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Examination Room

The Meanings of Alzheimer's Disease

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Abstract

Alzheimer's disease emerged around the 1900s as a rare disease that became synonymous with common dementia by the 1980s. In the 2010s, in vivo biomarkers of Alzheimer's pathophysiology then led researchers to emphasize the presymptomatic biology of Alzheimer's biomarkers, thus decentering dementia. Three consensus definitions were elaborated around biomarkers, and were rearticulated in 2024: biomarker-determined Alzheimer's disease; biomarker-informed "clinical-biological" Alzheimer's disease; and biomarker-independent, "all-cause" dementia. I consider their differences to hinge on the questionable legitimacy of the Alzheimer "biomarkerization" of aging. I encourage a focus on the actionable concept of brain health beyond Alzheimer's to motivate equitable health promotion.

1. Introduction: Approaching Alzheimer's Through Philosophy

When philosophers take an interest in science, they tend to do one of the following three things: "reflective" philosophy (asking how science impacts philosophy); "synoptic" philosophy (applying a broad theory such as evolution across different disciplines); or "embedded" philosophy, where they engage with particular scientific problems (Kaiser, Kronfeldner, and Meunier 2014). The approach adopted here is embedded in research on the biomedical object of Alzheimer's disease. It addresses the problems Alzheimer's has raised for biomedical researchers but from a slightly more academic philosophy perspective than those seen in scientific contexts.

Many biomedical researchers have undertaken informal philosophical work on Alzheimer's (for examples, see Daly and Keuck 2024). Sparse examples of philosophy literature engaging with Alzhemer's research do so either from a philosophy of medicine perspective on debates around health and disease in both contemporary (Schermer 2023) and historical (Villain and Michalon 2024) approaches, or a philosophy of science approach to hypotheses of the causes of Alzheimer's (Daly 2024).

Here, as the title suggests, the focus is on the different meanings of Alzheimer's disease in the past, present, and future. It is both a starting point for reflection on the concepts used by researchers, and an invitation to engage with the different meanings of Alzheimer's in our aging societies.

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2. The "Alzheimerization" of Dementia

At the end of the nineteenth century, several groups in Central Europe were working on cases of what would later be called "Alzheimer's disease." These were rare cases of amnesia, aphasia (language disorder), and behavioral dysregulation, taken together as "dementia," which occurred during midlife. Postmortem examination would reveal a peculiar signature of neuropathology that included senile "plaques" outside neurons and neurofibrillary "tangles" inside neurons known from cases of "senile dementia," a term in use since the 1830s to describe the well-documented phenomenon of age-related cognitive decline (Albou 2012). This dual clinical-neuropathological picture was put together in the clinic in which Dr. Alois Alzheimer worked in the late nineteenth and early twentieth centuries, where it functioned as an exploratory category to question the limits of the concept of senile dementia (Keuck 2018).

While the intense study of senile dementia in the United States and Europe would highlight the issue of age-related cognitive decline during the twentieth century, the rare Alzheimer's disease would have a stable meaning until the 1970s. Then, converging evidence from clinical and neuropathological studies suggested that these rare early-onset cases (midlife) and common later-life dementia (diagnosed after age 65) could be due to the same pathophysiological mechanisms, leading to the claim that Alzheimer's was actually responsible for most cases of age-related cognitive decline. This claim was accepted, and the "Alzheimer's disease movement" consolidated a unique diagnostic entity—requiring postmortem examination to confirm plaque and tangle pathology—as a major threat to the public health of an aging population (Fox 1989). The "Alzheimerization of dementia" gave further legitimacy to the notion that age-related cognitive decline was a "crisis worthy of funding" (Mullane and Williams 2019, 67).

In the 1980s, the proteins of "plaques" (amyloid-beta, Aβ) and "tangles" (tau) were isolated from cases of early-onset dementia and hypothesized to be responsible for later-onset dementia, which took the Alzheimerization of dementia for granted and also further consolidated it. In the early 1990s, data from rare familial cases of Alzheimer's similar to the first cases from Alzheimer's clinic would motivate the dominant "amyloid cascade hypothesis," according to which amyloid-β and tau were, respectively, "the trigger and bullet in Alzheimer disease pathogenesis," that is, amyloid before tau (Bloom 2014). This hypothesis serves a triple role in Alzheimer's research: not only to explain the disease but also to motivate disease-modifying treatments and even to redefine the meaning of Alzheimer's disease.

