



Alzheimer's disease in the computational era: from a deterministic disease to a multifaceted disorder

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The definition of Alzheimer's disease (AD) keeps changing over the years, which is critical for studying it, understanding it and developing treatments. Here, we initially review the different definitions proposed for AD, from its original characterization by Kraepelin in 1908 to the recent Alzheimer's Association revised criteria in 2024. We describe these definitions in parallel to the new knowledge gained, demonstrating how they vacillate between restricted and circumscribed clinicopathological characterizations and wider clinical and pathological ones. Then, we describe AD multifaceted clinical presentations, including very early subtle cognitive and behavioural changes, alongside its pathological multifactorial variability of core pathologies, co-pathologies and risk factors, encompassing changes in various cortical and subcortical brain regions and its genetic complex landscape. We suggest that all potential factors among the different levels should be considered to provide a patient-tailored clinical profile.

To address the richness and complexity of the data, we outline a metamodeling-based computational framework that allows diverse sources of evidence to be integrated without forcing them into a single monolithic model. Specifically, different data subsets are used to construct partial models, each addressing selected domains and factors; these models are then converted into probabilistic surrogate models with shared variables and parameters; and finally, the latent variables inferred from the surrogate models are related via a probabilistic coupling layer to create predictions of the trajectories of individual patients and intervention effects, staging, clinical stratification and attribution maps.

Taken together, the computational and data revolutions might enable us to expose the complexity of AD through large-scale patients' data, computational metamodeling and hypothesis-free analyses, leading to reconceptualization of AD from a monolithic diagnostic category into a stratified, mechanistically interpretable nosology, with practical implications at the individual patient level.

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Introduction

Alzheimer's disease (AD) stands as a profound scientific paradox: despite over a century of intensive investigation following Alois Alzheimer's seminal 1907 case report, its definition remains contentiously debated, and therapeutic approaches have achieved only modest clinical benefits. This definitional challenge reflects a fundamental tension in the field's conceptualization of the disease: whether AD represents a uniform pathobiological entity with variable clinical manifestation or, conversely, a heterogeneous syndrome encompassing distinct disease mechanisms that converge on common cognitive and neuropsychiatric outcomes. The successive refinement and, at times, revision of AD diagnostic criteria over the course of decades (from Kraepelin's clinicopathological characterization,¹ through the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) clinical framework,² to the recent biomarker-centric formulations by the Alzheimer's Association³) demonstrates how evolving knowledge and opinions have progressively shifted the conceptual boundary of the disease, with each iteration emphasising different facets while obscuring others. This pattern of definitional evolution suggests not merely incremental refinement but, rather, a fundamental recognition that AD cannot be captured adequately by a single unifying model centred on any solitary pathological process, whether amyloid accumulation, tau pathology, lipid metabolism, immune response or influence of co-pathologies. Consequently, the field faces an urgent imperative to develop integrative frameworks that acknowledge and systematically model the multifaceted nature of the disease.

This paper delineates the heterogeneity observed in the clinical presentation of AD and its pathological composition, neuroanatomical distribution and genetic underpinnings, not reflecting random variation but rather structured variation arising from distinct disease trajectories, unique routes through a multidimensional pathogenic landscape that differs across patients and cohorts. The work integrates evidence across four interconnected domains: cognitive-behavioural manifestations (including classical and newly defined cognitive deficits and neuropsychiatric symptoms), molecular and cellular pathology (encompassing mainly amyloid, tau, lipid metabolism, neuroinflammation, vascular pathology and co-pathologies), neuroanatomical substrate (including both regional atrophy patterns and network-level vulnerability) and genetic architecture (spanning monogenic factors, polygenic risk and pathway-specific variants related to amyloid, tau, lipid metabolism and immune function). Building upon this multidimensional synthesis, we introduce a Bayesian metamodeling framework capable of harmonizing diverse partial models into a coherent probabilistic representation, one in which individual patient trajectories reflect the cumulative consequence of distinct combinations of factors within each domain and wherein clustering of these trajectories reveals clinical phenotypes and biologically meaningful subtypes. Such an approach, made feasible by contemporary advances in

data science, digital phenotyping and high-dimensional modelling, promises to transform AD from a monolithic diagnostic category into a stratified and mechanistically interpretable nosology suitable for precision medicine and rational therapeutic intervention.

Nine definitions of AD, 1908–2024

Definition 1: Alois Alzheimer's (1906) and Emil Kraepelin (1908)—behavioural symptoms, parietal signs and memory impairment in a 51-year-old patient

As is classically the case in neurology, the definition of AD started with one patient, namely Auguste Deter (1850–1906). Auguste Deter was a 51-year-old woman who was referred to the Municipal Asylum for the Mentally Ill and Epileptics in Frankfurt am Main in 1901 owing to personality changes reflected in jealousy towards her husband, psychosocial impairment and rapid memory deterioration.⁴ There she was treated by Dr Alois Alzheimer, a physician interested in the neuropathology of dementia disorders. In a similar manner to the current practice of cognitive neurology, Alzheimer wrote down his conversations with her, which were later found in her file^{5,6}.

'What is your name? Auguste. Last name? Auguste. What is your husband's name? Auguste, I think. Your husband? Ah, my husband. She looks as if she didn't understand the question. Are you married? To Auguste. Mrs D? Yes, yes, Auguste D. How long have you been here? Three weeks. What is this? I show her a pencil. A pen. A purse and key, diary, cigar are identified correctly. When objects are shown to her, she does not remember after a short time which objects have been shown. In between she always speaks about twins. When she is asked to write, she holds the book in such a way that one has the impression that she has a loss in the right visual field. Asked to write 'Auguste D', she tries to write 'Mrs' and forgets the rest. It is necessary to repeat every word. Amnesic writing disorder. In the evening her spontaneous speech is full of paraphasias and perseverations. What year is it? Eighteen hundred. Are you ill? Second month. What are the names of the patients? She answers quickly and correctly. What month is it now? The 11th. What is the name of the 11th month? The last one, if not the last one. Which one? I don't know. What is the colour of snow? White. Soot? Black. The sky? Blue. Meadows? Green. How many fingers do you have? 5. Eyes? 2. Legs? 2'.

Summarizing her neuropsychological profile, it seems that she suffered mainly from temporal and social disorientation (for both self and other), in addition to a problem in intermediate episodic memory. It is not clear whether she had a partial neglect as Alzheimer suggested or a kind of apraxia, in addition to some language impairment, while naming and semantic knowledge were retained.

The patient stayed hospitalized while Alzheimer moved to the Royal Psychiatric Clinic in Munich, directed by Dr Emil Kraepelin, the prominent psychiatrist of the time. Hearing about her death, Alzheimer asked for her brain to be sent to him for pathological investigation. There, he found amyloid plaques, tau-containing neurofibrillary tangles (NFTs) and atrophy. Alzheimer was not the first to describe amyloid. In 1898, Dr Emil Redlich, a psychiatrist in Vienna,

first used the word 'plaques' to describe what he saw in the brains of two patients diagnosed with 'senile dementia'. Additionally, in 1907 the Czech psychiatrist Dr Oskar Fischer published cases with senile dementia and amyloid, which he described as 'drusen'.⁷

Alzheimer followed the advice of his mentor, Kraepelin, and presented the case in the South-West German psychiatrists conference in Tübingen (1906) under the title of 'About a strange, severe disease process of the cerebral cortex'. The conference was chaired by Dr Alfred Hoche, an opponent of Kraepelin, who neither allowed discussion of Alzheimer's presentation nor included it in the conference proceedings, stating that it was 'not suitable for a short report'.⁸ He then changed his mind, and the case was published in 1907, followed by a full paper in 1911.⁹ A few years later, Kraepelin coined the term 'Alzheimer's disease' (Alzheimer Krankheit) in his phenomenal textbook *Psychiatrie*, where he described the disease¹:

'A peculiar group of cases with very severe cell-changes has been described by Alzheimer. It is a matter of slow development of an extremely severe mental illness with the blurred appearance of an organic brain disease. Over the course of a few years, the patients gradually decline mentally, become weak in memory, poor in thought, confused, unclear, no longer able to find their way around, misunderstand people, and give away their things. Later, a certain restlessness develops; The sick chatter a lot, murmur to themselves, sing and laugh, run around, nest, rub, pick, and become unclear. Suggestions of a-symbolic and apraxic disorders are common; The affected people use old-age nonsense. They don't respond to requests, they don't make any gestures, they don't recognize objects and pictures, they don't carry out orderly actions, they don't imitate, they don't make any defensive movements when threatened, although they find being pricked with a needle very unpleasant. The language disorders in particular are very profound. The patients are still able to say individual words or sentences in an understandable way, but they usually fall into completely meaningless chatter.'

Kraepelin had two main scientific interests. One was the classification of neuropsychiatric disorders, for which he has been considered the originator of the Diagnostic and Statistical Manual of Mental Disorders (DSM). His other interest and belief was that mental disorders are brain disorders. He was therefore impressed by Alzheimer's case description, because Auguste Deter was a relatively young patient, with distinct mental dysfunctions based on clear brain pathology. He thus ignored similar clinical and pathological descriptions of elderly patients that were available to him, like those of Fischer, which were classified under a different entity, senile dementia (Fig. 1A).

Definition 2: the unified theory of Martin Roth (1955–1969) and the NINCDS-ADRDA criteria (1984)

More than 60 years elapsed until the British psychiatrist Sir Martin Roth challenged Kraepelin's approach. In a seminal work,¹⁰ he suggested that senile dementia is a neuropathological condition, different from other mental disorders. Moreover, in a series of papers in the late 1960s, Roth and colleagues suggested that senile dementia should not be classified separately from AD, despite the presumed clinical difference, because the majority of cases of senile dementia had neurofibrillary tangles and amyloid plaques.^{10–14} Following this conceptual change,¹⁵ in 1984, McKhann, Folstein, Katzman and others, representing the NINCDS-ADRDA published clinical criteria for the diagnosis of AD.² The core of these criteria included impairment in at least two cognitive domains (not limited to specific domains), which result in significant impairment in social or occupational functioning. The onset of cognitive symptoms had to be gradual, and the course had to be progressive. Finally,

other potential causes of dementia had to be excluded through clinical evaluation and laboratory tests.

