphosphorylated, leading to axonal and synaptic dysfunction and aggregation of tau into intracellular neurofibrillary tangles.

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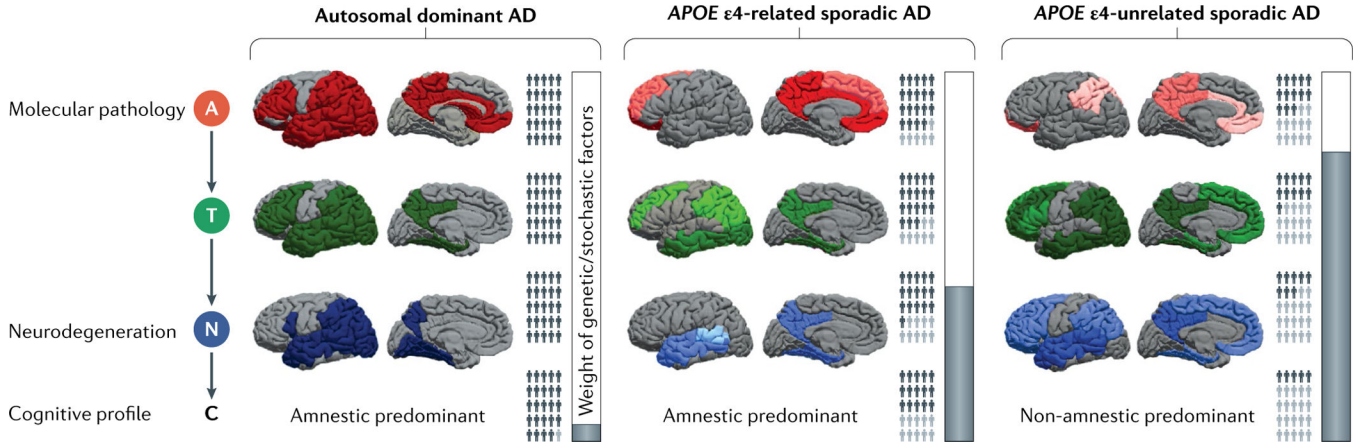

Fig. 1 |. The probabilistic model of Alzheimer disease.

We propose three Alzheimer disease (AD) variants — autosomal dominant AD, *APOE* ε4-related sporadic AD and *APOE* ε4-unrelated sporadic AD — on the basis of genetic backgrounds and featuring differences in lifetime risk of dementia, the influence of stochastic factors, topography and the burden of amyloid pathology (A), tau pathology (T), neurodegeneration (N) and cognitive symptoms (C). A, T and N burdens in various brain regions are represented by the intensity of red, green and blue, respectively, with darker colours indicating greater burden. The topography of pathology and its global burden are reported in TABLE 1. The relative burden within and between variants for A is based on REFS[113,117], for T on REFS[124,126–128] and for N on REFS[125–127,129]. The proportions of dark and light grey people (affected and unaffected individuals, respectively) are approximate representations for the lifetime prevalence of A^+, T^+, N^+ and cognitive impairment in the three AD variants. Autosomal dominant AD individuals almost invariably develop A, T, N and C. In sporadic AD, the interplay of *APOE* genotype with stochastic factors leads to a weaker cascade from A to T, N and C, resulting in fewer affected cases. The lifetime risk of dementia is very high (nearly 100%[12]) in autosomal dominant AD, intermediate (22–95%[133,134]) in *APOE* ε4-related AD and low (7–35%[133,134]) in *APOE* ε4-unrelated AD. The vertical bars graphically denote the weight of genetic and stochastic factors (white and grey, respectively).