3. The Alzheimer's "Continuum" and Related Definitions

Two major events would question the Alzheimerization of the syndrome of dementia. The first was the repeated, high-profile failures of amyloid-lowering clinical trials of people living with dementia in the 2000s and 2010s. Removing amyloid did not improve dementia. The second was the arrival of in vivo biomarkers to measure amyloid, tau, and neurodegeneration, reducing reliance on postmortem examination to confirm diagnosis of otherwise "probable" Alzheimer's based on 1980s' diagnostic criteria. Both of these events would lead to a separation of Alzheimer's and dementia. From 2007 onward (Dubois et al. 2007), a period of intense "conceptual engineering" (Lalumera 2023) of the Alzheimer's

concept would begin—that is, the changing of the meaning and extension of a given disease label because of knowledge-driven ("epistemic") and practical (for example, ethical) values.

Failed treatments and available in vivo biomarkers converged on the hypothesis that anti-amyloid (and anti-tau) trials were likely arriving too late. The protein had to be removed earlier than dementia. The concept that emerged to facilitate this was a "continuum" defended by leading Alzheimer's researchers from North America, Europe, and the pharmaceutical industry (Aisen et al. 2017). The Alzheimer's continuum is "a process in which pathophysiological changes accumulate and eventually culminate in clinically apparent disease, which then progresses with gradual worsening of cognitive and functional abilities" (Aisen et al. 2017, 8).

Why the continuum concept? It is "a seamless sequence in which adjacent elements (severities) are not perceptibly different from each other, although the extremes are distinct" (Aisen et al. 2017, 2). Two consequences of this conceptual shift from the clinical-pathological hybrid to a continuum are clear. First, that "functional decline occurs late in the continuum of AD" (2017, 4) compared to the hypothetical amyloid cascade. This claim thus provides the continuum's extremes: on the early end, amyloid and then tau accumulation; on the late end, cognitive decline. Second, the controversial claim that "AD can be diagnosed without dementia" (2017, 5)—in other words, the disease begins as soon as amyloid starts accumulating, in line with the amyloid cascade hypothesis.

There have been three classes of reactions to the Alzheimer's continuum based on knowledge-driven and practical values. All three embrace the idea of a presymptomatic window for action. Two expert groups—the Alzheimer's Association (AA), and the International Working Group (IWG)—embrace the Alzheimer's concept as a priority for public health and thereby the hypothetical cascade of amyloid and tau as the most relevant process to pathological, age-related, cognitive decline. The third group—the Lancet Dementia group—instead argues that most people with amyloid and tau biomarkers do not develop dementia, and understands dementia as "a diffuse clinical syndrome representing the gradual accumulation of multiple pathologies, arising from multiple interlocking risk factors over the life course" (Richards and Brayne 2010). Thus, in older adults, the relevance of amyloid and tau pathology to dementia—the Alzheimerization of dementia—is reduced by the Lancet dementia approach.

However, there are also important differences between the AA and the IWG. It is useful to understand differences by understanding the practical aim of each definition (Daly and Mastroleo 2024). The AA's biological construct (Jack et al. 2024) aims to increase the druggability of the pathophysiology of Alzheimer's disease for innovative research. By emphasizing the priority of the biological over the syndromic, biological Alzheimer's disease invites early targeting of Alzheimer's disease neuropathology with recent US Food and Drug Administration (FDA)-approved anti-amyloid antibodies (Sims et al. 2023; Van Dyck et al. 2023).

The logic of experimental drug discovery is not the priority of the IWG, whose primary authors are neurologists in memory clinics in Europe who are direct competitors for establishing the meaning of this term. These neurologists work on precision clinical diagnosis, and mobilize Alzheimer's as a concept to explain the memory complaints of people who arrive at their clinic. Three consequences of the IWG approach are clear: Its defenders rule out other causes of dementia when diagnosing the condition, underline the different empirical consequences for diagnosis associated with different definitions of

Alzheimer's, and warn against the inadequacies and possible harms caused by biological diagnosis in the absence of dementia (Villain and Planche 2024). Thus, these authors defend the clinical-biological diagnosis of Alzheimer's disease: cognitive complaints (clinical signs) plus biomarker positivity (biological) (Dubois et al. 2024). Prior to the arrival of symptoms, this group instead uses the concept of risk to describe biomarker-positive individuals on the Alzheimer's continuum: those with biomarker positivity and without symptoms are at risk for Alzheimer's disease but do not satisfy the clinical-biological diagnosis. Nevertheless, the IWG authors also recognize the legitimacy of "presymptomatic AD" for those who have a very high risk of progressing to dementia, mostly based on genetic risk. Finally, the IWG approach recognizes other modifiable risk factors as important targets for intervention, including lifestyle interventions (Frisoni et al. 2023).