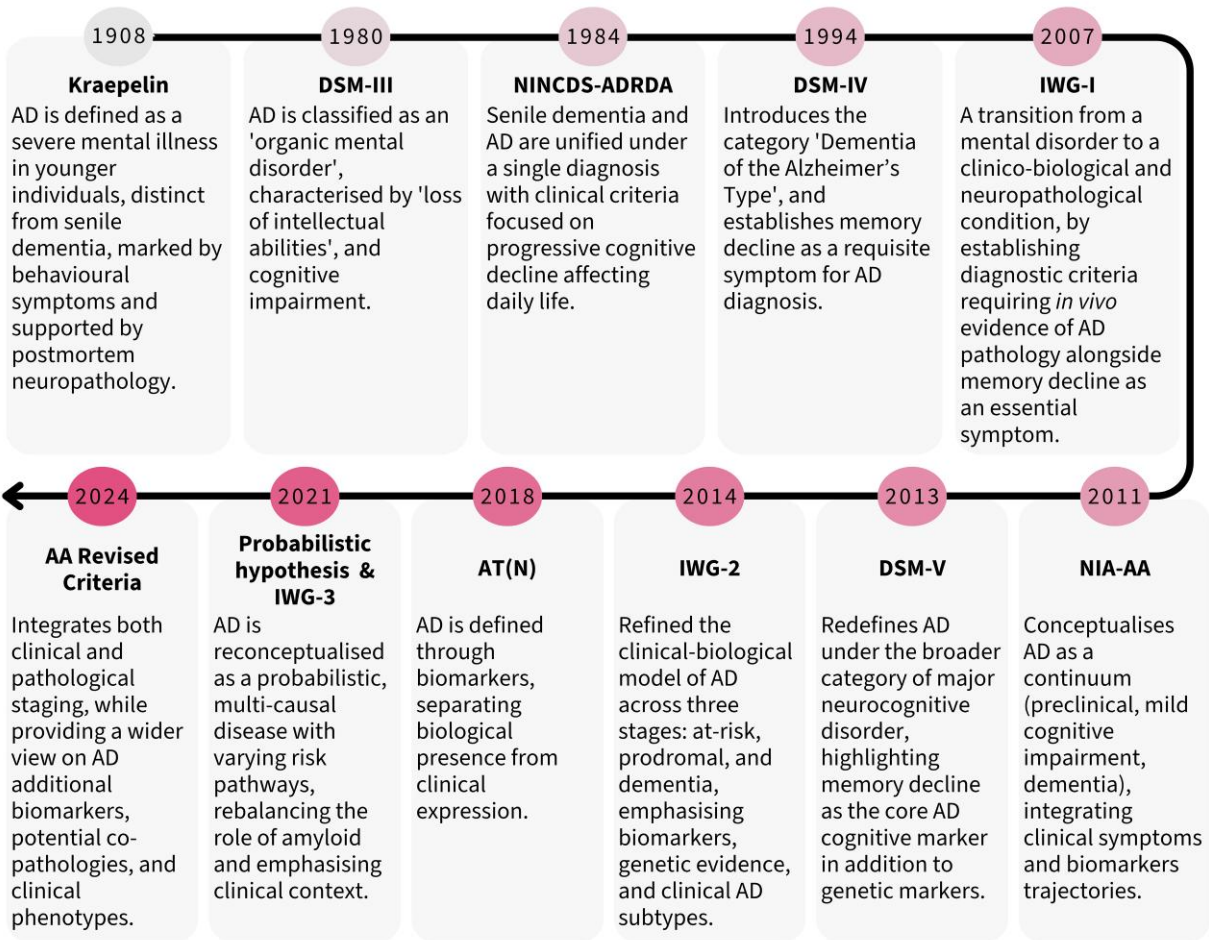
Definition 3: the amyloid hypothesis, Braak staging and the International Working Group-1

Three years later (1987), the British geneticist Dr John Hardy and his team set out to discover genetic mutations that could lead to AD.¹⁶ Hardy has built on the idea that familial AD and sporadic AD are indistinguishable in terms of clinical symptoms and neuropathology,¹⁷ in addition to the discovery of a mutation related to AD on chromosome 21, suggesting it could alter the expression of the amyloid- β (A β) peptide.¹⁸ Following these discoveries, and in an attempt to focus on a single family line because of the variations in the linkage between chromosome 21 in AD patients, Hardy and his team placed an advert in an Alzheimer's Society newsletter, seeking help from families in whom more than one person had developed the disease. The 23rd letter Hardy read was by a woman named Carol Jenings. After collecting blood from Ms Jenings and her family members, the team looked for a shared mutation. It was in 1991 that they discovered said mutation, in the gene coding for the amyloid precursor protein (APP),¹⁹ leading to overproduction of A β .²⁰ Two years later, Hardy and Higgins published an opinion paper entitled 'The amyloid cascade hypothesis', suggesting that although the Jenings family mutation is very rare, it is the same process that also underlies the prevalent later-onset sporadic AD.^{21,22}

At the same time (1991), Braak and Braak²³ published their neuropathological staging criteria of AD-related changes based on 83 brains of demented and non-demented individuals. Initially, they searched for amyloid plaques, but these varied widely, not only within architectonic units but also from one individual to another. The NFTs containing hyperphosphorylated tau exhibited a distribution pattern that led the authors to define six stages of the disease. The first two stages are characterized by NFTs in the trans-entorhinal cortex, followed by two limbic stages (NFTs in both the trans-entorhinal region and proper entorhinal cortex), then in all iso-cortical association areas.

To cope with this and other scientific advancements of the intervening 20 years, a group of experts led by Dr Bruno Dubois²⁴ proposed new research criteria for the diagnosis of AD. In 2007, the International Working Group (IWG) for New Research Criteria for the Diagnosis of AD provided a new conceptual framework proposing that the diagnosis of AD relies on specific *in vivo* biomarkers. This approach shifted AD from a clinical to a clinical-biological entity. The IWG-1 started with a core diagnostic criterion of early episodic memory impairment, which might be either subjective or objective. However, they noted that this criterion is non-specific and is found both in normal ageing and in non-AD dementias. They nonetheless specified that amnesia should be supported by neuropsychological tests, claiming that memory deficits that do not improve with cueing are specific to AD. They also stressed the concept of an amnesic syndrome of the hippocampal type, indicating that the amnesic syndrome in AD is the consequence of damage to the medial temporal lobe (MTL).²⁵ To this core criterion they added, for the first time, supportive biological features criteria. The first supportive feature was the presence of MTL atrophy, although atrophy in AD is not necessarily found primarily in the MTL, and AD heterogeneity was already suggested.²⁶ Nonetheless, MTL atrophy is in line with the Braak staging²³ and with memory deficits. They also mentioned bilateral temporoparietal hypometabolism on fluorodeoxyglucose (FDG)-PET as a sensitive biomarker for AD. Finally, they noted several amyloid-related biomarkers, including

A Milestones in the evolution of Alzheimer’s disease conceptualisation through the lens of its diagnostic criteria



B Clinical and biological breadth of AD according to the various clinical and research diagnostic criteria

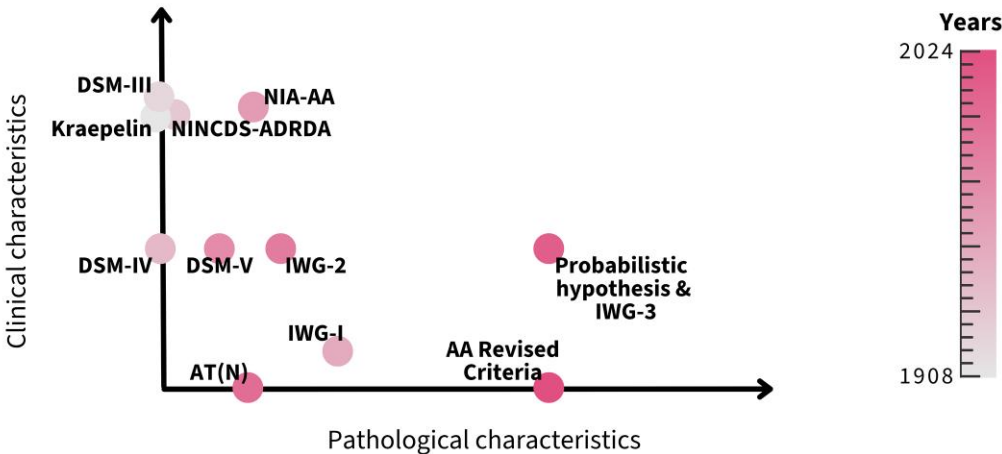


Figure 1 Milestones in the evolution of Alzheimer’s disease conceptualization through the lens of its diagnostic criteria. (A) A chronological timeline summarizing the principal conceptual contribution of each AD criterion in the past 120 years since its original definition. (B) The conceptualization of AD based on its clinical (y-axis) and pathological (x-axis) characteristics, illustrating a progressive shift from clinically anchored towards increasingly biology/pathology-driven definitions of AD. Colour intensity reflects chronological order. AA = Alzheimer’s Association; AD = Alzheimer’s disease; AT(N) = Amyloid, Tau, Neurodegeneration system; DSM = Diagnostic and Statistical Manual of Mental Disorders; IWG = International Working Group; NIA = National Institute on Aging; NINCDS-ADRDA = National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer’s Disease and Related Disorders Association.

CSF low A β_{1-42} concentrations and cortical amyloid deposition imaged by Pittsburgh Compound B (PiB) PET, or proven AD autosomal dominant mutation (coding for the formation of amyloid) within the immediate family. They also mentioned CSF increased total tau or phospho-tau concentrations as biomarkers for AD. Apart from the crucial diagnostic value of these biological criteria, importance lies in their introduction of a potential diagnosis at the stage of mild cognitive impairment (prodromal stage) or even before clinical symptoms appear (presymptomatic stage).

