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INVITED ARTICLE

Reducing confusion surrounding expert conceptions of Alzheimer's and dementia: A practical analysis

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Abstract

Biological, clinicobiological and clinical conceptions of Alzheimer's disease and related dementias are being promoted simultaneously to different practical ends. The co-existence of contemporary conceptions and the 'scary label' associated with older diagnostic criteria create the possibility of misunderstanding and harm. In this comment, we argue in favour of socio-ethical interventions targeted to health workers and the general public so as to lower the uncertainties introduced by contemporary diagnostic criteria and to articulate how they relate to established criteria.

KEYWORDS

Alzheimer's, biological definition, confusion, dementia, practical analysis

Alzheimer's disease is currently understood as an age-related brain disease associated with 70% of over 55 million cases of dementia worldwide, characterized by progressive amnesia, language disorders (aphasia) and behavioural dysregulation (WHO, 2023). However, Alzheimer's disease has not had a fixed meaning, but has changed throughout history. This is because researchers in the biomedical sciences adapt or 'engineer' their concepts in ways that are not only knowledge-driven but also outcome-driven (Lalumera, 2023). We can usefully divide the history of Alzheimer's into two periods since the first descriptions of it around 1906 by Dr. Alois Alzheimer: before and after the founding of the United States Alzheimer's Association in 1980 (Figure 1).

The first descriptions of Alzheimer's disease at the turn of the 20th century described this clinical syndrome along with a post-mortem description of pathology within the brain – senile 'plaques' outside neurons and neurofibrillary degeneration in 'tangles' inside the neurons (Keuck, 2018). However, unlike today, the cases of Alzheimer's disease described were exceedingly rare, and concerned patients in their 40s and 50s. Since this period, there has been an oscillation between a focus on brain pathology and a focus on the ageing process to understand ('senile') dementia (Ballenger, 2006). These are two distinct philosophical projects: a focus on Alzheimer's as a specific disease, versus a focus on the clinical syndrome of dementia as part of ageing (Daly & Keuck, 2024). Their synthesis in the 1970s and 1980s

