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Alzheimer's Disease: A New Paradigm, New Treatments, New Challenges, New Approaches

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ABSTRACT

Alzheimer's disease (AD) is a progressive neurodegenerative disorder and the most common cause of dementia. Recent advances have shifted the focus from symptomatic treatments to early, disease-modifying strategies. This article reviews new therapeutic approaches, particularly monoclonal antibodies such as lecanemab and aducanumab, which aim to reduce amyloid-beta accumulation. Despite promising outcomes, safety concerns and high costs remain. Additionally, the development of biomarker-based diagnostic tools has led to ethical and clinical challenges in early detection. The article also highlights non-pharmacological interventions, such as multidomain lifestyle modifications, which may enhance cognitive reserve and delay disease onset. A public health framework is needed to integrate precision medicine, screening policies, and preventive strategies to address the increasing burden of Alzheimer's disease.

Keywords: Alzheimer's Disease, Biomarkers, Cognitive Reserve, Monoclonal Antibodies, Public Health

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INTRODUCTION

Alzheimer's disease (AD) is a progressive and neurodegenerative disorder predominantly observed in the elderly population and represents the most common cause of dementia cases worldwide. The prevalence of AD increases with advancing age. Approximately 10% of individuals over the age of 65 and 35%-50% of those over the age of 85 are affected. In Türkiye, the average life expectancy is increasing (currently 78.3 years), and the proportion of elderly individuals is rising rapidly. While the population aged 65 and over was 7.5% in 2012, it reached 9.9% in 2023. This figure is projected to rise to 20.8% by 2050 and 27.7% by 2075 (Turkish Statistical Institute [TURKSTAT], 2024).

The pathophysiology of AD is characterized by abnormal protein aggregations, such as the accumulation of amyloid-beta (Aβ) plaques and the hyperphosphorylation of tau proteins. The interaction of these biological processes with neuroinflammation, oxidative stress, and synaptic dysfunction accelerates the neurodegenerative progression of the disease. However, the exact etiology of AD remains incompletely understood, and it is thought to arise from a complex interplay of multiple risk factors, including genetic components (e.g., the APOE ε4 allele), environmental influences, and aging (Jack et al., 2018).

Even in its earliest stages, AD dementia necessitates caregiving and imposes a significant burden on families, caregivers and healthcare systems. The magnitude of this burden increases in parallel with disease progression and symptom severity. Worsening cognitive impairment leads to greater loss of functional independence, increased demand for intensive care, and a growing societal burden. Therefore, slowing disease progression constitutes a critical goal for individuals with AD, their loved ones, and the healthcare system. At present, treatment primarily aims to slow disease progression.

In a study conducted by Chandler et al. (2024), it was shown that slowing disease progression by 20% in patients with early-stage AD could have meaningful effects on cognitive, functional, and behavioral outcomes. According to findings from the NACC database, slowing disease progression by 20% over five years in individuals with mild cognitive impairment (MCI) and mild dementia was associated with 1.7 points (10.8%) and 1.6 points (12.9%) less cognitive decline, respectively, in terms of the Systematic Symptom Score (SSS). The same intervention was also associated with approximately 20% less behavioral deterioration in Neuropsychiatric Inventory (NPI-Q) scores, and it was reported to reduce the likelihood of becoming entirely dependent by 22.2% in the MCI group and 21.6% in the mild dementia group. According to ADNI data, slowing disease progression by 20% or 30% within four years contributed to reductions in cognitive decline by 20.4% and 29.6%, respectively.

These findings suggest that slowing the progression of early AD may enable patients to preserve their functional autonomy and quality of life for a more extended period (Chandler et al., 2024). Therefore, clinicians and policymakers must develop strategies to improve access to treatment during the early stages of the disease. Slowing disease progression in its early phase—preserving cognitive and functional abilities and maintaining relative independence—can benefit patients, their families, and society. This carries critical implications for patients, caregivers, clinicians, researchers, and policymakers (Desai et al., 2024).

The preclinical stage and early diagnosis have gained significant importance today due to the possibility of biological diagnosis through cerebrospinal fluid (CSF) and even blood samples, as well as the development of new-generation therapies aimed at clearing amyloid from the brain to slow the disease process. However, this emerging period has also introduced new ethical and societal challenges, along with the need for novel approaches that had not been previously discussed or fully recognized. This article aims to examine these issues and potential approaches related to this evolving landscape and to initiate a framework that may guide our country and policymakers.

