Title: Challenges in a biological definition of Alzheimer's disease

Short Title: A biological definition of Alzheimer's disease

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Abstract:

It has been suggested that the diagnostic landscape of Alzheimer's disease (AD) is undergoing a profound transformation, marked by a shift towards a biomarker-based approach, as proposed by the revised criteria for diagnosis and staging of Alzheimer’s disease. These criteria advocate for diagnosing AD solely on biomarkers, without requiring clinical symptoms. This paper explores the drivers behind this transition, primarily influenced by the FDA's approval of amyloid-lowering treatments. We evaluate the proposed criteria, which allow for an AD diagnosis based on amyloid “A” or phosphorylated tau “T1” positivity through surrogate amyloid PET imaging, CSF, or plasma biomarkers, and consider the arguments for and against their use. The merits of the new criteria include a clearer definition of AD, which is currently used interchangeably to refer to both the presence of neuropathology and the clinical syndrome. We argue that a purely biological definition risks a category error and emphasize the need for longitudinal data to establish the lifetime risk of dementia in amyloid and tau-positive individuals. We also caution against limiting the scope of biomarker-based AD diagnosis to amyloid and tau alone. In conclusion, we recommend that the criteria remain within the research domain for the present, while advocating for the considered adoption of plasma biomarkers in clinical practice.

Recent years have seen rapid evolution in Alzheimer’s disease (AD) research. In 2021, the Food and Drug Administration (FDA) approved aducanemab to treat patients with Alzheimer disease and in 2023 it approved lecanemab for a similar indication.1 That same year, at the Alzheimer’s Association International Conference (AAIC) the phase III clinical trial data for donanemab and data on the utility and adoption of a range of AD plasma biomarkers were presented.2–4 At that meeting, the National Institute on Aging and the Alzheimer’s Association (NIA-AA) convened a working group that presented a draft proposal for revised criteria for the diagnosis of AD.5 Because the NIA now serves on an advisory capacity, its co-sponsorship came under scrutiny because it was seen to extend beyond its research scope. The recently published 2024 AA criteria are known as: Revised criteria for diagnosis and staging of Alzheimer's disease: Alzheimer's Association Workgroup.6–8

The NIA-AA initially published AD diagnostic guidelines in 2011.9 These characterised an AD disease continuum, from preclinical AD to mild cognitive impairment (MCI) due to AD to AD dementia. Around the time when these guidelines were published, in vivo biomarkers of AD (amyloid and tau) PET and CSF (amyloid and tau measures) were developed, and these allowed an antemortem diagnosis of AD neuropathological change. As a result, the 2018 NIA-AA research criteria proposed the amyloid (A)/tau (T)/neurodegeneration(N) system, with an A+T+ biomarker profile required for a biological definition of AD.10

The 2024 AA criteria propose the adoption of a purely biologically-based construction of AD to inform clinical practice as well as research.5 Based on these criteria, a diagnosis of AD can now be made based on either amyloid “A” or phosphorylated tau “T1” positivity using surrogate amyloid PET imaging or CSF or plasma biomarkers (p-tau217). The “N” classification was removed from the core biomarker criteria. Crucially, although the criteria highlight the value of clinical judgement for the diagnosis, the biological AD definition does not require the presence of clinical symptoms. The criteria do not advocate for the screening of preclinical disease, although those with subjective cognitive concerns may be tested. A diagnosis of AD, which can be made in the absence of clinical symptoms, will have significant implications for clinical practice and patient care. In addition, 2024 draft U.S. FDA guidance proposes that a change in a surrogate biomarker concentration alone can be accepted as evidence of efficacy in the licensing of treatments for asymptomatic preclinical AD individuals.11 This could mean that a biomarker result could be used to both diagnose AD (2024 AA criteria) and as evidence of treatment response (2024 FDA draft criteria), in an asymptomatic individual.

Proposed reasoning for updating the criteria.

The 2024 AA criteria can be seen as an inevitable outcome of FDA approval of amyloid-lowering treatments based at least partly on surrogate biomarker endpoints and the proposed sole use of biomarker concentrations as indicators of treatment efficacy in asymptomatic trial participants.12,13,11 The criteria distinguish between an asymptomatic AD “disease” phase and an “illness” stage, when symptoms are evident. Proponents of the criteria assert that this approach aligns with other areas of medicine, particularly oncology, where surrogate biomarkers are used to screen and diagnose disease prior to symptom development. With the advent of treatments targeting AD pathology, the new definition seeks to conceptually align the diagnosis of AD with an integrated set of biological markers and clinical stages that begin in the presymptomatic state. This approach aims to improve diagnostic precision, identify eligible participants for clinical trials (including those without symptoms), and target and monitor treatment responses.

Arguments for and against the proposed draft criteria.

One advantage of a purely biological definition is that it clearly conceptualises Alzheimer’s disease as a distinct pathological process, separate from the clinical manifestations of the various diseases that cause cognitive decline. This strictly biological definition may help to avoid the confusion caused by the term "Alzheimer's disease," which can refer to both the underlying biology and the dementia syndrome. If abnormal amyloid and tau accumulation are risk factors for developing Alzheimer's dementia, it would be important to identify and mitigate this at the earliest possible timepoint. This could be comparable to identifying and treating cerebrovascular disease risk factors, such as hypertension. Ongoing studies such as AHEAD 3-45 Study (BAN2401-G000-303) may provide valuable insights into treatment outcomes in this asymptomatic amyloid positive population.14 However, secondary prevention studies may not have a long enough period of follow up or adequate sample size to provide meaningful information on efficacy in terms of dementia risk reduction.15 A consensus biological definition of Alzheimer’s disease could set the stage for earlier and more precise identification of clinical trial participants. The second advantage is that biomarker use in clinical trial recruitment has helped to increase diagnostic validity within those trials.16 Patients and carers could use such information to facilitate earlier care planning and inform decisions to enter presymptomatic treatment trials.