Definition 4: National Institute on Aging and Alzheimer's Association (2011)

The National Institute on Aging and Alzheimer's Association (NIA-AA) committee gathered in 2011 to revise the NINCDS-ADRDA criteria² almost 30 years after their presentation.^{27–30} A main contribution of the new criteria was to redefine AD as encompassing a continuum of stages, recognizing that pathological changes in the brain occur years before clinical symptoms become apparent. These criteria referred to a preclinical stage, based on AD pathology in the brain, such as amyloid plaques and tau neurofibrillary tangles, in individuals who do not yet manifest clinical symptoms or have only minimal symptoms.²⁸ This stage preceded mild cognitive impairment (MCI),^{31–34} defined as individuals with objective cognitive impairment beyond what is expected for their age but without significant functional impairment.²⁹ Finally, AD-dementia represents a later symptomatic stage, in which individuals exhibit progressive cognitive and functional decline that interferes significantly with activities of daily living.³⁰ The diagnosis of AD was still based on clinical grounds, with memory impairment, particularly in the episodic memory domain, serving as a key cognitive feature. However, the criteria acknowledged the heterogeneity of clinical presentations and encouraged a comprehensive assessment of various cognitive domains, continuing the theoretical background behind the NINCDS-ADRDA criteria. The 'Jack curves' that were incorporated in the criteria depict the hypothetical gradual increase in AD abnormal biomarkers along the AD continuum.^{28,35} Nonetheless, given that further testing of this model was required, the preclinical AD diagnostic criteria were considered a research construct not ready for clinical use, and biomarkers, such as imaging studies (e.g. PET and MRI) and CSF analysis for A β and tau, were considered as supportive evidence of AD pathology.^{29,30}

Definition 5: DSM III, IV and V

The division between neurology and psychiatry is not clearly demarcated and was introduced relatively late in modern medicine.³⁶ AD was originally described in the psychiatric milieu, and although nowadays considered as a neurodegenerative disorder, behavioural and psychological symptoms, also referred to as neuropsychiatric symptoms, are prominent features of the disease, even in early stages.^{37–39} Accordingly, Auguste Deter, Alzheimer's famous patient, presented to the Frankfurt Hospital mainly owing to neuropsychiatric symptoms, and her case was coined in Kraepelin's *Psychiatrie* textbook. Later on, the DSM also clearly included AD as a diagnosis. Interestingly, despite the prominence of neuropsychiatric symptoms in AD, the DSM focused on cognitive impairment. Psychiatry, as a medical field, is well acquainted with complex definitions, because the psychiatric model is often descriptive, unlike the classic biological model that underlies modern medicine. The DSM-III (1980) categorized AD under 'organic mental disorders',

defining the disease as a loss of intellectual abilities of sufficient severity to interfere with social or occupational functioning, recognizing various cognitive symptoms ('dementia is multifaceted and involves memory, judgment, abstract thought, and a variety of other higher cortical functions').⁴⁰ In DSM-IV (1994), the term Dementia became central, and AD was placed under the category of 'Dementia due to Alzheimer's disease'.⁴¹ The criteria included significant cognitive decline beyond what would be expected owing to normal ageing, with memory impairment as a key feature. Additional cognitive deficits in areas such as language, motor skills and problem-solving were also considered. DSM-V (2013) introduced major changes in the classification of neurocognitive disorders, merging various disorders, including AD, into a single category called 'Neurocognitive Disorders'.⁴² AD specifically was mentioned under the subtype 'Major Neurocognitive Disorder due to Alzheimer's disease'. The criteria encompassed significant cognitive decline and interference with daily functioning. Memory impairment continued to be a crucial aspect, along with deficits in at least one other cognitive domain. The term 'Minor Neurocognitive Disorder', which parallels the clinical diagnosis of MCI, was also introduced.

Definition 6: IWG-2 (2014)

Following the NIA-AA criteria (2011),^{27–30} in addition to the limitations of the IWG-1 criteria (2007), when biomarkers of AD pathology were not as advanced in development and implementation,²⁴ new members joined the IWG team, and revised criteria were proposed. In 2014, the IWG refined its diagnostic algorithm by reconsidering the biomarker categories and their role in AD pathology.⁴³ The IWG-2 criteria retained the concept of AD as a continuum, acknowledging both the preclinical (asymptomatic) and symptomatic phases (prodromal through dementia). In a similar manner to the NIA-AA 2011 criteria, the framework included three main phases:

- (i) Asymptomatic at risk for AD: individuals who have evidence of AD pathology by imaging or CSF biomarkers but no cognitive symptoms.
- (ii) MCI owing to AD or prodromal AD: similar to the NIA-AA 2011 criteria, the IWG-2 recognized MCI as an intermediate stage between normal ageing and dementia. Unlike the IWG-1 criteria, which mentioned episodic memory as the main clinical deficit, the revised criteria stated that the impairment typically involves multiple cognitive domains, with episodic memory often being an early and prominent feature. Biomarkers were considered as supportive evidence at this stage.
- (iii) AD-dementia: individuals with clinically evident cognitive and functional decline. Biomarkers, along with clinical and neuropsychological assessments, are used to support the diagnosis.

Definition 7: AT(N) (2018)

In 2018, the NIA-AA working group proposed a new research framework (i.e. dedicated to clinical research and trials) entitled 'Amyloid, Tau, Neurodegeneration', often referred to as the 'AT(N)' system or framework.⁴⁴ Building on the 2011 preclinical AD criteria that introduced into the definition the concept of amyloid and neurodegeneration biomarkers, the AT(N) system categorizes AD based on the presence of biomarkers for A β (PET or CSF), tau (PET or CSF phospho-tau) and neurodegeneration (FDG-PET, anatomical/structural MRI or CSF total tau). A novel aspect of these revised criteria, besides relying heavily on biomarkers, was that the AT(N) framework allowed clinicians and researchers to categorize individuals into different profiles of AD based on the presence or absence of these biomarkers. In this classification system, absence of all three biomarkers indicates no evidence of AD

pathological changes, whereas A β positivity is a prerequisite for inclusion within the Alzheimer's continuum, regardless of positivity or negativity status combinations of tau and neurodegeneration. Any other biomarker profile consisting of A β negativity, marks non-AD pathological changes.

The working group also coupled the above biomarker profiles with the clinical syndromes described in the 2011 criteria (cognitively unimpaired, MCI and dementia) and introduced a numerical clinical staging that could be used in clinical trials: (1) asymptomatic with normal cognition; (2) transitional cognitive decline, also referred to as subjective cognitive decline; (3) MCI; (4) mild dementia; (5) moderate dementia; and (6) severe dementia.

Definition 8: the probabilistic hypothesis and IWG-3 (2021)

The 'Probabilistic Hypothesis of Alzheimer's Disease', developed by Frisoni, Dubois and colleagues,⁴⁵ provides an alternative approach to the amyloid hypothesis. The authors claimed that although the amyloid hypothesis fits the autosomal dominant form of AD (ADAD) well, it might be less applicable to sporadic forms. The probabilistic hypothesis draws three variants of AD: (i) ADAD; (ii) apolipoprotein E ϵ 4 (APOE ϵ 4)-related sporadic AD; and (iii) APOE ϵ 4-unrelated sporadic AD, each with varying levels of amyloid influence and increasing roles for stochastic factors, such as environmental exposures and lower-risk genetic factors. In this framework, the weight given to amyloid pathology decreases in the latter forms of AD, whereas the importance of other variables (including non-genetic and environmental factors) increases. Thus, the probabilistic approach highlights that AD, especially in its sporadic form, might be driven by a combination of factors, rather than a strict chain of amyloid-driven events. This model allows for a more flexible understanding of the disease and opens new avenues for research into prevention and treatment strategies, potentially shifting the focus towards addressing these stochastic influences. This perspective was also reflected in the IWG-3 clinical criteria, published by Dubois, Frisoni and colleagues the same year.⁴⁶ Rather than relying heavily on biomarker positivity, as in the AT(N) framework, IWG-3 emphasises the integration of clinical symptoms with biomarkers and suggests a risk-based approach: individuals with autosomal dominant mutations are considered at certainty of developing AD, whereas cognitively unimpaired individuals who are APOE ϵ 4 homozygotes and those with positive biomarkers are at high risk, and those with mixed biomarker results are at uncertain risk. This model sees AD as a clinical-biological entity, especially in the preclinical stages. The 2024 revision of these criteria strengthened this view further, particularly in light of the critical implications of assigning an AD diagnosis to cognitively unimpaired individuals and the importance of evaluating clinical outcomes in prevention trials.⁴⁷

Definition 9: Alzheimer's Association revised criteria for diagnosis and staging of AD (2024) and the IWG critique

In 2024, the AA released updated diagnostic criteria for AD,³ reflecting significant advances in biomarker research and imaging technology. Although the criteria consider clinical data and staging, they regard AD as a biological entity. There are three crucial advancements in the new criteria. The first concerns biomarkers, especially blood-based biomarkers. The new framework centres on three main biomarker modalities: the two well-established ones (PET and CSF) and, for the first time, the new, rapidly advancing

field of blood-based biomarkers. PET biomarkers include the two 'core biomarkers' of tau and amyloid. Amyloid allows for earlier and more definite diagnosis of early stages, while tau-PET plays a crucial role, by detecting tau deposition in specific brain regions and disease staging. CSF biomarkers include key indicators such as the A β 42/40 ratio and phosphorylated tau (p-tau181, p-tau217 and p-tau231) levels. Newer markers, such as microtubule-binding region (MTBR)-tau243 and non-phosphorylated tau fragments, were also mentioned, particularly in advanced stages. Importantly, the new criteria also included the newly developed plasma adaptations of the above-mentioned CSF ones, although only one (p-tau217) was found to be equivalent to the CSF ones. Second, the criteria also account for co-pathologies commonly seen with AD, such as vascular damage (detected via MRI) and α -synuclein, the hallmark of Parkinson's disease and related disorders. It also includes a non-specific AD biomarkers category, which encompasses inflammatory processes, with accumulating evidence demonstrating their eminent role in AD,^{48,49} and neurodegeneration blood biomarkers; both have been suggested to predict cognitive deterioration in amyloid-positive MCI patients.⁵⁰ In doing so, these criteria open the door for each potential co-pathology to be included. The third advancement is clinical staging. Although biomarkers play an essential role, the new criteria also consider clinical evidence building on the numerical clinical staging introduced in the 2018 criteria, although clinical symptoms are not required for AD diagnosis. The criteria now include seven clinical stages. Stage 0 is introduced for individuals with genetic mutations linked to AD but without any detectable biomarkers or symptoms (not present in the 2018 criteria). In subsequent stages, in a similar manner to the 2018 criteria, individuals move from preclinical biomarker positivity without and with mild symptoms to MCI (stage 3), with the final three stages (4–6) encompassing progressive dementia and severe cognitive impairment.