New Therapeutic Approaches in Alzheimer's Disease (AD)

For nearly 25 years, treatment options for AD have been mainly limited to symptomatic management. However, recent intensive research efforts have focused on disease-modifying therapies, leading to several promising developments. Traditionally, acetylcholinesterase inhibitors (rivastigmine, donepezil, galantamine) and NMDA receptor antagonists (memantine) have served as standard treatments to alleviate mild to moderate symptoms of AD (Tan et al., 2014). While these medications were considered groundbreaking in the history of AD treatment, they are not effective in halting or slowing disease progression. Instead, they provide temporary relief from cognitive and behavioral symptoms.

In contrast, a new class of monoclonal antibodies targeting amyloid plaques has emerged as a promising type of disease-modifying therapy with the potential to slow disease progression. Alongside anti-amyloid antibody treatments, other emerging disease-modifying strategies are under development. These include tau-targeted therapies (e.g., tau antibodies and aggregation inhibitors), approaches modulating microglial activity through anti-inflammatory pathways, gene therapies, and several other investigational treatments (Cummings et al., 2024). It is hoped that these biological therapies—particularly when combined with early diagnosis—will enhance therapeutic efficacy and bring us closer to the goal of delaying disease progression. Nonetheless, further research and the development of novel strategies are needed to optimize the efficacy and safety of these interventions (Sevigny et al., 2016).

The following sections will briefly review these newly introduced therapeutic agents, which not only offer renewed hope but also raise novel questions regarding early and biological diagnosis.

Recent advances in treating AD have highlighted monoclonal antibodies (mAbs) as promising disease-modifying therapeutic agents. These therapies, approved by the U.S. Food and Drug Administration (FDA) (2023), specifically target β-amyloid (Aβ) plaques, a hallmark feature of AD. Two mAbs—aducanumab and lecanemab—have received FDA approval. While all monoclonal antibodies primarily aim to remove amyloid-beta plaques, they operate via different mechanisms.

Aducanumab targets fibrillar Aβ and oligomers with high affinity, while lecanemab preferentially binds to Aβ protofibrils, with a 10:1 selectivity ratio compared to plaque-bound Aβ. Donanemab recognizes a specific pyroglutamate-modified form of Aβ found exclusively in plaques.

Aducanumab was the first disease-modifying treatment approved by the FDA in 2021. It is indicated for early AD with confirmed Aβ pathology. Although efficacy data varied across Phase III trials, dose-dependent reductions in plaque burden and some cognitive benefits were observed.

Lecanemab received approval in 2023 for patients with mild cognitive impairment (MCI) or early-stage AD dementia. Phase II and III trials demonstrated significant plaque clearance and a slowing of cognitive decline, with one trial reporting a 27% reduction. PET imaging confirmed plaque elimination in 81% of participants.

For both drugs, the most commonly reported adverse events were amyloid-related imaging abnormalities (ARIA), particularly cerebral edema (ARIA-E) and microhemorrhages (ARIA-H) (Van Dyck et al., 2023).

Currently, the most prominent and debated monoclonal antibody is lecanemab. In the study "Lecanemab in Early Alzheimer's Disease" by Van Dyck et al. (2023), lecanemab was estimated to provide a 27% clinical benefit in slowing AD progression. This 18-month, multicenter, double-blind Phase 3 trial enrolled participants aged 50 to 90 with early-stage AD characterized by mild cognitive impairment or mild AD dementia and confirmed amyloid pathology via PET imaging or cerebrospinal fluid (CSF) analysis.

In the lecanemab group, the most commonly reported adverse events (occurring in more than 10% of participants) included infusion-related reactions, cerebral microhemorrhages, macrohemorrhages, and superficial siderosis, along with ARIA-H (amyloid-related imaging abnormalities—hemorrhage), ARIA-E (amyloid-related imaging abnormalities—edema), headaches, and falls. These adverse events were predominantly asymptomatic, typically occurred within the first three months of treatment, and resolved in 81% of cases within four months (Van Dyck et al., 2023).