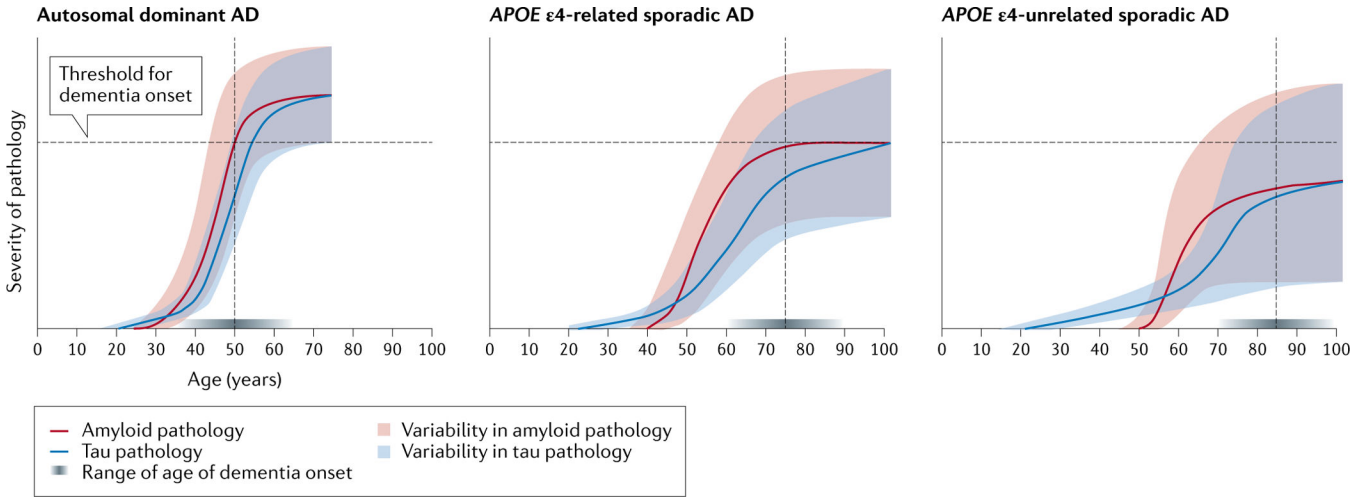

Fig. 2 |. The lifetime dynamics of Aβ and tau in the three Alzheimer disease variants.

The curves represent the dynamics of Aβ (red) and tau (blue) deposition in the three Alzheimer disease (AD) variants. Age is shown on the *x* axis and the severity of the molecular pathology is shown on the *y* axis. The curves were generated by taking the dynamic biomarker model of Jack et al.[18] as a template and warping it in accordance with evidence from the literature on the differences among autosomal dominant AD, *APOE* ε4-related sporadic AD and *APOE* ε4-unrelated sporadic AD regarding the following: the onset of Aβ and tau deposition (the intersections between the Aβ and tau curves with the *x* axis)[58,59], the rates of change of patholog (curve slopes), the age of symptom onset (dotted vertical lines)[87,106,107], the varoability of Aβ and tau pathology among individuals (shaded areas), the crossing of the clinical symptom threshold (dotted horizontal lines)[12,133,134] and the range of age of dementia onset (horizontal shaded grey bar immediately above the *x* axis, where darker shades denote greater frequency density of the age of dementia onset)[106–110]. In the younger ages, the curve for tau lies above the Aβ curve to denote age-related tau deposition, which is thought to be necessary for Aβ to trigger further and extensive AD-related tau spread to neocortical areas[58,59]. The curves for Aβ and tau are steeper (denoting a more aggressive disease neurobiology) in autosomal dominant AD than in the *APOE* ε4-related and *APOE* ε4-unrelated sporadic variants. When the burdens of Aβ and tau pathologies reach a certain threshold, cognitive impairment becomes manifest. This occurs at around 50 years of age in autosomal dominant AD[87], 75 years in *APOE* ε4-related sporadic AD[106,107] and 85 years in *APOE* ε4-unrelated sporadic AD[106,107]. In all cases, in the final stages of the disease, the Aβ and tau curves reach a plateau. The intersection of the shaded areas with the threshold for dementia onset denotes the lifetime prevalence of dementia, with all individuals with autosomal dominant AD crossing the threshold at some point in their lifetime[12], while a minority of non-*APOE* ε4 carriers[133,134] and an intermediate proportion of *APOE* ε4 carriers[133,134] do. Solid population-based data on the age of onset in *APOE* ε4 carriers and *APOE* ε4 non-carriers are lacking. The data in the literature were either estimated retrospectively on the basis of proxy reports in diagnostic cohorts not representative of the general population or estimated in well-conducted prospective population-based studies that had small sample sizes. Indeed, the two largest population-based studies (the Rotterdam Study and the Framingham Study)

comprised only 134 and 43 cases, respectively[106,107]. However, it is widely accepted that carrying the *APOE* ε4 allele reduces the age of onset by about 12 years[108–110]. The curves for autosomal dominant AD are cut at around 60 years, assuming an average dementia duration of around 10 years[88]. The shaded areas denote the predicted variability of individual trajectories of Aβ and tau pathologies based on the probabilistic model that we are proposing. The variability of trajectories is inversely proportional to the penetrance of genetic factors and directly proportional to the impact of stochastic factors: smaller in autosomal dominant AD, intermediate in the *APOE* ε4-related variant and largest in the *APOE* ε4-unrelated variant.