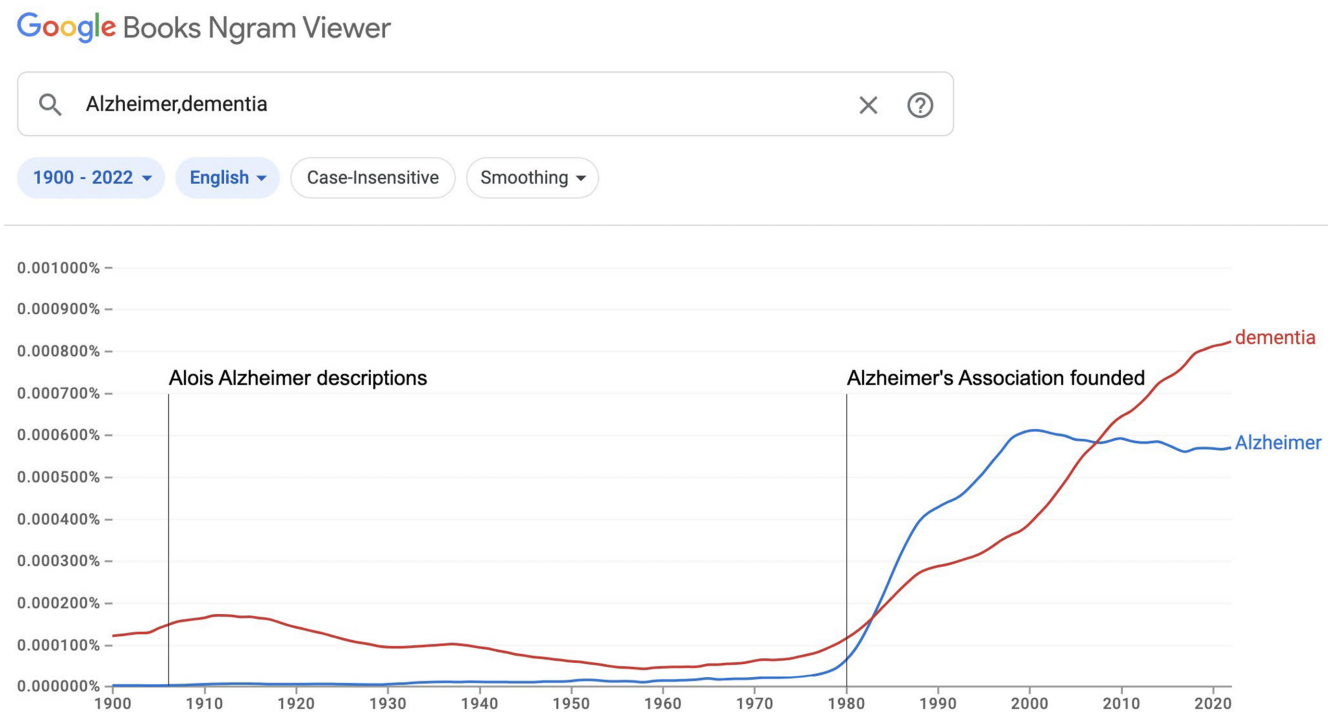

FIGURE 1 Two periods of usage of the term 'Alzheimer's' compared with 'dementia': A 70-year period of infrequent use when understood as a rare disease compared to age-related dementia (the Alois Alzheimer period), versus a public health problem where Alzheimer's is understood as the major cause of age-related dementia, in which their use is comparable (Alzheimer's Association period). Importantly, the vast increase in use of the term 'Alzheimer' corresponds to the birth of the Alzheimer's Association (1980), which has played a major role in promoting, as well as setting the meaning of the term. Both frequency and meaning have stayed relatively stable in common usage since the turn of the 21st century. Produced on 12 September 2024 with Google Ngram Viewer (https://books.google.com/ngrams/) of attested historical uses of the term 'Alzheimer' and 'dementia' (1900–2022).

led to the Alzheimer's movement, which consolidated Alzheimer's as a unique diagnostic entity and its perception as a major threat to the public health of an ageing population (Fox, 1989).

Since 1980, the Alzheimer's Association has played the most important global role in promoting Alzheimer's and setting its definition through fundraising and public awareness, collaboration in the first clinical diagnostic criteria in 1984 before biomarkers were available (McKhann et al., 1984), running four leading *Alzheimer's & Dementia* journals and international congresses (the yearly 'AAIC'), and consistent highly-cited work on reconceptualizing the Alzheimer's entity in our era of biomarkers of which the latest paper mentioned below on biological diagnosis is only the latest example. It has thus achieved its mission of getting Alzheimer's disease into daily discourse, comparable with dementia (Figure 1).

Historically, Alzheimer's was understood as a '*clinicopathological*' entity: clinical dementia plus plaques and tangles in post-mortem pathology (Keuck, 2018; Villain & Michalon, 2024). However, since the late 2000s, in vivo biomarkers of the brain proteins amyloid-beta and tau (found in the post-mortem 'plaques' and 'tangles' respectively) have replaced post-mortem pathological confirmation of Alzheimer's disease diagnosis, leading to new definitions and the term '*clinicobiological*' that refers to people who are positive for biomarkers of Alzheimer's and also have abnormal cognitive symptoms (Villain & Michalon, 2024). Work in philosophy shows that one concept (in this case, pathological age-related cognitive decline) can inspire many conceptions, allowing us to understand expert disagreement (Lalumera, 2014). In our post-biomarker era, there are three major expert conceptions in the literature related to the concept of pathological age-related cognitive decline: the Alzheimer's Association biological conception (Jack et al., 2024), the Lancet commissions clinical conception (Livingston et al., 2017, 2020, 2024), and the overlapping International Working Group clinicobiological conception (Dubois et al., 2021), based on the consensus of different expert groups (Table 1). Their co-existence is an important social fact in the Alzheimer's research space, suggesting that expert conceptions are fixed in guidelines by consensus groups agreeing on different knowledge-driven values and practical aims (Daly & Keuck, 2024; Lalumera, 2023). Conceptions should be understood in light of their practical aims which may not be made fully explicit in the

TABLE 1 Practical and theoretical features of three consensus conceptions related to Alzheimer's dementia.