However, the FDA has reported deaths associated with ARIA-related edema in patients receiving lecanemab, raising concerns about the drug's safety profile (Maki et al., 2025). Moreover, the risk of hemorrhagic complications has been shown to increase with age, with higher rates observed in the lecanemab group, whose mean age was 71.4 ± 7.9 years. A significant concern regarding lecanemab is the increased incidence of ARIA—particularly brain edema and hemorrhage—in patients carrying the APOE ε4 allele, a common genetic risk factor for AD (Martorana et al., 2025).

Additionally, some studies have questioned the claimed efficacy of lecanemab. For example, one study suggested that the therapeutic benefit is significantly lower in women and in APOE ε4 carriers, implying a possible genetic basis for reduced responsiveness. The author argues that these differences were not adequately discussed in the published article and that the efficacy data for lecanemab may have been overstated (Kurkinen, 2023).

Due to these findings, the efficacy and safety profile of lecanemab and similar monoclonal antibodies has not been universally accepted worldwide. While lecanemab (Leqembi) has been approved in countries such as the United States and Japan, it has faced resistance in Europe. European authorities have adopted a more skeptical stance for several reasons. The European Medicines Agency (EMA) initially rejected the marketing authorization for lecanemab. Although a subsequent application was accepted, the EMA concluded that the anticipated benefits of the drug did not outweigh the significant risks of adverse effects, particularly cerebral hemorrhage and edema.

Some experts argue that the observed improvements in disease progression are too modest to provide meaningful clinical benefit to patients, raising further questions about the drug's role in the treatment landscape (Martorana et al., 2025). Another major obstacle to global approval of lecanemab is its high cost. In the United States, the annual price of lecanemab is approximately $26,500. If similar pricing were applied in Europe, the annual treatment costs could reach €133 billion—exceeding half of Europe's total pharmaceutical expenditures.

Such unsustainable pricing and high economic burden may severely limit or completely preclude access to the drug, particularly in countries with constrained healthcare budgets. Furthermore, estimates of lecanemab's cost-effectiveness are based on the assumption that it delays disease progression by three years; however, the clinical trial data supporting this assumption are limited to an 18-month follow-up period (Jönsson et al., 2023).

Biological Diagnosis of Alzheimer's Disease (AD) and Emerging Biomarkers

Until recently, the clinical diagnosis of AD primarily relied on conventional diagnostic criteria, which allowed for classifications such as "possible" or "probable" AD. A definitive diagnosis required postmortem identification of β-amyloid (Aβ) plaques and neurofibrillary tangles (NFTs) in the brain (McKhann et al., 1984). However, recent advances in fluid biomarkers and neuroimaging have enabled the in vivo detection of AD pathology, leading to the development of new diagnostic criteria by the International Working Group (IWG) and the National Institute on Aging–Alzheimer's Association (NIA-AA). These guidelines redefined AD by introducing diagnostic categories for asymptomatic individuals with biomarker evidence of pathology (Dubois et al., 2014; Jack et al., 2018).

Biological diagnostic frameworks such as the ATN model—evaluating amyloid plaques (A), tau pathology (T), and neurodegeneration (N)—enable more precise characterization of AD subtypes and disease stages. Understanding these subtypes and stages facilitates the use of therapies tailored to the disease's biological underpinnings (Almeida et al., 2024).

The role of biomarkers in the diagnosis of AD is becoming increasingly critical. Commonly used cerebrospinal fluid (CSF) biomarkers include low Aβ42 levels and elevated levels of phosphorylated tau (p-tau) and total tau (t-tau). In addition, new imaging techniques, particularly amyloid and tau PET scans, support in vivo diagnosis. A significant recent advancement is the ability to detect specific biomarkers—such as p-Tau217, Aβ42/40 ratio, and neurofilament light chain (NfL)—in blood, which is expected to greatly simplify the diagnostic process (Jack et al., 2024).

Moreover, biomarker algorithms enhanced by artificial intelligence, neuroimaging, and neuropsychological testing now enable the detection of AD pathology during the preclinical stage. These developments contribute to a deeper understanding of AD pathophysiology and offer new opportunities for designing early intervention strategies (Atri, 2019; Jack et al., 2018).

At this point, we observe a divergence between the NIA-AA and IWG groups regarding the diagnostic framework for AD, as reflected in the recently published guidelines. According to the 2024 IWG criteria, individuals who are biomarker-positive but cognitively normal cannot be diagnosed with AD. In contrast, the 2024 AA criteria allow for an AD diagnosis based solely on biomarker positivity, even in the absence of cognitive impairment (Jack et al., 2024).