Conversely, the Lancet commissions are opposed to the Alzheimerization of dementia from a priority-setting point of view and focus on providing actionable guidance to individuals and policymakers for dementia prevention. Indeed, from the first Commission in 2017, the focus was not on Alzheimer's but on "all the different types of dementia" (Livingston et al. 2017, 2675). This zooming out from amyloid and tau thus spreads the net much wider with regard to causes of, or contributors to, dementia. The Lancet commissions insist on the need for action against fourteen modifiable risk factors, including low education, air pollution, and poor physical, mental, and social health, which, at the level of the population, may be responsible for up to 45% of cases worldwide (Livingston et al. 2024). Epidemiological data from the Framingham Heart Study and the Alzheimer's Consortium have shown that in Europe and the United States, the age-specific incidence of dementia has been falling by more than 10% per decade since the 1980s (Satizabal et al. 2016; Wolters et al. 2020), suggesting that public health gains can be made against dementia despite an aging population, though the authors of these studies have also pointed out that the factors behind the positive trends remain unknown. The Lancet commissions mark an important "de-Alzheimerization" of dementia. However, there is the risk of imprecision with such a nonspecific approach to risk and its reduction, and the evidence base supporting "multi-domain interventions" for older adults to reduce dementia risk through conscious behavior change—focusing on intensive cognitive, physical, and social stimulation alongside nutritional interventions—is weak (Hafdi, Hoevenaar-Blom, and Richard 2021).

Table 1. Features of three definitions related to Alzheimer's dementia

Expert group	Alzheimer's Association	The International Working Group	The Lancet commissions on dementia
Definition	Biological Alzheimer's disease: amyloid and tau biomarkers	Clinical-biological Alzheimer's disease: dementia with amyloid and tau biomarkers	Clinical dementia due to multiple causes, including Alzheimer's and other types of dementia
Main practical aim	Drug development	Precision diagnosis	Health promotion
Main population concerned	Amyloid-positive (40% of over-70s)	100 million people with early or severe Alzheimer's dementia	High-risk individuals

Causal scheme	Deterministic amyloid cascade	Probabilistic amyloid cascade	Interlocking pathologies
Main therapeutic strategy	Amyloid biomarker reduction	Biomarker reduction; lifestyle modification	Lifestyle modification, public health measures
Evidence base	Familial Alzheimer's; recent clinical trial results	Recent clinical trial results; multi-domain interventions	Falling incidence of dementia; multi-domain interventions
Strengths	Early intervention	Protects asymptomatic individuals from the Alzheimer's label	Highly actionable
Limitations	Low-performance biomarkers	Situates prevention in the memory clinic	Imprecise and historically individualistic

Sources: Partly adapted from Daly and Mastroleo (2024); Daly and Keuck (2024).

4. From the Alzheimerization of Aging to Public Brain Health

Approximately 40% of the population over the age of 70 is amyloid-positive—that is, has biological Alzheimer's disease (Jansen et al. 2022). However, less than 30% of amyloid-positive people without cognitive complaints will develop dementia during their lifetime, and as people get older, amyloid-positivity becomes a weaker predictor of future decline (Brookmeyer and Abdalla 2018). Thus, amyloid positivity is more worrying in younger individuals.

I argue that biological Alzheimer's no longer represents the Alzheimerization of dementia but of aging itself. This term, the "Alzheimerization of aging," has been used in the past to describe the skewing of research funding toward Alzheimer's as opposed to other age-related diseases by the US National Institute of Aging (Adelman 1995). But I use it to describe a bias that exaggerates the therapeutic and prognostic relevance of biomarkers of Alzheimer's to people who are asymptomatic with amyloid-positivity, a significant proportion of the population over the age of 70. Anti-amyloid drugs may have limited societal impact, since they are expensive, not available in most healthcare systems, their therapeutic value is limited to a small statistical slowing of cognitive decline visible only with hundreds of patients with clinical-biological Alzheimer's, and they pose a notable risk of harm through side effects that include brain bleeding and swelling that can (rarely) result in death (Ebell et al. 2024).

Against a backdrop of serious care inadequacies, the biological conceptualization of dementia has been criticized for promoting techno-scientific solutions to what is also a public health and social problem (Fletcher 2023). Furthermore, given the stakes and harms of the "scary label" of Alzheimer's (Lalumera 2023), there is no need to use pathologizing language to target biomarkers for drug development. Alzheimer's disease belongs in the memory clinic as a specific clinical-biological entity, where it incidentally originated (Villain and Michalon 2024). It invites both pharmacological and non-pharmacological interventions for affected individuals, and protects people without cognitive decline from a potentially harmful label. However, by reserving its disease labeling to the state of cognitive decline and waiting for patients to display detectable changes, the clinical-biological

"dementia prevention in memory clinics" approach (Frisoni et al. 2023), inspired by the IWG definition, treats dementia as a private problem for individuals, rather than a public health problem.