The IWG criticised the AA criteria, stressing the importance of referring to AD as a clinical-biological construct rather than a pure biological or pathological entity.⁴⁷ Specifically, they call out the definition of stage 1 as problematic, arguing that biomarker-positive cognitively normal individuals should not be labelled as having AD. As these definitions evolve, this difference in opinion in the field emphasises the importance of developing personalized, highly sensitive cognitive-clinical markers for AD to be combined with the biological ones.

Towards a comprehensive definition of AD

A review of AD definitions over >100 years showed pendular shifts between varieties of clinically grounded (cognitive and behavioural) and pathology-driven definitions that have been shaped not only by the clinicopathological nature of the disease, but intrinsically, by medical traditions (Kraepelin and Alzheimer, Roth and IWG, NIA and AA) and the technologies available at the time (development and availability of biomarkers that were introduced by the IWG and taken further by the NIA-AA 2018 criteria, Hardy's genetics research) (Fig. 1B). These shifts are not simply methodological or regulatory; they reflect a deeper question about what constitutes the disease itself. Is AD fundamentally a cognitive dysfunction constitutive of the disease process, as traditional medicine teaches, or a biological entity defined by molecular pathology, even in the absence of cognitive change.^{3,47} Therefore, a new comprehensive definition of AD is crucially needed.

In view of recent works identifying behavioural and functional neuroanatomy evidence for subtle changes in people with preclinical (genetic or pathology-based) AD,^{51–54} we point to the relevance of the clinicopathological approach to AD. Moreover, in accordance with the computational and data revolutions, which enable the inclusion of a very large amount of data and the computing of a precise profile for each individual patient, we suggest opening up the definitions to a large array of data, depicting AD as a cognitively and behavioural heterogeneous, neuroanatomically based, pathologically multifactorial and genetically variable disorder.

Level 1: AD as a cognitive-behavioural heterogeneous disorder

Roth's revolution in AD diagnosis was accompanied by opening up the landscape of the clinical picture of the disease. To this end, Roth and co-workers listed practical tasks of everyday life, including competence in personal, domestic and social activities; cognitive tasks, mainly of orientation, remote memory, recent memory and concentration; and mental states, such as depression, delirious states or paraphrenia.¹³ Notably, in the Cambridge dementia tradition associated with Roth,¹³ orientation is not only knowing the date and place, which was designated by the authors under 'information'; rather, it is the organized ability to situate oneself in the current world and maintain a coherent relationship to its context,^{55,56} an ability that differs from memory and information.^{57,58} Roth's clinical work helped to establish orientation as a core marker of cognitive decline, especially because it is often one of the earliest cognitive functions to deteriorate when cortical and/or hippocampal systems are affected.^{53,59–61} Roth's approach was followed in the NINCDS-ADRDA criteria (1984),² which allowed for broader clinical cognitive manifestations of AD as deficits in two or more areas of cognition in the criteria for probable AD. Specifically, they mentioned deficits in orientation to place and time, memory, language skills, praxis, attention, visual perception, problem-solving skills, social functions (e.g. mentalization/theory of mind),⁶² and basic activities of daily living and instrumental activities of daily living.^{2,63–65} With respect to cognition, a recent big-data analysis of 14 571 Montreal Cognitive Assessment tests (of these, 6584 of patients diagnosed with cognitive impairment owing to AD, Lewy-body disease, vascular dementia or fronto-temporal dementia) showed orientation and memory to be most prominently affected in the AD group, followed by attention and visuospatial processing, more than executive and language functions,⁶⁶ thus supporting the observations by Roth and colleagues. Notably, some cognitive faculties were further sub-classified based on clinical and neuroanatomical properties (see below, 'AD as a brain-network disorder'). Another important domain listed in the NINCDS-ADRDA criteria² is neuropsychiatric symptoms, previously known as behavioural and psychological symptoms of dementia. Recent studies have emphasised the importance of neuropsychiatric symptoms in AD, including depression, persecutory ideas, diurnal rhythm disturbance, anxiety, apathy, aggression, hallucinations, delusions and disinhibition.^{67–73} These may appear early in the course of the disease, manifesting prior to the stage of dementia as the recently coined term 'mild behavioural impairment'³⁹ and even as a presenting symptom.^{73–75} Therefore, the clinical view of AD should include not only an open approach to a wide range of ecologically evaluated cognitive domains and daily functioning but also an in-depth evaluation of neuropsychiatric symptoms. Finally, symptom presentations vary between patients. Some patients may present with a predominant amnesia, whereas

others may present with a remarkable disorientation. Moreover, a certain deficit may be accompanied by another one in some patients, and other combinations may characterize other patients. This diversity may be extended further while combined with the biological and neuroanatomical domains, as described below. This suggests that the cognitive and behavioural deficits in AD are, in fact, a multidimensional construct (Fig. 2, level 1).

Some cognitive deficits may be quantified reliably by neuropsychological tests, whereas other cognitive deficits, such as processes underlying basic person–environment interactions in daily life and neuropsychiatric symptoms, require different approaches. In recent years, new digital measures have been developed and implemented either to capture classical cognitive functions with more precise quantification or to derive information concerning cognitive aspects that have limited access by pencil-and-paper testing.^{54,81–86} Several such tools were shown to be sensitive in detecting cognitive changes as early as the preclinical stages of AD [cognitively unimpaired (CU) people with a genetic predisposition for AD or presence of a biomarker of core pathology],^{54,85} supporting the ability to detect clinicopathological changes at these stages. Most of these tools focus on memory and learning functions. For instance, in the Face–Name Associative Memory Exam (FNAME),^{87–89} participants are asked to pair unfamiliar faces with names and occupations. Performance in CU older adults was correlated with entorhinal tau deposition.⁸⁷ Performance in the Neotiv app,⁹⁰ a smartphone-based, self-administered, remote cognitive assessment examining pattern separation and associative memory through mnemonic discrimination tasks and complex scene recognition and recall tasks, was found to be correlated with amyloid accumulation in the precuneus and with tau accumulation in the perirhinal cortex and the anterior hippocampus in a CU sample.

Spatial navigation and orientation ecologically valid tests also showed high discriminative ability in the preclinical stage.⁹¹ Likewise, virtual environment navigation tests differentiated CU APOE $\epsilon 4$ carriers from non-carriers and revealed recruitment of a navigational compensatory mechanism. These include measures such as the Sea Hero Quest, which is a gamified way-finding test,⁹² the Apple Game, featuring a path-integration task,^{61,93} and the Virtual Supermarket Test, in which participants are passively moving in an environment.⁹⁴ Moreover, it was found that CU A β^+ individuals exhibit deficits in forming and retaining a cognitive map of a virtual maze when compared with A β^- ones.^{95,96} In a more extended manner, the Clara app evaluates mental orientation in the temporal, spatial and social domains, in which participants are asked to compare the cognitive distance between themselves and two familiar life events, locations and people they know, respectively. This task was found to be highly sensitive in differentiating between CU, MCI and AD at the individual level,^{57,59,97} and between CU people with and without amyloid and high-tau deposition as detected by tau- and amyloid-PET.⁹⁸

With respect to executive function and processing speed, the Harvard Automated Phone Task consists of navigating an interactive voice response system to complete health-related and banking tasks.⁶⁴ Significant associations were found between Harvard Automated Phone Task rate and interaction between amyloid and either entorhinal cortex tau or inferior temporal and precuneus tau.^{99,100} Processing speed has also been shown to be correlated with global amyloid burden in several digital batteries.^{89,101,102} Language functions and speech were shown to be identifiable in the preclinical stage.^{103–106} Advances in automatic speech recognition, machine learning and large language models now enable detailed analysis of acoustic and linguistic features of spoken