In this context, the IWG recommends re-evaluating the "Revised AA Criteria (2024)" and proposes an alternative conceptual framework in which AD is defined as a clinical-biological entity intended for use in clinical settings (Dubois et al., 2014).

Another important question concerns whether initiating treatment after symptom onset is genuinely effective in halting disease progression, given that amyloid-β accumulation begins 20 to 30 years before clinical symptoms appear. Therefore, interventions targeting Alzheimer's pathology should ideally commence prior to dementia onset. Current recommendations for monoclonal antibody use align with this perspective. The National Institute on

Aging–Alzheimer's Association (NIA-AA) has even proposed that individuals who are biologically positive for AD—despite having no cognitive impairment—be considered as having AD and, thus, eligible for treatment (Jack et al., 2024).

As a logical consequence of this framework, one of the most critical determinants of prognosis and therapeutic efficacy in AD is the establishment of a time window for early diagnosis and intervention. Longitudinal multimodal biomarker studies have shown that the continuum of AD includes a long latent phase—referred to as preclinical AD—that begins decades before symptom onset. Treatment may offer the best opportunity to slow disease progression during this preclinical phase. Effective therapies initiated at this stage may delay or even prevent cognitive decline. The recent success of anti-amyloid immunotherapy trials in symptomatic AD has fueled enthusiasm for testing such strategies at the earliest possible stage (Rafii & Aisen, 2023).

At this juncture, one of the key questions we aim to address emerges once again—an issue for which definitive answers remain elusive: How many individuals with a biological diagnosis of AD progress to clinical Alzheimer's dementia? Moreover, should we initiate treatment in all biomarker-positive individuals, even without cognitive symptoms?

In a retrospective observational cohort study comparing survival rates and relative mortality risk across different stages of AD—including AD-related mild cognitive impairment (MCI) and Alzheimer's dementia—with cognitively normal individuals, it was found that the median survival time for participants who progressed to MCI due to AD or to Alzheimer's dementia ranged from 3 to 12 years, with shorter survival durations observed at more advanced stages of the disease. Greater disease severity was associated with higher mortality, particularly among younger individuals. For instance, in a 65-year-old patient, disease severity increased the risk of death more than in an 80-year-old patient.

Participants with AD-related MCI had a mortality risk comparable to cognitively normal individuals after adjusting for confounding factors. These findings suggest that preventing or delaying the progression of AD may contribute to lower mortality—and more importantly, such a benefit may be more pronounced in relatively younger individuals (Crowell et al., 2023).

Evidence also indicates that within 5 to 10 years following a diagnosis of AD-related MCI, approximately 30% to 50% of individuals progress to Alzheimer's dementia. This rate is even higher—approximately 15% greater—among individuals with amnestic MCI (Angevaare et al., 2022).

On the other side of the coin, preclinical AD affects a significant portion of cognitively unimpaired older adults—individuals who, under the 2024 AA criteria, would be diagnosed with AD based on biological markers. Today, blood-based biomarkers can detect very early changes in the AD continuum with high accuracy. However, the key uncertainty lies in whether these individuals will ultimately progress to clinical dementia.

For instance, in a relatively short 18-month study, no significant differences were observed using assessments such as plasma phosphorylated tau (p-tau)181 levels, cognitive performance measures, and brain MRI volumetrics, including hippocampal volume and cortical thickness (Pais, 2023). In contrast, an 8-year longitudinal study by Chen et al. (2022) demonstrated that cognitive tests such as the Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS13) and the Mini-Mental State Examination (MMSE), along with cerebrospinal fluid (CSF) and plasma p-tau181, CSF sTREM2, and brain volume measurements, could predict long-term cognitive decline.

Furthermore, lifetime risks of Alzheimer's dementia vary significantly by age, sex, and disease stage, whether preclinical or clinical. For example, a woman with amyloidosis only has an estimated lifetime risk of 8.4% at age 90 but 29.3% at age 65. Individuals under the age of 85 who present with mild cognitive impairment, amyloidosis, and neurodegeneration have a lifetime risk exceeding 50%. Consequently, most individuals with preclinical AD will not develop Alzheimer's dementia during their lifetimes (Brookmeyer & Abdalla, 2018).