Table 1 |

Brain pathology associated with the three Alzheimer disease variants

Pathology	Feature	Alzheimer disease variant		
		Autosomal dominant	***APOE* ε4 sporadic**	**Non-*APOE* ε4 sporadic**
Aβ	Global burden	+++[97,98]	++[117,118]	+[117,118]
	Topography	Precuneus; isthmus of cingulate gyrus, posterior cingulate and anterior cingulate gyri; rostral middle frontal gyrus, pars opercularis and pars triangularis of inferior frontal gyrus; orbital frontal gyrus; paracentral gyrus; postcentral gyrus; lateral temporal gyrus; lateral parietal gyrus; lateral occipital and pericalcarine gyri; and caudate nucleus[81,89,90]	Precuneus; isthmus of cingulate gyrus, posterior cingulate and anterior cingulate gyri; medial and lateral orbitofrontal gyrus; rostral middle frontal and superior frontal gyri; and paracentral gyrus[113,117]	Precuneus; isthmus of cingulate gyrus, posterior cingulate and anterior cingulate gyri; medial and lateral orbitofrontal gyri; paracentral gyrus; superior parietal lobe; and supramarginal gyrus[113,117]
Tau	Global burden	+++[91]	++[126]	+++[126]
	Topography	Precuneus; isthmus of cingulate gyrus and posterior cingulate gyrus; middle and inferior frontal gyri; medial and lateral temporal gyri; lateral parietal lobe; lateral occipital lobe[91]	Precuneus; isthmus of cingulate gyrus and posterior cingulate gyrus; middle frontal gyrus; medial, middle and inferior temporal gyri; lateral parietal lobe; lateral occipital lobe[124,126–128]	Precuneus; isthmus of cingulate gyrus and posterior cingulate gyrus; superior, middle and inferior frontal gyri; medial, middle and inferior temporal gyri; lateral parietal lobe; lateral occipital lobe[124,126–128]
TDP43	Global burden	Variable: −/+[93,94]	++[130]	+[130]
	Topography	Hippocampus and amygdala[93]	Amygdala, hippocampus, medial frontal gyrus[130]	
α-Synuclein	Global burden	Variable: −/+/++[94–96]	++[131]	+[131]
	Topography	Amygdala[96]	Not reported	Not reported
Cerebral amyloid angiopathy	Global burden	+++[97,98]	+++[119]	+[119]
	Topography	Type 1 or type 2 (REF.[17])	Type 1 (REFS[120–123])	Type 2 (REFS[120–123])
Neuroinflammation	Topography	Colocalized with tau and Aβ pathology[99]	Colocalized with tau and Aβ pathology[99,167–170]	Weaker colocalization with tau and Aβ pathology[99,167–170]
Neurodegeneration	Global burden	+++[12]	+[126]	++[126]
	Topography	Precuneus; pars opercularis of inferior frontal gyrus; medial, superior and middle temporal gyri; lateral parietal lobe; lateral occipital lobe[81,90,92]	Precuneus; isthmus of cingulate gyrus and posterior cingulate gyrus; medial, superior, and middle temporal gyri; temporoparietal junction[125–127,129]	Precuneus; isthmus of cingulate gyrus and posterior cingulate gyrus; superior, middle and inferior frontal gyri; medial, superior and middle temporal gyri; temporoparietal junction; parietal lobe[125–127,129]

The number of plus signs reflects the global burden of brain pathology based on studies comparing autosomal dominant Alzheimer disease (AD) with sporadic AD, and *APOE* ε4-related sporadic variants with *APOE* ε4-unrelated sporadic variants. Head-to-head comparisons among autosomal dominant AD, *APOE* ε4-related AD and *APOE* ε4-unrelated sporadic AD are not available. Global burden: +, low; ++, intermediate; +++, high. Regions listed under ‘topography’ are those mainly affected by pathology. Cerebral amyloid angiopathy type 1 is with capillary involvement, whereas type 2 is without capillary involvement. The topography of Aβ, tau and neurodegeneration and their burden are graphically represented in FIG. 1. Aβ, amyloid-β; TDP43, TAR DNA-binding protein 43.