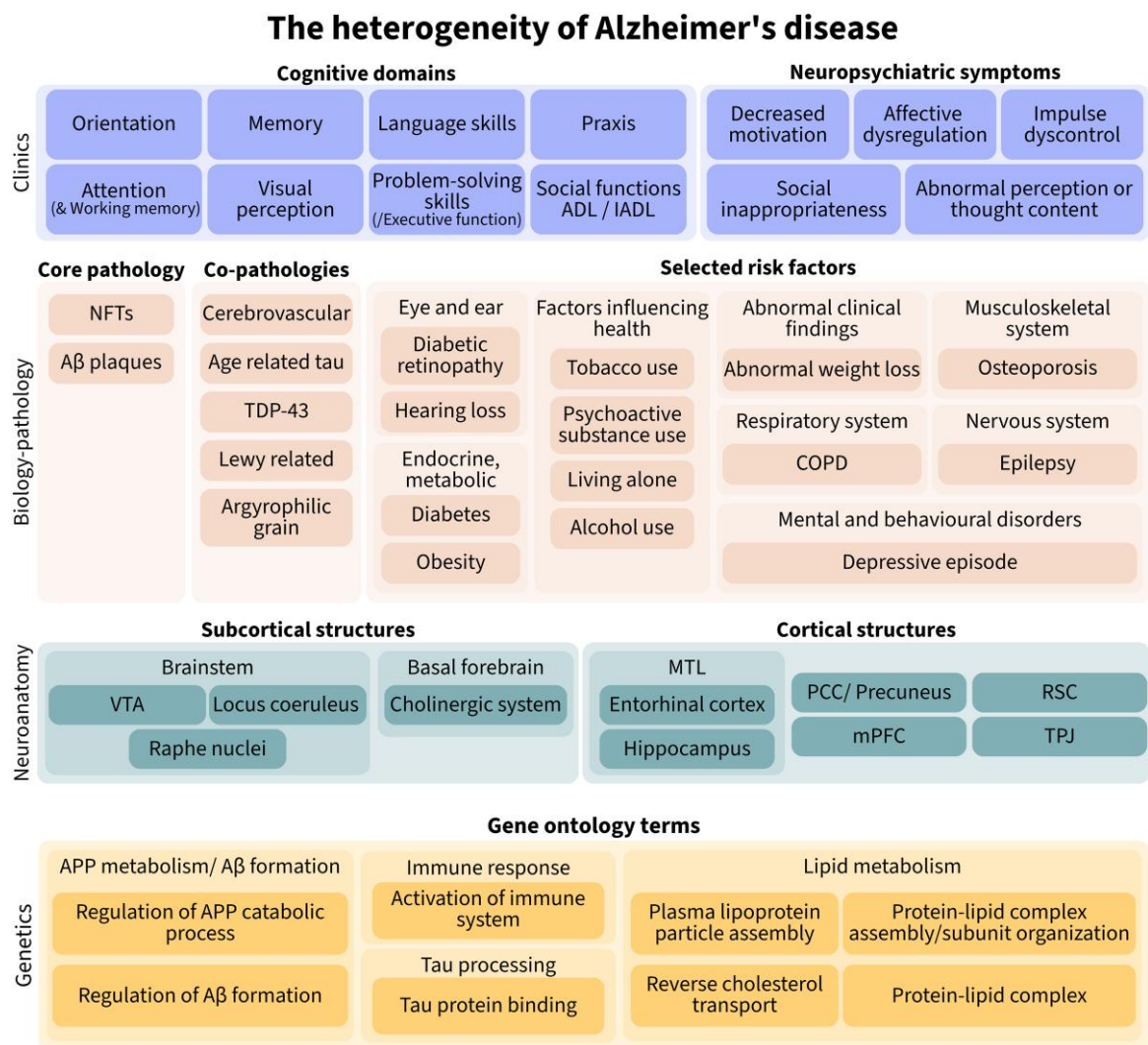


Figure 2 The clinical, biological–pathological, neuroanatomical and genetic heterogeneity of Alzheimer’s disease. On the clinical level (level 1), AD includes categories of cognitive² and behavioural changes.⁷³ On the pathological level (level 2), patients present not only with core AD pathologies,³ but usually also with co-pathologies,⁷⁶ alongside prominent risk factors (risk factors with an odds ratio of ≥ 2.50 as reported by Elias *et al.*⁷⁷ are mentioned). Different neuroanatomical structures (level 3) may be affected, including cortical and subcortical structures.^{78,79} On the genetic level (level 4), four gene ontology terms associated with common risk variants for late-onset AD are mentioned, including APP metabolism and A β formation, tau processing, immune response and lipid metabolism.⁸⁰ A β = amyloid β ; AD = Alzheimer’s disease; APP = amyloid precursor protein; COPD = chronic obstructive pulmonary disease; mPFC = medial prefrontal cortex; PCC = posterior cingulate cortex; RSC = retrosplenial cortex; TPJ = temporoparietal junction; VTA = ventral tegmental area.

language production.¹⁰⁷ Likewise, the Novoic platform, through its Automatic Story Recall Task, asks participants to listen to short stories and retell them immediately and after a delay. Using this platform, AI-derived speech and language features differentiated A β^+ from A β^- CU participants.^{108,109} Moreover, machine learning-derived acoustic and lexical-semantic scores, extracted from people’s recordings, were associated with CSF amyloid in CU older adults.¹¹⁰

Overall, such tools demonstrate how subtle yet evident changes may be detected in people who are otherwise CU in the preclinical stages of AD, expanding the scope of cognitive assessment, in addition to making it more accessible, with increased ecological validity. Furthermore, the self-administered tests not only enable identification of dynamic response and error patterns, but also obtaining a large-scale ground truth and increasing sensitivity to subtle changes in longitudinal tests. Taken together, the landscape reached by a digital, large-scale collection of a variety of cognitive and behavioural deficits in patients along the AD continuum enables us to construct a patient-specific cognitive-behavioural

picture of AD-related deficits. This, in turn, may be mapped to different phenotypes, which may be evaluated further by means of inter-relationships, hierarchy, severity and, specifically, relationships to biological, anatomical and genetic factors.

Level 2: AD as a multifactorial biological-pathological disorder

The latest criteria for diagnosis and staging of AD (2024)³ (Definition 9) represent a significant shift by also incorporating molecular mechanisms, biological pathways and biomarkers, both related and unrelated to the ‘core biomarkers’ of amyloid and tau, taking into account the involvement of multiple potential pathological mechanisms in AD. These include AD non-specific biomarkers of inflammatory and immune processes and neurodegeneration, in addition to those characterizing brain co-pathologies commonly observed in AD, including vascular brain injuries and α -synuclein. Notably, other potential factors, such as environmental toxic

agents¹¹¹ or influence of specific pathogens that have been mentioned in AD research,^{112–114} were not included in these criteria. The integration of these factors in the AD landscape is well defined in the framework of the exposome. The term 'AD-exposome' has recently been introduced to account for both behavioural and endogenous and exogenous environmental factors that contribute to the development and progress of AD.^{115–117} Behavioural factors include lifestyle and activity patterns such as physical inactivity, smoking, alcohol use, diet, sleep, social isolation and education. Endogenous factors refer to internal biological states, including genetics, metabolism, lipid profile, hormones or inflammation. Exogenous factors are related to external environmental exposures, such as air pollution, toxic agents, infections and socioeconomical status (Fig. 2, level 2, and Fig. 3).⁷⁷

With respect to the endogenous neural exposome, neuroinflammatory processes have long been suggested to take part in AD pathology (Fig. 3, different categories).^{48,49} Major players in the AD-related inflammatory process are the microglia, which are CNS-innate immune cells with core functions of phagocytosis, surveillance and capacity for releasing soluble factors.¹¹⁸ Accumulating evidence suggests that microglia are characterized by transition between two states along the pathological progression of AD: neuroprotective activation in asymptomatic AD and a pro-inflammatory state in later disease stages.¹¹⁹ This shift from neuroprotective to pro-inflammatory might be related to genetic variations, such as mutations in *CD33* and *TREM2*, genes of the innate immune system and microglia that increase the odds of AD, or environmental changes leading to microglial priming owing to systemic infections.^{120–122} Given that different states of microglia exist,¹¹⁸ a specific activation state, disease-associated microglia (DAM),¹²¹ was suggested. A recent report suggests that physical exercise changes microglia to DAM, leading to reduction in A β plaques.¹²³ In line with that, glial fibrillar acidic protein (GFAP) is now considered as a plasma and CSF biomarker for astrocyte reactivity in the newest AD criteria.³ This exemplifies the genes-pathology-environment inter-relationships.

Another major endogenous factor is the vascular one (Fig. 3, 'Endocrine' and 'Circulatory system'). The vascular hypothesis of AD posits that vascular dysfunction plays a crucial role in the pathogenesis of the disease. Mounting evidence suggests that vascular risk factors, such as hypertension, diabetes and hyperlipidaemia, are associated with an increased likelihood of developing AD.¹²⁴ Several mechanisms have been suggested, including cerebral amyloid angiopathy (found in 85%–90% of AD cases at autopsy⁷⁶), cerebral atherosclerosis, or chronic cerebral hypoperfusion resulting from reduced cerebral blood flow, as key factors in the onset of AD.¹²⁵ It has also been suggested that these could lead to blood-brain barrier breakdown, oxidative stress and neuroinflammation, which, in turn, might promote the accumulation of A β and tau.¹²⁶ Notably, a recent large-scale study showed vascular and mixed AD-vascular pathology to exhibit different cognitive (language and motor) and brain network patterns from non-vascular AD (general cognition) clinicopathological profiles.¹²⁷

With respect to hormones, the metabolic hypothesis of AD states that significant alterations in brain energy metabolism, particularly in glucose utilization, lies in the basis of AD pathology (Fig. 3, 'Endocrine and metabolic').¹²⁸ AD patients exhibit reduced cerebral glucose uptake and metabolism, associated with decreased activity of key glycolytic enzymes, impaired mitochondrial function and reduced expression of glucose transporters, such as GLUT3 and GLUT4.¹²⁹ Additionally, insulin resistance and oxidative stress play crucial roles in AD pathogenesis, linking

peripheral metabolic disorders, such as type 2 diabetes, to increased AD risk.¹³⁰

An important exogenous domain is the role of pathogens in AD development (Fig. 3, 'Infectious diseases'). Emerging evidence suggests that chronic infections might contribute to AD pathogenesis through various mechanisms. The main theory, as mentioned above, suggests that infections trigger and sustain processes of neuroinflammation.¹¹² Alternatively, a thought-provoking theory claims that A β production might be a defensive response to infection, because A β has been found to have antimicrobial properties, suggesting that it might be part of the innate immune system. This, in turn, contributes to plaque formation and subsequent neurodegeneration.¹³¹ Specifically, several pathogens have been implicated in AD pathogenesis,¹¹³ including herpes simplex virus 1 (HSV-1),¹³² *Chlamydia pneumoniae*,¹³³ spirochetes¹³⁴ and periodontal pathogens.^{113,135} Further research is important to determine their potential inclusion in AD-definition criteria and phenotyping and, ultimately, as treatment targets.

Another evident exogenous exposome domain is toxicity (Fig. 3, toxicity). Exposure to heavy metals, including lead, manganese and cadmium, has been implicated in AD pathogenesis through mechanisms involving oxidative damage, disruption of cellular processes and promotion of A β aggregation. The interplay between these toxic elements might create a self-propagating cycle of neurodegeneration.¹³⁶ Another example is related to an altered gut microbiome, which has been associated with increased levels of pro-inflammatory cytokines and activation of microglia, in turn exacerbating AD pathology, including amyloid plaques and neurofibrillary tangles.¹³⁷ Furthermore, the gut-brain axis appears to play a crucial role, with bacterial products such as lipopolysaccharides potentially contributing to neuroinflammation and AD pathogenesis.¹³⁸

Taken together, different endogenous and exogenous pathological mechanisms may underlie and/or facilitate AD progression, and their roles and mutual interactions still need thorough evaluation. Moreover, other neurodegenerative comorbidities that often occur in addition to AD, such as diffuse Lewy body disease, transactive response DNA binding protein 43 (TDP-43) or limbic-predominant age-related TDP-43 encephalopathy (LATE) may interfere with clinical symptoms and with the ongoing neuropathological process. Likewise, synucleinopathy and TDP-43 proteinopathy show distinct cognitive (visuospatial-dysexecutive and amnesic, respectively) and brain-network profiles.¹²⁷

Level 3: AD as a brain-network disorder

The neuroanatomical structures affected by AD along its progression is another crucial aspect to consider. Earlier studies have demonstrated that the MTL, specifically the hippocampal formation, are the regions most severely affected by NFTs in AD.^{139–141} NFTs were suggested to accumulate in a stereotypical pattern, as depicted by Braak staging, beginning in the entorhinal cortex (Braak I–II), followed by MTL regions, the hippocampus and limbic regions (Braak III–IV) and, finally, association areas in frontal and parietal regions (Braak V–VI).²³ However, more recent studies suggest other regions to be significantly affected early in the course of the disease, emphasising its heterogeneous nature (Fig. 2, level 3).