This suggests that more parameters are needed to guide decisions regarding who should receive treatment. Lifetime risk estimations can aid in interpreting the clinical relevance of biomarker-based screening for AD (Brookmeyer & Abdalla, 2018). Overcoming the prevailing "confirmation bias" is essential to advance the diagnosis and treatment of AD and to move toward precision medicine with a more nuanced understanding of amyloid biomarkers (Souchet et al., 2023). These findings underscore the need to consider not only biomarkers like amyloid but also additional parameters—such as those reflecting brain compliance—in the evaluation of amyloid-positive individuals who have not yet developed dementia.

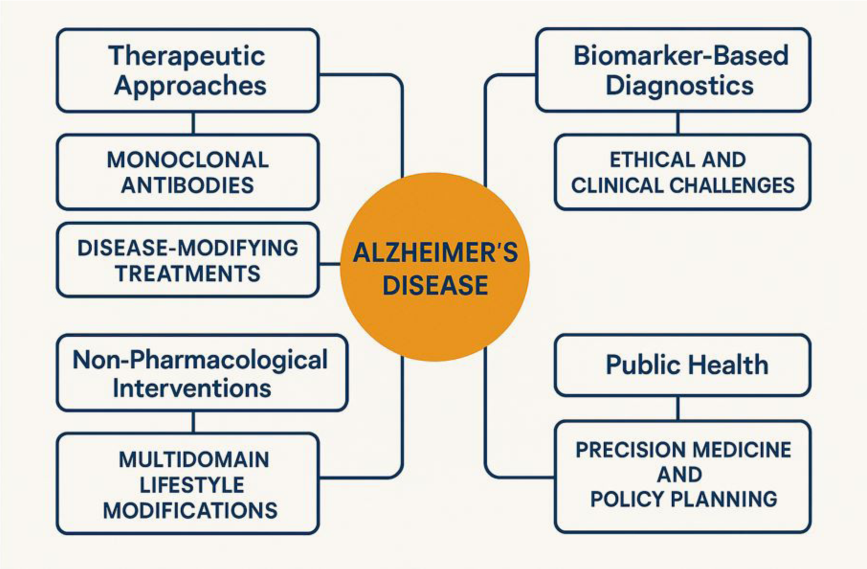

Figure 1. Multidimensional framework of Alzheimer's disease domains

The figure outlines therapeutic, diagnostic, and public health components of Alzheimer's disease, emphasizing the integration of clinical strategies with ethical and policy considerations.
Note. Created by the author.

In conclusion, emerging therapeutic approaches currently under development aim to target individuals at risk for AD prior to symptom onset or during the earliest stages when only mild signs are present. These developments pave the way for a system of primary prevention in which the general population—particularly individuals aged 50 and above—could undergo regular screening using plasma biomarkers. Such screening could detect disturbances in Aβ metabolism even before the accumulation of fibrillar amyloid in the brain begins, enabling the early identification of high-risk individuals (Gustavsson et al., 2021; Rafii & Aisen, 2023).

However, the models tested for such screenings are complex and remain inconclusive. Nevertheless, various strategies exist for identifying these individuals, including population-wide and tiered screening approaches. For example, the TRC-PAD (Trial-Ready Cohort for Preclinical/Prodromal Alzheimer's Disease) infrastructure describes a stepwise process to efficiently and cost-effectively screen a large population. This approach involves voluntary online enrollment, web-based cognitive assessments, and subsequent plasma biomarker analysis for eligible candidates (Rafii & Aisen, 2023).

Each of these strategies, however, poses unique ethical challenges. To justify the ethical costs associated with current risk classification methods, the drugs developed must provide substantial health benefits to individuals identified as being at risk of developing AD. Evidence supporting such significant benefits from available drug candidates remains limited (Gustavsson et al., 2021).

Public Health Perspective and Non-Pharmacological Approaches

One approach that also offers a public health perspective involves non-pharmacological treatment strategies. Maki et al. from Japan—one of the countries where lecanemab has been approved for use—highlighted the drug's side effect profile and economic burden. They suggested that non-pharmacological interventions in individuals with MCI or AD may enhance cognition and cognitive reserve (CR), thereby helping individuals better resist the effects of AD pathology. Promoting social engagement in people with AD—such as participating in household chores, food service, or folding laundry, all of which involve reciprocal social interactions—may support cognitive reserve by engaging multiple cognitive domains. Even individuals over 90 with AD can actively participate in such roles. Furthermore, these interventions may potentially reduce the underlying AD pathology in the brain, including amyloid-β plaques and hyperphosphorylated tau proteins (Maki et al., 2025).