Concept	**Pathological age-related cognitive decline**		
Conceptions	**Biological**	**Clinicobiological**	**Clinical**
Covering term	Alzheimer's disease, (including asymptomatic disease)	Alzheimer's disease and asymptomatic at risk patients	Dementia, including Alzheimer's disease and others
Expert group	Alzheimer's Association	The International Working Group	The Lancet Commissions
Main practical aim of the conception	*Research and development* Increase the number of, and validate, new diagnostics and therapies	*Clinical practice* Confirm Alzheimer's as the cause of cognitive complaints	*Health promotion* Offer practical guidance for risk reduction to individuals and policymakers
Main population concerned	Over 400 million people on the Alzheimer's continuum	100 million people with early or severe Alzheimer's dementia	The entire population
Main causal scheme	The amyloid cascade hypothesis	A probabilistic amyloid cascade	Interlocking causes and pathologies
Main therapeutic strategy	Biomarker reduction	Biomarker reduction and lifestyle modification	Lifestyle modification
Compatibility with layperson understanding	Low	Medium	High

Note: Partly adapted from table 3 and figure 1 of Daly and Keuck (2024).

scientific papers themselves, which naturally emphasize knowledge-driven ('epistemological') goals to ground their acceptability to the research community.

The Alzheimer's Association recently presented their 'Revised criteria for diagnosis and staging of Alzheimer's disease: Alzheimer's Association Workgroup' (Jack et al., 2024). Even at the earliest stage (one of six), the presence of a disease-defining brain protein – the beta-amyloid of senile plaques – 'is sufficient to establish a diagnosis of AD [Alzheimer's *disease*]'. Does this mean we should diagnose amyloid-positive people as having Alzheimer's disease? In Box 4 (p. 10), the authors warn clinicians: 'AD can be diagnosed in asymptomatic individuals, but we do not believe this should be done for clinical purposes at this time' (Jack et al., 2024), and state elsewhere that since 'disease-targeted therapies have not been approved for cognitively unimpaired individuals with AD … [asymptomatic diagnosis is for] the context of observational or therapeutic research studies'. In other words, it is not epistemology, but rather therapeutic practicality, that the authors use to warn against asymptomatic diagnosis.

Accordingly, we argue that the main practical aim of the Alzheimer's Association biological disease conception can be better labelled as 'research and development'. This practical aim can be understood as part of the 'Accelerating Medicines Partnership® Program for Alzheimer's Disease (AMP® AD)', a massive public–private partnership of which the Association has been a major player since 2014. AMP® AD has the following aims (https://www.nia.nih.gov/research/amp-ad, Accessed 12 September 2024):

> '…to transform the current model for developing new diagnostics and treatments by *jointly identifying and validating* promising biological targets for therapeutics … The ultimate goal is to *increase the number of new diagnostics and therapies* for patients and reduce the time and cost of developing them'
>
> (emphasis added).

In other words, it is likely that the practical aims of experimental drug research and development activities – both publicly (e.g. NIA-NIH) and privately funded (e.g. pharmaceutical industry) – have led the Association to expand clinical diagnosis to embrace the biological. Both the biomarkers themselves and the therapies targeting them are recognized to be experimental or insufficiently validated in nature (Mastroleo & Holzer, 2020). It is not surprising that the Association has wholeheartedly (and controversially) embraced recent advances with amyloid-lowering antibodies, thought to 'move the dial' on research and development progress despite significant controversy. This aligns with the Association's prioritizing a cure over the last decade (Caspi, 2019).

