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# The critical need for defining preclinical biomarkers in Alzheimer's disease☆

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**Abstract** The increasing number of afflicted individuals with late-onset Alzheimer's disease (AD) poses significant emotional and financial burden on the world's population. Therapeutics designed to treat symptoms or alter the disease course have failed to make an impact, despite substantial investments by governments, pharmaceutical industry, and private donors. These failures in treatment efficacy have led many to believe that symptomatic disease, including both mild cognitive impairment (MCI) and AD, may be refractory to therapeutic intervention. The recent focus on biomarkers for defining the preclinical state of MCI/AD is in the hope of defining a therapeutic window in which the neural substrate remains responsive to treatment. The ability of biomarkers to adequately define the at-risk state may ultimately allow novel or repurposed therapeutic agents to finally achieve the disease-modifying status for AD. In this review, we examine current preclinical AD biomarkers and suggest how to generalize their use going forward.


*Keywords:* Alzheimer's disease; Alzheimer's Disease Neuroimaging Initiative; Amyloid-β; Apolipoprotein E ε4; Asymptomatic; Cerebrospinal fluid biomarkers; Epigenomics; Metabolomics; Mild cognitive impairment; Neuroimaging biomarkers; Peripheral blood biomarkers; Preclinical; Proteomics; Tau; Transcriptomics

## 1. Introduction

Alzheimer's disease (AD) is the most common form of dementia in the elderly, making up between 50% and 60% of all cases, with dementia with Lewy bodies combined with frontotemporal dementia (FTD) making up the other large segment (15%–25%) [1]. AD is a neurodegenerative disease that features loss of memory and impairment of cognitive function but is often difficult to differentiate from other forms of dementia, especially in the early clinical stages. Two major forms of AD have been recognized, a familial (genetic), early-onset AD (EOAD) form comprising a small percentage of those afflicted, and a sporadic late-onset AD (LOAD) variety affecting most AD patients. Although EOAD has a genetic basis and has been closely tied to the amyloid hypothesis [2] of the disease, LOAD has genetic associations and probably results from a combination of environmental factors, genetic susceptibilities, and yet to be determined influences. Some of these environmental factors are particularly relevant to the military. The growing military population exposed to significant stressors, especially over the last 15 years of multiple deployments, provides evidence that unique combat-related environmental factors can influence the risk of developing AD, possibly via shared and yet to be defined mechanisms associated with traumatic brain injury (TBI) and posttraumatic stress disorder (PTSD) [3].

There are clear signs that both military and civilian populations have increasing risks of AD going forward. A recent study by the Department of Veterans Affairs showed that their subject groups with PTSD had double the risk of



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developing dementia [4], whereas veterans with moderate or severe TBI had two to four times the risk of developing AD or other dementias as they age [5]. The increased risk of AD conferred by TBI is a growing concern not only in the military but also in the civilian arena, particularly as it relates to sport-related concussive injury. The World Health Organization currently estimates that approximately 35.6 million people are afflicted by AD worldwide. In the United States, approximately 7 million people older than 65 years are known to suffer from AD, and this number is expected to triple by 2050. According to the 2013 facts and figures from the Alzheimer's Association (AA) [6], although the number of deaths from major diseases such as cancer and cardiovascular disease has declined in the past decade, the number of deaths related to AD has increased 68% during the 2000 to 2010 period (Fig. 1). Major advances in treatment for the various diseases, except AD, are reflected in these statistics, as well as the increasing longevity of our population. In addition, the increasing numbers of AD-related deaths reflect an augmented precision by the medical community in diagnosing clinical dementia and documenting the suspected cause of demise. In an era of decreasing autopsy confirmation of clinical dementia diagnoses, the absolute numbers may be uncertain, but the trend is irrefutable.