The SMARRT project (Supporting Multidomain Alzheimer's Risk Reduction Trial)—a randomized controlled trial evaluating the impact of personalized, multidomain interventions on reducing Alzheimer's risk—investigated how managing modifiable risk factors could influence the course of the disease. In this study, 172 individuals aged 70 to 89 who had at least two of the following eight modifiable risk factors were randomized into intervention and control groups: physical inactivity, uncontrolled hypertension, poor sleep quality, use of medications harmful to cognition, severe depressive symptoms, uncontrolled diabetes, social isolation, and smoking. The intervention group received individualized goals delivered with the support of a health coach and nurse (e.g., daily step counts, reading goals, sleep duration monitoring). In contrast, the control group received educational materials at regular intervals. After a twoyear follow-up period, cognitive function improved by more than 74% in the intervention group. This study highlighted the value of non-pharmacological treatments in reducing Alzheimer's risk and preserving cognitive function, especially considering their low cost and ease of implementation compared to drug-based treatments (Yaffe et al., 2024).

Indeed, the 2024 update of the Lancet Commission on Dementia emphasized the high potential for prevention, suggesting that nearly half of all dementia cases could theoretically be prevented by addressing 14 modifiable risk factors. These include physical inactivity, smoking, traumatic brain injury, depression, hearing loss, hypertension, high cholesterol, obesity, excessive alcohol consumption, social isolation, vision loss, air pollution, and—most notably—low educational attainment, which is closely linked to cognitive reserve (Livingston et al., 2024). Dementia risk reduction efforts should begin early and continue across the lifespan. Risk can be modified independently of APOE genetic status. Multicomponent interventions targeting multiple risk factors may offer substantial benefits for individuals at both high and low genetic risk for dementia. Even addressing a subset of these factors could yield meaningful benefits. For example, a modeling study in the United Kingdom estimated that treating hypertension, promoting smoking cessation, and providing hearing aids could reduce dementia prevalence by 8.5% and save the UK £1.86 billion annually (Livingston et al., 2024).

The Need for Change in National Aging and Dementia Policies

In conclusion, advances in biomarker-based diagnostics and the development of disease-modifying therapies such as lecanemab represent significant milestones in the fight against AD. However, challenges persist in achieving effective early intervention and personalized treatment strategies, as well as in addressing the multifactorial nature of the disease, which also gives rise to new ethical and societal concerns. Experts suggest that while amyloid-clearing therapies may address one aspect of Alzheimer's pathology, combination therapies targeting additional mechanisms of disease may be required in the future (Kwon, 2024).

A holistic approach that integrates novel biomarkers, combination therapies, lifestyle interventions, and a deeper understanding of AD pathophysiology will improve patient outcomes and quality of life in the coming years. It increasingly appears that the transition from “biological AD” to clinical dementia is primarily determined by “cognitive reserve.” Thus, there is an urgent need for population-level screening tools capable of accurately measuring this parameter.

Research funding and policy direction should shift from broad, nonspecific biomarker searches toward efforts focused on characterizing cognitive reserve and disease resilience. Identifying individual risk profiles—and the corresponding disease subtype—would enable tailored, person-specific interventions. Consequently, subtype-focused studies represent another critical area that requires prioritization and support.