On the other hand, the International Working Group is mostly made up of neurologists who work in state-funded tertiary memory clinics in Europe, and who are therefore interested in the Alzheimer's concept primarily in their clinical practice context for their patients who consult them with early memory complaints. The fact that most asymptomatic people that met the criteria of the biological Alzheimer's disease conception will not develop dementia in their lifetime is what leads them to reject this definition because of its low immediate clinical relevance and potential harm to patients (e.g. anxiety, overtreatment; Dubois et al., 2021; Villain & Planche, 2024) and public health (e.g. spending scarce resources ineffectively, avoiding population harm). Conversely, the practical relevance of clinicobiological Alzheimer's disease (biomarkers plus cognitive symptoms) to their practice is offering explanatory value for what they see in the clinic: confirming Alzheimer's pathology as a cause of cognitive complaints, and explaining this to patients and their families so as to identify and anticipate care needs. This definition is not incompatible with research and development aim, since a secondary aim is including those patients' clinical trials, such as privately sponsored amyloid-lowering trials or of other interventions including lifestyle (Frisoni et al., 2023). Both the US Alzheimer's Association biological criteria and the International Working Group clinicobiological definitions consider Alzheimer's to be caused by a biological process leading to illness (signs and symptoms of dementia) on a continuum (Aisen et al., 2017). They differ in where they draw the line of whether biology alone counts as risk (IWG) or disease (AA) (Schermer, 2023).

The Lancet commissions (Livingston et al., 2017, 2020, 2024) conception is more radically clinical: it chooses dementia as the covering term and is deliberately not related to Alzheimer's biomarkers, but instead targets all-cause dementia in the ageing population, understood as 'a diffuse clinical syndrome representing the gradual accumulation of multiple pathologies, arising from multiple interlocking risk factors over the life course' (Richards & Brayne, 2010). The definitions adopt a gerontological life-course perspective (with authors generally from psychiatry and/or public health), and serve to offer actionable guidance to individuals and policymakers who wish to have an impact on dementia prevention through lifestyle modification across the lifetime. This is centred around action against 14 modifiable risk factors including low education, air pollution and poor physical, mental and social health, which when taken together at the level of the population, may be responsible for up to 45% of cases worldwide (Livingston et al., 2024).

We can thus now define Alzheimer's disease as a biological disease as soon as amyloid starts to accumulate in the brain, regardless of symptoms. But should we? If jointly identifying and validating druggable targets with federal and industry partners, it may be indeed useful to characterize a specific disease-associated process such as amyloid deposition as pathogenic and thus a desired druggable target. If talking with members of the lay public, given the 'scary label' (Lalumera, 2023) of Alzheimer's, it is likely to be personally, socially and even legally harmful (Bunnik et al., 2022; Vaishnav et al., 2024; Villain & Planche, 2024). If offering practical advice to people concerned about their brain health, it is more useful to speak about interlocking dementia without commitment to the theoretical biology of Alzheimer's, since lifestyle is where they are most likely to impact their health, and the link between later-life lifestyle factors and AD biomarkers is at best tenuous (Reijs et al., 2017).

CONCLUSION: WITH GREAT POWER COMES GREAT RESPONSIBILITY

The ethical soundness of using different conceptions related to Alzheimer's or dementia depends on one's practical goals (e.g. research and development, clinical practice, health promotion; see Table 1) in light of the consequences of such charged terminology. This is where the Alzheimer's Association enters into a new tension between its 'cure' and 'care' aims (Caspi, 2019). Indeed, the Alzheimer's Association was born out of the idea that the term 'senile dementia' was actually 'Alzheimer's disease' (Fox, 1989) and on their website www.alz.org, it is still stated that 'Alzheimer's is the most common form of dementia. It causes problems with memory, thinking and behavior'. (Accessed 12 September 2024); that is, a clinical conception. The history of psychiatry shows that criteria developed for research seep into clinical practice and broader society (Kendler et al., 2010). By simultaneously promoting the personal definition of the older 'care' entity to raise funds and awareness, while also promoting its experimental 'cure' definition for drug development, the Alzheimer's Association risks sowing confusion among those who come into contact with both entities, particularly non-experts. As the leading global player in influencing the meaning of Alzheimer's disease, the Alzheimer's Association should draw on ethical frameworks on biomarker disclosure in research and practice (Bunnik et al., 2022) and organize social interventions with health workers and the lay public, which are urgently needed to lower the uncertainties introduced by new conceptions and articulate how they relate to the older ones and the lived experience of people with dementia.

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Timothy Daly: Conceptualization; writing – original draft; writing – review and editing; methodology; validation. **Ignacio Mastroleo:** Methodology; writing – review and editing; validation; writing – original draft.

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CONFLICT OF INTEREST STATEMENT

No conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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