It is unlikely that fair and far-reaching dementia prevention will happen in memory clinics. Embracing the weak probabilistic relationship between Alzheimer's biomarkers and dementia, the Lancet Commission approach considers "promoting resilience" to dementia as a public health priority across society (Livingston et al. 2017, 2677). However, even the Lancet approach remains squarely and explicitly within the disease paradigm, rather than seeing brain health as a positive entity. This has two consequences: a focus on individual risk, and individual responsibility to reduce it. Indeed, the main authors of the Lancet Commission are explicit in their endorsement of the idea that "interventions to prevent dementia should target those at high risk" (Livingston and Costafreda 2023, 750). Moreover, when dementia charities or health-promotion policies mention brain health, they tend to do so in a way that reinforces the idea that risk is a moral problem for individuals to act on (Lawless, Augoustinos, and LeCouteur 2018; Horstkötter, Deckers, and Köhler 2021). This individual "high-risk" approach started in a paradigm of individualistic lifestyle modification that overlooked the need for ambitious population-level approaches to dementia risk reduction (PLADRR) (Walsh et al. 2022).

The PLADRR approach is gaining momentum,[1] as evidenced by the inclusion of PLADRR authors in the 2024 Lancet Commission, with its section 3 on a public health approach (Livingston et al. 2024). This population-level shift is necessary for a variety of reasons. Falling dementia rates have been interpreted through the lens of lifestyle (Mukadam et al. 2024), even though there is no conclusive evidence suggesting that any one lifestyle activity can reduce dementia risk. Thus, the major unknown for individuals is at the level of action—for example, whether it is worth consulting medical services about one's Alzheimer's biomarker status (Bunnik et al. 2022), taking an anti-amyloid drug (Høilund-Carlsen et al. 2024), or undertaking lifestyle action to improve brain health (Horstkötter, Deckers, and Köhler 2021). Anyone who chooses to act in these ways does so without certainty that such actions will ultimately lead to improved quality of life.

The falling rates of dementia correspond, at least partially, to a reduction in health inequalities between the inter-war period and the post-World War II boom, which continued until the 1980s (Bambra 2024). The opposite—that is, the negative impact of health inequalities—can be evidenced by new multi-modal approaches that show that socioeconomic disparities and reduced access to healthcare and participation in society, lead to accelerated brain aging (Moguilner et al. 2024). Since the neoliberal 1980s, and our post-2010 "crisis" period (Bambra 2024), health inequalities have worsened in the twenty-first century.

I consider that the falling incidence of dementia may be little more than a positive symptom of reduced health inequalities in the postwar twentieth century as a result of broader societal changes, including "poverty reduction through a redistributive welfare system, improved healthcare access, and enhanced democracy" (Bambra 2024, 203). The "high-risk" lifestyle approach is therefore unlikely to significantly reduce the incidence of

[1] "Population-Level Approaches to Dementia Risk Reduction (PLADRR) Research Group," https://coghealth.net.au/population-based-approaches-to-dementia-risk-reduction-research-group/.

dementia in the population (Walsh et al. 2022), and I consider action against health inequalities to be an urgent priority for dementia risk reduction and brain health in general.

As suggested by its name, even PLADRR remains focused on dementia, despite the fact that risk factors for dementia (related to education, overall health, and air pollution) have no specificity for this syndrome. This is symptomatic of widespread disease-centered thinking about the brain, rather than health-centered. As a comparison, at the level of the World Health Organization (WHO), it was during the twentieth century that a public health approach to mental health was explicitly developed: "public mental health." For brain health, WHO released its first position paper only in 2022 (WHO 2022). This means that public brain health is an extremely young and underdeveloped entity (Daly 2025).

WHO offers five priority areas for brain health promotion across the life course: "physical health, healthy environments, safety and security, learning and social connection, and access to quality services" (WHO 2022, 28). Importantly, all of these priority areas can be understood in terms of "low-tech medicine," which is a public health approach, inviting us to rethink the sustainability of healthcare interventions and reinvent future brain health care and prevention within society, rather than waiting for new technological discoveries to solve these problems (Sarfati et al. 2024). This is an extension of the project of anthropologist Margaret Lock, who in 2013 concluded her study of Alzheimer's research by arguing that dementia is unlikely to be "wiped out" like an infectious disease, and that we should prioritize comprehensive policy change to engage with the reality of aging (Lock 2013). In other words, to respect the right to brain health, "population-based health must be put on equal footing" with individual approaches (Cosgrove and Shaugnessy 2020, 65) such as anti-amyloid medications and lifestyle interventions.

In conclusion, I argue that, given the probabilistic relationship between biomarkers of Alzheimer's disease and dementia, we should be wary of the risk of the Alzheimer "biomarkerization" of aging. Moreover, given growing health inequalities, we should collectively focus on brain health promotion, promoting population-level resilience to different kinds of brain pathology beyond dementia by embracing a rights-based "brain health for all" vision of society (Daly 2025).

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