In a notable study, a detailed neuropathological analysis was conducted on post-mortem brain samples from 889 individuals with a Braak stage above IV to classify AD subtypes based on neuroanatomical patterns of tau pathology.¹⁴² By examining the ratio of NFT density in the hippocampus (CA1, subiculum) and association cortices (middle frontal, inferior parietal and superior temporal



Figure 3 Medical risk factors for Alzheimer's disease. UK Biobank derived ICD-10 diagnoses identified as risk factors for AD (represented by circles) are shown, categorized by colour according to the ICD-10 classification. The size of each circle corresponds to the prevalence of the specific factor within the AD group. The colour intensity of each circle reflects the associated odds ratio. (Reprinted from Elias et al.,⁷⁷ licensed under CC-BY.) AD = Alzheimer's disease.

cortices), the classification algorithm identified two different atypical AD subtypes: hippocampal-sparing AD and limbic-predominant AD. Patients identified with the hippocampal-sparing

subtype presented with cortical related disorders, including visual disturbances (posterior cortical atrophy),^{143,144} primary progressive aphasia^{145–147} and behavioural changes (which may be related to

the dysexecutive or behavioural phenotypes),^{148–150} whereas the limbic-predominant subtype was associated with an amnesic phenotype.¹⁴² These findings were more recently replicated and extended through *in vivo* tau-PET imaging, enabling the identification of tau pathology patterns in different disease stages in living patients.^{148,151–153} The tau-PET studies further distinguished tau regional patterns associated with non-amnesic and hippocampal-sparing clinical presentations, including occipitoparietal regions in posterior cortical atrophy, left lateral temporal and inferior parietal cortices in logopenic variant primary progressive aphasia, and temporoparietal with relative sparing of the frontal cortices in behavioural and dysexecutive subtypes. Therefore, modelling of tau propagation across the AD continuum has suggested four major pathological subtypes, corresponding to clinical AD manifestations: the limbic subtype follows a progression pattern resembling Braak staging, which is commonly associated with the amnesic syndrome; the MTL-sparing subtype (as named by the authors,¹⁵³ although the following variants also present with limited involvement of the MTL), shows early tau accumulation in medial parietal regions,¹⁵⁴ particularly the precuneus, and in the frontal cortex, which is linked to behavioural and dysexecutive symptoms; the posterior subtype is marked by early occipital involvement and is most frequently associated with visuospatial impairment, and in its extreme may progress to posterior cortical atrophy; and the lateral temporal subtype, which shows left-lateralized temporoparietal tau deposition, corresponding in its extreme form to logopenic variant primary progressive aphasia.¹⁵³ Regional tau deposition was linked to reduced connectivity within well-known domain-specific networks, giving rise to clinically distinct AD manifestation.¹⁵⁵ In line with these findings, a growing body of evidence suggests that tau pathology does not spread randomly but rather propagates along functionally connected neural circuits, highlighting the critical role of large-scale brain networks in shaping tau trajectories and their cognitive and behavioural consequences.^{156–159}

Important information has also been derived by studying changes in brain metabolism, as detected by FDG-PET. Hypometabolism was observed in heteromodal cortices in the dysexecutive AD subtype, temporoparietal areas in the amnesic AD subtype, and frontotemporal areas in the behavioural AD subtype.^{51,148,149,160} Moreover, the dysexecutive subtype was identified as having three different phenotypes: patients with predominantly left parietofrontal hypometabolism showed impairment in verbal working memory and verbal fluency, in addition to executive dysfunction; those with right parietofrontal disturbance showed alterations in related visual abilities; and those with bi-parietal involvement presented with predominant cognitive flexibility and inhibition impairment.¹⁶¹

Another line of research has focused on patterns of brain atrophy.^{162–165} One model¹⁶³ proposed a two-dimensional representation of AD heterogeneity, composed of atrophy severity and typicality. The severity axis reflects neurodegeneration levels, ranging from minimal atrophy to severe neurodegeneration. The typicality dimension captures the affected brain regions alongside unique variant characteristics: at the one end is the limbic-predominant variant, associated with late-onset AD, amnesic presentation and higher prevalence of APOE ϵ 4 carriers. At the other extreme is the hippocampal-sparing variant, associated with early-onset sporadic AD, higher prevalence of non-amnesic syndrome, aggressive and faster progression of disease, higher cognitive reserve and brain resistance/resilience, and APOE ϵ 4 non-carriers. Typical AD refers to tau-related pathology and atrophy in both the hippocampus and association cortex.

Moreover, different co-pathologies have been suggested to interact with these variants. For instance, TDP-43 co-occurrence is increased in both typical and limbic-predominant AD (in addition to its involvement in LATE, which still needs further examination) and has been suggested to contribute to the restriction of the pathology to the MTL in the limbic-predominant variant, whereas cerebral amyloid angiopathy was suggested to play a crucial role in hippocampal-sparing AD. This approach supports a shift from viewing AD as comprising discrete subtypes towards understanding it as a continuous spectrum shaped by multiple pathological and individual-level factors.¹⁶³

Level 4: genetic variability in predisposition to AD

Genetic predispositions to sporadic AD include, in addition to monogenic effects that were related directly to AD development (variants of large effects, i.e. APOE ϵ 2/ ϵ 3/ ϵ 4 haplotypes),^{45,166} polygenic variables for the disease itself and for potential risk factors. In recent years, large-scale genome-wide association studies (GWAS) have compared allele frequencies between cases and controls to discover thousands of alleles associated with the risk of complex (polygenic) diseases.^{167–169} These results led to the development of risk predictors of increasing accuracy, known as polygenic risk scores.^{170,171} The scores are computed as the total count of risk alleles carried by an individual, where the weight of each allele is typically assigned to its effect size. Polygenic scores for predicting traits are computed in a similar manner as counts of trait-increasing alleles, weighted by their effect size. Numerous studies have demonstrated highly robust associations of polygenic scores with their respective traits.^{172,173} Prediction accuracy varies across traits (explaining 1%–30% of the variance in the trait/liability to disease), with further variation in accuracy across cohorts, genotyping platforms, sex, age and other demographic parameters. Although polygenic scores are typically not sufficiently reliable to provide accurate individual-level diagnosis, they are promising tools for adjusting for genetic predisposition to diseases or risk factors.^{174,175} Polygenic scores can be applied not only directly to the AD continuum but also to established risk factors in the framework of the neural AD-exposome (exposures over the lifespan of an individual to gene–environment interactions).¹¹⁵ Summary statistics (i.e. association effect sizes per allele across the genome) are nowadays available to this end from GWAS^{169,176} or catalogues of scores, such as PGScatalog (<https://www.pgscatalog.org/>) or polygenic risk score knowledge base (<https://prs.byu.edu/>). Several methods were developed in recent years to optimize the set of variants that are included in a polygenic score, and to refine the weight of each allele, in order to account for the correlation between alleles (linkage disequilibrium) and the genetic architecture of the trait or disease (e.g. LDpred2,¹⁷⁷ PRSs¹⁷⁸ and lassosum¹⁷⁹). Therefore, the richness of genetic vulnerability to developing AD, both directly and through risk factors, is now available and should be considered.

Recent large-scale GWAS of AD have identified susceptibility loci converging on four primary biological pathway clusters: (i) A β formation and APP metabolism; (ii) tau processing; (iii) immune response; and (iv) lipid metabolism.^{80,180} The involvement of A β , tau and inflammation have been discussed above. Lipid metabolism, however, remains underappreciated as a core pathological mechanism, despite substantial evidence implicating it as a fundamental driver of disease (Fig. 2, level 4). Dysregulated lipid metabolism, specifically accumulation of lipids in glia, was noted as a third major AD pathology right from the start, in Alois Alzheimer's original report (termed 'adipose saccules').⁵ This phenomenon was recently rediscovered as a distinct dysfunctional

microglial state, termed lipid-droplet-accumulating microglia.¹⁸¹ Research revealed a complex disruption of cholesterol metabolism and lipid-protein mechanisms. Cholesterol homeostasis is profoundly disturbed in AD, characterized not by simple excess or deficiency but by impaired trafficking^{182–184}; *de novo* cholesterol synthesis and catabolism are reduced in the entorhinal cortex and the hippocampus of AD patients (yet, cholesterol levels were normal, which might suggest a reaction to impaired trafficking),¹⁸⁵ whereas free cholesterol accumulates pathologically within NFT-bearing neurons¹⁸⁶ and specific cortical layers,¹⁸⁷ suggesting a fundamental failure of distribution. Lipid raft composition is altered early in disease progression, even before NFT formation, with depletion of cholesterol and plasmalogen alongside accumulation of gangliosides and ceramide. These structural changes disrupt normal lipid-protein binding and assembly while facilitating pathological interactions, including the APP/BACE1 proximity that promotes amyloidogenic processing; notably, A β plaques themselves incorporate cholesterol and gangliosides, suggesting that lipid dysregulation feeds directly into core AD pathology.¹⁸⁸

Taken together, the linkage between distinct clinical symptoms and biomarkers contributes to the conceptualization of AD as a heterogeneous disorder composed of several subtypes, not only with respect to clinical manifestations and pathology, but also with respect to its expression in the underlying brain networks involved and genetic predispositions.¹⁸⁹ A step forwards in this direction was proposed by the European multidisciplinary task force, suggesting a ‘patient-centred diagnostic workflow’ encompassing major known clinical-pathological syndromes in cognitive neurology.¹⁹⁰ Moreover, the different clinical, biological/pathological, neuroanatomical and genetic expressions might not only stand alone but might also be classified according to different subtypes and/or on a continuum of different combinations varying between two or more poles.