The social and psychological burden associated with caring for those afflicted with AD remains difficult to quantify. The health-care costs associated with managing these individuals are staggering and threaten to bankrupt not only the United States but also the rest of the world economies if left unchecked. In the United States alone, AD-related health-care costs were estimated in 2010 to surpass $170 billion and projected to exceed $1 trillion by 2050 [7]. Such a societal need and cost have driven significant research funding by governments, pharmaceutical companies, and private organizations toward developing successful remedies for AD. Unfortunately, the progressive course of this illness has yet to be significantly impacted by any of the developed therapeutic strategies to date. Projected delays in disease onset by as little as 5 years, resulting from a successful therapeutic strategy, have the potential to reduce the Medicare costs of AD nearly in half [8].

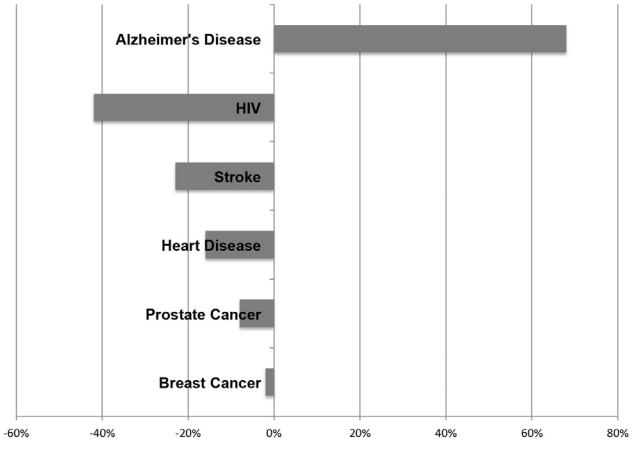


Fig. 1. Bar chart representation of estimated percent changes in reported deaths related to specific diseases during the 2000 to 2010 period, based on World Health Organization statistics [6]. HIV, human immunodeficiency virus.

Patient selection for therapeutic AD trials has been predicated on the presence of symptomatic disease, either mild cognitive impairment (MCI) [9] or AD [10], based on recently updated clinical criteria. There has not been a clear distinction, unfortunately, in the development and testing of therapeutic agents targeting the treatment of EOAD versus LOAD, despite their distinct etiologies and clinical trajectories and relatively rare occurrence of the former. Although certain transgenic animal models approach pathogenic modeling of human EOAD [11,12], no such models exist for LOAD, which would need to replicate both etiologic genetic predisposition and environmental factors. Although military blast-related TBI is associated with certain neuropathologic features similar to those of chronic traumatic encephalopathy [13], including overexpression of phosphorylated tau (p-tau), these changes remain distinct from those associated with LOAD [14]. Although drugs directed toward attenuating the amyloidogenic process may be supported in cases of EOAD [15], similar clinicopathologic evidence is lacking for LOAD. Unfortunately, the bulk of drugs tested so far in the clinic have been in LOAD (MCI or AD) subjects and focused toward modulating amyloid pathophysiology. Resultant efficacy measures in these investigations have either been unimpressive or lacking in late-stage clinical trials for the various therapeutic agents tested to date and with significant associated cost of these failures. An upcoming therapeutic clinical trial for genetically defined EOAD [16], the Alzheimer's Prevention Initiative, may have a higher likelihood of efficacy because of the improved definition of the afflicted pathobiologic networks in the proposed subjects and treatment during the preclinical stage of the disease. Unfortunately, EOAD subjects comprise only a small portion of the afflicted population, and therapeutic success in this group of subjects may not necessarily generalize to those with LOAD.

As a result of this lack of therapeutic efficacy in LOAD, many geriatricians and neurodegenerative disease specialists have postulated that the neural substrate in this disorder may not be responsive to currently used pharmacologic agents after the onset of clinical symptoms. Although possible that the right therapeutic agent has not been tested yet, the wide variety of drugs examined make this less likely. For many, the lack of therapeutic success may result from the decision to initiate treatment trials during the clinical stages of AD. The lack of efficacy documented within these well-financed and well-developed drug trials certainly supports this clinical observation. As a result, over the last 5 years, there has been a push to better understand the preclinical (asymptomatic) stages of AD and consider secondary prevention studies [8], where the neural substrate may remain more receptive to therapeutic intervention.

The preclinical stages of AD are based on documentation of the temporal neuropathologic changes in clinically