Despite these putative advantages of using a biological definition of AD in clinical trials and

clinical care, several questions arise regarding the widespread use of the proposed AA criteria. First, does the biological definition of AD fall into the trap of a category error? A category error is made when we assign a problem to a category that is not appropriate for solving it. An example of a category trap is the use of blood glucose concentrations to define type II diabetes.17 Because biomarkers such as blood glucose level are continuously distributed variables, it is difficult to establish a clear threshold that distinguishes between healthy and potentially harmful levels that warrant a diagnosis and subsequent intervention. Defining such thresholds can prove elusive, particularly when considering the heterogeneity of the populations, and contributory environmental factors that affect the risk of developing complications of diabetes. Establishing thresholds introduce an intermediate or “grey zone” for biomarker cut points, which require clinical interpretation, integrating the result in the context of the history, examination, and clinical judgment. By equating pathological changes with the disease itself and relying on rigid biomarker causal pathways, using fixed cut points, we would move away from appreciating the complex interplay of etiologies that drive the dementia process.18

Further work is required to establish the lifetime risk of dementia in amyloid and tau positive individuals, particularly Aβ biomarker positivity is not always deterministically associated with a dementia outcome19 and tau is more strongly associated with cognitive status and neurodegeneration than amyloid18. While the presence of increased brain amyloid is necessary for the propagation of tau beyond the medial temporal lobe, we know that AD amyloid-beta (Aβ) biomarker positivity alone is not sufficient.20,21 This may be due to a substantial lag before tauopathy spreads beyond the medial temporal lobe. For example, young-onset dysexecutive AD is characterized by a high tau load during the MCI phase and will progress faster than late-onset limbic-predominant AD.22 Consequently, as late-onset limbic-predominant AD typically happens later in life, many people with elevated amyloid will die of other causes before this progression takes place.

There is a danger of narrowing of the scope of biomarker-based AD diagnosis with a focus purely on the amyloid and tau hypotheses. However, these processes are not fully elucidated with questions remaining over the causal relationship between Aβ or tau and AD.23 This could detract from other important contributory pathological mechanisms and that dementia in most older people is characterised by co-pathology, including TDP-43, Lewy bodies and cerebrovascular changes.24,25 Amyloid and tau imaging have revealed the constraints of solely focusing on plaque and tangle pathology. This limitation has led to the recognition of other contributors, such as limbic TDP-43 proteinopathy.26 The heterogeneous nature of late onset AD with both a long natural history of the disease and variation in presentation may mean that the specificity of these biomarkers for AD dementia is uncertain.

Technological progression should not automatically be assumed to be beneficial for the health and well-being of populations. Are we risking overmedicalisation and introducing iatrogenic harm? The balance between risks and potential benefits of a biological AD diagnosis will differ between AD severity stages, e.g. compared to patients with ‘early’ symptomatic AD, the potential clinical benefits of amyloid lowering agents in asymptomatic individuals is even more uncertain, mainly owing to limitations in interpreting trial outcomes in the context of a long natural disease course.15,27

The prevalence of amyloid positivity in asymptomatic individuals aged 80 to 89 years is around 40% and the same study estimated that 22% of all adults over the age of 50 will be amyloid positive. 28 This means that 26 million people in the United States alone may be amyloid positive. According to the new criteria, such individuals can now be classified as having AD. Because the predictive accuracy of amyloid positivity for dementia is uncertain,19 diagnosing them with AD will introduce unintended harms including distress for patients and carers. Who will benefit from the potentially significant expansion in the number of people who qualify for a drug treatment? Focusing resources on amyloid and tau lowering treatments will divert funds from already underfunded effective evidence based psychosocial interventions and social support for patients and caregivers.29,30 We do not yet have effective treatments that can arrest the disease process before it causes symptoms; if we did, we would support this biologically defined criteria.

Looking towards the future

Defining the presence of AD purely on biomarker evidence of amyloid and tau positivity does not reflect the complexity of the dementia construct and we are concerned that such an approach may cause more harm than good. Such an approach has value in research settings, where it can be used to frame hypotheses, but it is not yet appropriate for use in clinical practice. We do not propose rejecting the criteria in its entirety. The incorporation of plasma biomarkers may have diagnostic utility for diagnosing people with symptomatic AD4. However, it is important that the criteria incorporate the full range of pathological mechanisms that contribute to the AD dementia process. A biologically reductionist approach cannot capture the multiple processes involved in Alzheimer’s dementia, including the role of psychological and social factors. Rather than eliminating these from our understanding of dementia, we must embrace complexity. This will ensure that we do not invest false therapeutic certainty in the dominant hypotheses of the day. To date, there is no evidence that targeting tau is associated with clinical benefit in people with AD. Indeed, the modest clinical outcome data from Aβ therapy trials shows the danger of assuming that risk factors or biomarkers for a disease *are* the disease2,18.

The proposed narrowly defined biological model of sporadic AD is currently insufficient, unrelated to etiological complexity and a long pathological process, and overshadows other biopsychosocial models31 and risk-modification strategies32. It is important to maintain a clear distinction between the definition of AD pathology and the clinical syndrome of AD dementia. If there really was utility in defining an illness on the basis of a minimal set of features that are (1) present in all patients and (2) potentially modifiable, then the most propitious definition of AD dementia would be as a disorder of social function, since it is the quality and quantity of social support that can determine a patient’s quality of life and speed of disease progression.

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