Combining data and theory: towards explanatory integrative modelling of the heterogeneity of AD

In the first part of this paper, we presented the different definitions introduced for AD over the years, showing that not all hypotheses about AD are mutually exclusive, and each offers valuable insights into different facets of the disease. In the second part, we suggested expanding the definitions of AD by means of both multiple domains (cognition/behaviour, biology/pathology, neuroanatomy and genetics) and the heterogenic factors within domains. In each domain, we suggested an inclusive approach: all AD-related cognitive, behavioural and neuropsychiatric symptoms; the full range of biological, pathological, medical and lifestyle-related factors; characterization of the neuroanatomical substrate across discrete brain regions and large-scale networks expressed through a constellation of structural degeneration, functional and metabolic aberrations, and pathological protein deposition; or expression of the different genetic variants, both direct and indirect ones (currently considered only as a general marker in stage 1 of the AA 2024 AD criteria³). This expansion might seem problematic, because statistical power will be difficult to achieve for derivations to be drawn conclusively. Although most available research AD databases currently consist of, at most, a few thousands participants, and results are focused on a few data modalities, the data and computation revolutions enable the evaluation of many more individuals with valuable variable data and the incorporation of these data into multimodal analyses.¹⁹¹ Yet, most computational models

for AD are largely limited to predicting outcomes based on a sparse number of categorical domains and modalities. To move beyond purely phenomenological or descriptive accounts and towards a quantitative operational framework, data on AD must be integrated into a unifying model. Such a model should capture the key aspects of disease progression across the above-mentioned multiple relevant domains and factors within domains, based on the available data, while building on accumulated knowledge from past modelling efforts for different aspects of AD based on data available at the time.^{192–197} Although the task of constructing such a unifying model appears daunting and will require multiple iterations and a community effort, it will provide a critical framework for researchers and clinicians, through which to assess systematically the relative importance of different domains and pathways to identify the most critical drivers of pathology. It would also provide testable predictions about how, when and to what extent each factor contributes to disease progression, furnishing a basis for both mechanistic studies and targeted interventions. In this sense, the goal is not simply to define overlapping syndromes or AD subtypes, but to create an integrated, data-driven model that can be tested and refined in practice, thus transforming theoretical constructs into actionable strategies for diagnosing and treating AD.

More specifically, a useful unifying model of AD should serve several complementary purposes that go beyond description of empirical patterns. First, it would integrate multiple levels of data, from cognitive-behavioural measures through biology, pathology and molecular biomarkers, neuroimaging and genetics, into a coherent framework. Second, it would account for different potential factors within each level. Third, it would consider temporal aspects, such as different progression rates of AD subtypes¹⁹⁸ and development of risk factors,¹⁹⁹ that have crucial effects. Fourth, it would offer a mechanistic explanation of how the different factors interact over time to drive disease onset and progression, as opposed to focusing on any single pathology. Fifth, by identifying key causal pathways and feedback loops, the model would illuminate points of intervention, suggesting testable targets for drug development and/or lifestyle or medical interventions. Sixth, it might help to decide whether there are different trajectories in AD development,^{153,200} different subtype clusters,^{142,155,201} a continuum between certain poles,¹⁶³ or motifs that balance one another.^{202,203} Seventh, although clinical trials currently focus on group comparisons or target one pathology and focus on one primary clinical outcome, integrative modelling that takes into account the many variables in play might help to stratify patients into distinct subtypes/trajectories/motifs, thereby facilitating more personalized approaches, which could ultimately translate into more effective clinical trial design and later clinical care.^{198,204} Finally, it would be predictive, generating hypotheses about disease evolution and individual outcomes that can be validated or refined through longitudinal data.

Constructing such an integrative unified model is inherently difficult for several reasons, not least because the relevant data tend to be noisy, sparse, ambiguously labelled and sometimes contradictory. Moreover, disparate data sources often pertain to different aspects and scales of the disease, and it might be impractical to consolidate them into a single ‘one-size-fits-all’ model. In particular, it is not even clear what the mathematical representation of such a model should be. Instead, different aspects of AD should be modelled using different representations based on the datasets and focusing on different spatiotemporal scales (e.g. molecular versus systemic or slow versus fast processes). A more practical alternative is to adopt a divide-and-conquer strategy: initially, build smaller, specialized models that each capture a particular facet of

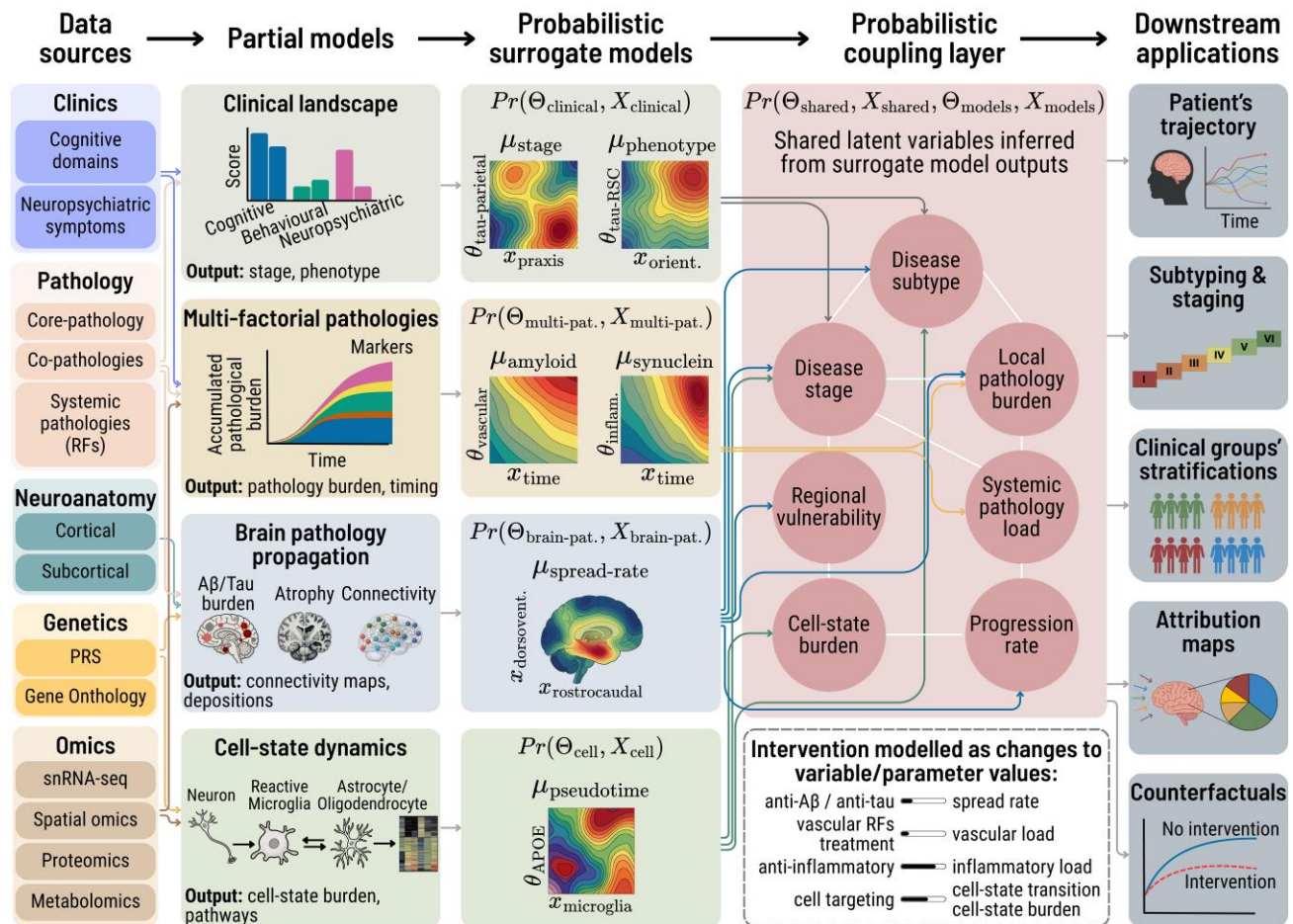


Figure 4 Schematic representation of Bayesian metamodeling for Alzheimer's disease. Heterogeneous data spanning the five levels of clinics, pathology, neuroanatomy, genetics and omics (first column) are fed into partial models (second column). Each partial model aims to capture some aspects of Alzheimer's disease, drawing on one or several inputs to yield a desired output (e.g. predictions and classifications). To provide a common probabilistic language across these partial models, each model is converted to a probabilistic surrogate model (third column), a probability distribution $Pr(\Theta_{\text{model}}, X_{\text{model}})$ over a subset of its parameters Θ_{model} (e.g. spread rate and APOE effect) and variables X_{model} (e.g. regional damage and time), which approximates the behaviour of the original model. The probabilistic coupling layer (fourth column) then couples the surrogate models by formally defining how the parameters or variables from the surrogate models ($\Theta_{\text{models}}, X_{\text{models}}$) inform shared latent parameters and variables of interest ($\Theta_{\text{shared}}, X_{\text{shared}}$). In this layer, shared variables are not merely additional outputs; they serve as common probabilistic quantities that enable several models to exchange information. For example, Θ_{shared} may correspond to latent parameters governing disease dynamics (e.g. risk-dependent priors), and X_{shared} may capture the inferred patient state (e.g. disease subtype, disease stage and regional vulnerability). Interventions are modelled as targeted changes to variable and parameter values (e.g. anti-tau therapy as lowering the spread rate). The inferred posterior distribution then supports a range of downstream applications and final outcomes (fifth column). AD = Alzheimer's disease; brain-pat. = brain-pathology; orient. = orientation; RFs = risk factors; RSC = retrosplenial cortex.

AD (e.g. in the clinical domain, separate models for vascular, metabolic or immune responses; or domain-specific decline in the cognitive level); then, fuse these models. Bayesian metamodeling is an integrative modelling approach that implements this strategy by converting each sub-model into a probabilistic surrogate model that captures the dependencies between model inputs and output, followed by their harmonization in a joint probabilistic model via auxiliary coupling variables (Fig. 4).^{205,206} By synchronizing distinct insights within one overarching Bayesian structure, one gains a cohesive but still operationally flexible model of the disease, far more tractable than attempting to force every dimension of AD pathology into a single monolithic representation.