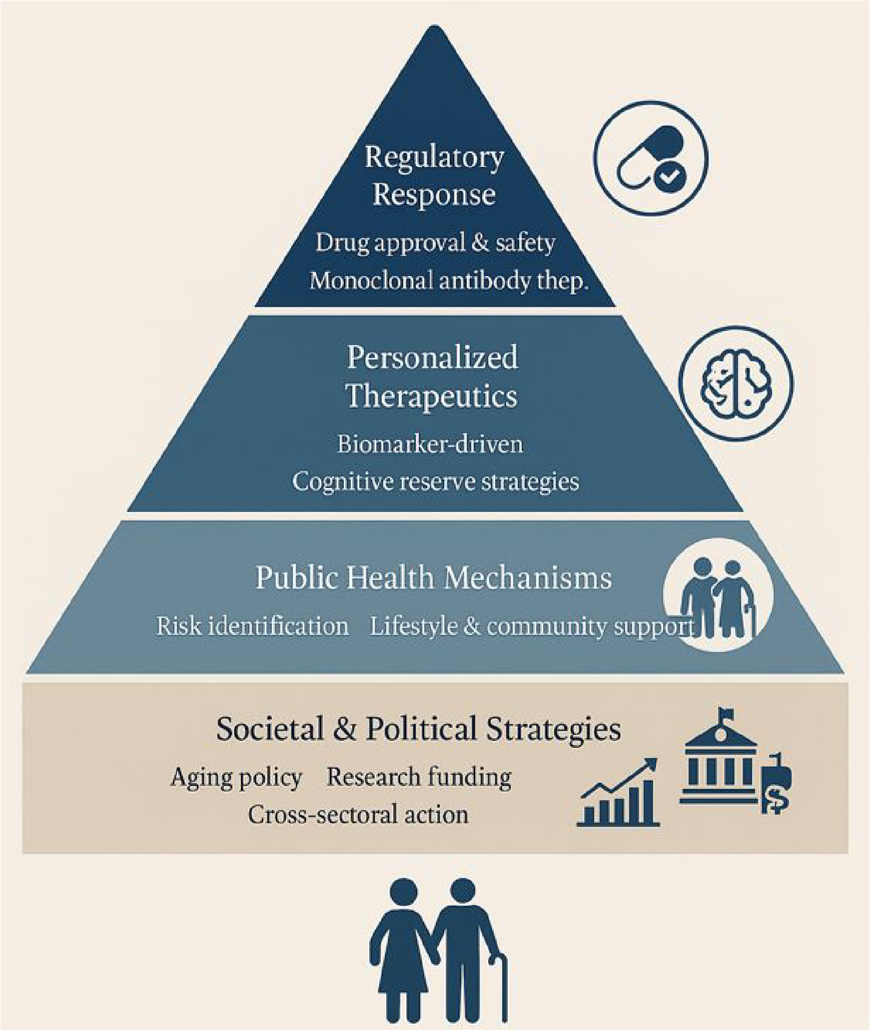

Figure 2. From drug approval to societal strategy: A multilevel framework for Alzheimer's disease

Note. Created by the author.

On the other hand, modifying the 14 risk factors identified by the Lancet Commission could potentially prevent or delay up to half of all dementia cases. However, achieving this goal requires more than individual-level interventions; it necessitates national and international government policy changes, prioritizing high-risk populations, and implementing personalized intervention strategies (Livingston et al., 2024). One of the important potentials for our country is the creation of a database such as e-NABIZ. It seems possible to collect data from this data that will show real risks, as Yiğit et al. (2024) did. The same system can be used for screenings and risk warnings that will consist of several phases.

Targets such as improving dementia care and implementing holistic state plans aimed at early diagnosis and risk reduction, like Japan's Orange Plan, which anticipates that approximately 10% of the population will face cognitive decline in the next few decades, can be planned (Japan Health Policy NOW – The New Orange Plan, 2015). In addition, many policies and actions can be rapidly developed, such as creating an institute dedicated to this field within the Presidency of the Turkish Health Sciences Institutes (TUSEB), which was established for strategy development and, if necessary, project financing.

CONCLUSION

In conclusion, regulatory authorities can no longer approach the issue solely through the narrow lens of approving or rejecting newly developed disease-modifying treatments for Alzheimer's disease (AD). We are facing an aging population, a rise in neurodegenerative disorders, and a growing burden of Alzheimer's-related dementias—factors that demand new and diverse approaches and political strategies at the societal level.

Such policy planning must be multi-dimensional. While developing personalized therapeutic strategies is essential, the broader public health and societal dimensions must not be overlooked. Health authorities must begin to adopt a comprehensive view of aging and dementia in our country to address the emerging societal burden of dementia in the coming years. This includes supporting research that considers all relevant aspects of the disease, promoting public health through multiple mechanisms, identifying individuals at risk, and delivering personalized management strategies through practical and proactive government policies.

Ethical Approval: This study does not involve human participants, clinical interventions, or data requiring ethical committee approval. Therefore, ethical approval was not necessary.

Authors' Contributions: LH conceptualized the study design. DE conducted the literature review and wrote the draft. BT participated in draft writing and formatting. LH and TA contributed to the review and editing processes. All the authors participated in the results and discussion. All authors read and approved the final version of the manuscript.

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