To reiterate, according to the lines we have drawn here, a Bayesian metamodel should include partial models that describe the principal facets of AD and its progression, including: progression of the different cognitive and behavioural ecologically evaluated symptoms; molecular cascades of the hallmark pathologies, such

as amyloid, tau and other misfolded proteins; dynamic shifts in key cellular subpopulations (e.g. microglia, astrocytes and neurons) over the disease course; activation or suppression of intra- and inter-cellular signalling pathways that drive those shifts; mechanisms governing these processes across multiple, nested time scales; network-level and spatiotemporal propagation of pathology and atrophy; vascular, metabolic and inflammatory dynamics that modulate or, in some instances, initiate those processes; associative and mechanistic links connecting genetic or polygenic risk scores to specific pathways; and translation of the evolving pathological-biological state into cognitive, behavioural and functional trajectories.

A practical implementation of this framework might begin with a carefully selected set of concrete partial models that capture key aspects of AD and its progression, each grounded in specific data modalities and mathematical representations, then expand iteratively as additional processes, datasets and models are incorporated (Table 1 and Fig. 4, columns 1 and 2). A longitudinal clinical

Table 1 Partial models for Alzheimer’s disease

Model class	Representative use in the metamodel	Typical data	Research/clinical questions	Question enabled by coupling	Example references
Imaging-to-clinical mapping model	Map imaging patterns to cognition, symptoms or functional status	MRI; PET; regional imaging summaries; cognitive/functional scores	Which imaging features best explain present cognitive phenotype?	Can mechanistic latent variables improve interpretability and prediction of clinical state?	Davatzikos et al., ²⁰⁷
Disease progression/staging/subtype model	Infer latent disease stage and subtype from cross-sectional or short longitudinal multimodal data	MRI, PET, CSF/plasma biomarkers, cognition, diagnosis labels	What is the patient’s AD stage and subtype trajectory?	How do stage and subtype couple to propagation, cell-state change and cognitive decline?	Hernandez et al., ²⁰⁸ Fontijn et al., ²⁰⁹ Young et al., ^{195,210} Venkatraghavan et al., ²¹¹
Longitudinal forecasting model	Forecast future cognition, diagnosis or biomarker trajectories for individuals	Repeated cognitive scores; MRI; PET; CSF/plasma; demographics	What will diagnosis/neuropsychological grade/ventricle volume probably be in 1–3 years?	Does adding mechanistic propagation or genetic priors improve person-specific forecasts?	Nguyen et al., ¹⁹⁶ Maheux et al., ¹⁹⁷ Marinescu et al., ²¹²
Semi-mechanistic biomarker cascade model	Model interactions among amyloid, tau, neurodegeneration and cognition in a compact dynamical framework	Longitudinal AT(N)-style biomarkers; cognition	What biomarker ordering and coupling best explain observed trajectories?	How do external modules, such as genetics or vascular load, perturb the cascade parameters?	Bossa & Sahli, ²¹³ Mazer et al., ²¹⁴
Cellular-state/single-cell trajectory model	Model disease-related shifts in neuronal, glial and immune cell states across progression	sc/snRNA-seq; cell-type proportions; pseudotime; spatial transcriptomics; proteomics	Which cell states and pathways change with disease stage?	How do cellular changes explain imaging trajectories or clinical heterogeneity?	Keren-Shaul et al., ¹²¹ Mathys et al., ²¹⁵ Gabbito et al., ²¹⁶ Green et al., ²⁰⁰
Vascular/metabolic/inflammatory modulator model	Represent non-core drivers or modifiers of AD progression	Vascular imaging; perfusion; metabolic markers; inflammatory plasma/CSF markers; comorbidity data	Are vascular/metabolic/inflammatory changes early, late or subtype-specific contributors?	Do these modulators change propagation, cell-state shifts or cognitive decline independently of amyloid/tau?	Iturria-Medina et al., ²¹⁷ Nguyen et al., ²¹⁸
Brain pathology spread model	Model regional propagation of amyloid, tau, atrophy or hypometabolism across brain networks	Structural connectome; regional tau/Aβ PET; MRI atrophy; FDG-PET	Given a current regional pathology pattern, what future spatial pattern is expected?	How do genetics, vascular burden or cell-state changes alter propagation speed, seeding or regional vulnerability?	Raj et al., ¹⁹² Iturria-Medina et al., ¹⁹³ Vogel et al., ¹⁵³
Genetic risk model	Represent APOE/PRS/PHS effects on onset age, progression speed or pathway-specific vulnerability	Genotype; APOE; GWAS-derived scores; age/sex	How does inherited risk shift hazard or expected onset age?	Which downstream cascades or subtypes are preferentially modulated by genetic risk?	Desikan et al., ¹⁹⁴

Examples for computational models related to the different factors of the clinical, pathological, neuroanatomical and genetic explanatory levels and their interactions. Potential benefits from coupling of these models are suggested. Aβ = amyloid-β; AD = Alzheimer’s disease; APOE = apolipoprotein E; AT(N) = Amyloid, Tau, Neurodegeneration system; CSF = cerebrospinal fluid; FDG-PET = fluorodeoxyglucose positron emission tomography; GWAS = genome-wide association study; MRI = magnetic resonance imaging; PET = positron emission tomography; PHS = polygenic hazard score; PRS = polygenic risk score; sc/snRNA-seq = single-cell/single-nucleus RNA sequencing.

trajectory statistical model might predict future cognitive, behavioural, functional or diagnostic trajectories from multimodal patient-level data; such models can describe the change in core pathologies over time and their relationship to clinical outcomes.^{195–197,207–214} Multifactorial models might also consider vascular, metabolic, inflammatory or cellular-state processes.^{217,218} Brain-network models can describe the neuroanatomical propagation of pathologies based on structural and molecular neuroimaging, classifying individuals into disease subtypes and progression stages.^{153,192,193} A fourth type of partial models, the omics-based models, including transcriptomic, proteomic, metabolomic or spatial-omic models, might help to relate molecular and cellular states to pathology, imaging and clinical phenotypes.^{121,200,215,216} Other models might also be considered; for instance, a genetic risk model, including APOE and polygenic risk scores, that estimates predisposition, modifies prior probabilities over disease trajectories, and constrains parameters of the other models.¹⁹⁴

Each partial model can be developed independently, then converted into a probabilistic surrogate model (Fig. 4, column 3). In practice, this involves selecting a subset of the parameters and variables in the model that are relevant for coupling, evaluating the model repeatedly across a range of parameter and input values, and learning a probability distribution over this subset using established probabilistic modelling methods.^{205,219–221} This surrogate can then be coupled with other surrogate models through shared variables in the metamodel (Fig. 4, column 4). These shared variables provide a formal layer, in which model-specific parameters and variables jointly inform shared latent quantities, such as patient-level disease stage, subtype, pathology burden, regional vulnerability, cell-state burden and progression rate. This enables questions to be addressed that no model can address alone. The same framework can represent interventions as targeted changes to variables or parameters (Fig. 4, column 4, bottom), such as reducing tau spread rate, vascular load, inflammatory load or cell-state transition burden. The inferred posterior distribution then supports downstream applications, including prediction of individual disease trajectories, individualized staging along the disease continuum, stratification into clinical and biological subgroups, attribution of pathology to specific drivers and brain regions, and counterfactual comparison of predicted trajectories with or without intervention (Fig. 4, column 5); such comparison can also help to assess which mechanisms mediate an intervention effect and compare competing mechanistic hypotheses within a shared probabilistic representation.

Each partial model can be constructed independently, calibrated with the data modality most appropriate to it, then coupled probabilistically through shared latent variables, such as time-aligned disease stage, regional cell loss or systemic inflammation load. Importantly, the metamodel could host several alternative formulations within the same category, e.g. multiple published models of amyloid and tau spread, meaning that competing hypotheses are compared and weighed against the data in a single probabilistic space. Because additional partial models could be added iteratively, the metamodel would remain a living framework that assimilates new evidence, propagates uncertainty across domains and generates patient-specific forecasts that are mechanistically interpretable while honouring the full clinical, biological, neuroanatomical and genetic heterogeneity. Realizing this vision is a considerable undertaking, yet the ability to develop each component independently makes the effort inherently collaborative and iterative, allowing the research community to converge, over time, on an increasingly comprehensive and unified model of AD.

Conclusion: approaching AD as a computationally informed heterogeneous, multifactorial and multifaceted disorder

In this paper, we attempted to draw a picture of AD^{26,222} as evolving over four different domains: cognitive-behavioural symptomatology; biological–pathobiological factors; neuroanatomical basis; and genetic traits. Each domain is treated as a complex system, combining a large range of factors, including different symptoms, molecular, cellular and system-level mechanisms, brain network data, and direct and indirect genetic influences.^{159,223} We suggest that dynamic interactions between factors over time produce the emergent heterogeneity evident in AD. Such a complex framework might be the root cause of our struggle to understand and advance robust AD treatment or prevention approaches. Moreover, this complexity might be interpreted in different manners according to co-existing or alternative underlying hypotheses. The new era of digital health, including the ability to handle big clinical data, apply novel algorithms and modelling, consider sub-models and build metamodels, compare competing hypotheses and consider probabilities against the data, can help us to tackle this complexity and better understand the interrelationships between the different domains, the factors within each domain, hypotheses developed in the AD field over time, and data gathered in observational studies and clinical trials. Such a large-scale and far-reaching effort is beyond the capacity of a single research group or institute and might require years to bear fruit. Nonetheless, the insights gathered here provide a roadmap for an improved and more nuanced diagnosis of AD that leverages tools and methods only recently developed and made available. A global effort that combines expertise of researchers and clinicians across multiple disciplines can result in such large-scale, data-driven models for a comprehensive understanding of AD. This, in turn, will help to identify more robust targets for treatment and prevention that are urgently needed. Finally, such an approach might also be applied to other complicated, multifaceted and heterogeneous disorders, including other neurodegenerative disorders,¹⁵⁹ epilepsy syndromes and mental health conditions, that remain to be comprehended scientifically and managed better.

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Competing interests

The authors report no competing interests.

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