



## Featured Article

# Forecasting the prevalence of preclinical and clinical Alzheimer's disease in the United States

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**Abstract**

**Introduction:** We forecast the prevalence of preclinical and clinical Alzheimer's disease (AD) and evaluated potential impacts of primary and secondary preventions in the United States.

**Methods:** We used a multistate model incorporating biomarkers for preclinical AD with US population projections.

**Results:** Approximately 6.08 million Americans had either clinical AD or mild cognitive impairment due to AD in 2017 and that will grow to 15.0 million by 2060. In 2017, 46.7 million Americans had preclinical AD (amyloidosis, neurodegeneration, or both), although many may not progress to clinical disease during their lifetimes. Primary and secondary preventions have differential impact on future disease burden.

**Discussion:** Because large numbers of persons are living with preclinical AD, our results underscore the need for secondary preventions for persons with existing AD brain pathology who are likely to develop clinical disease during their lifetimes as well as primary preventions for persons without preclinical disease.

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**Keywords:**

Alzheimer's disease; Forecast; Intervention; Prediction; Prevalence; Prevention; Statistics

**1. Introduction**

Knowledge of the pathogenesis of preclinical Alzheimer's disease (AD) has grown enormously. Several National Institute on Aging and the Alzheimer's Association (NIA-AA) joint working groups have developed guidelines for the stages of preclinical AD and revised criteria for diagnoses [1–3]. The preclinical period begins years before onset of clinical disease [4,5]. The diagnosis of persons with preclinical disease is potentially important because persons may be more likely to benefit from

disease-modifying treatments if interventions occur before the occurrence of significant brain damage [6]. We use the terms primary prevention to refer to interventions designed to be implemented before the occurrence of brain pathology and secondary preventions to refer to interventions designed to slow progression to clinical disease (e.g., mild cognitive impairment [MCI] or AD) among persons who already have some brain pathology [7]. A recent consensus report that reviewed the current state of evidence on interventions to prevent cognitive decline and onset of dementia concluded that although at present no specific prevention interventions are strongly supported by the available scientific evidence, cognitive training, blood pressure management, and increased physical activity may provide some prevention benefit [8]. Recently a number of promising drugs failed to show clinical benefit in double-blind placebo-controlled trials in persons with mild-to-moderate dementia due to

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AD, and one hypothesis for those disappointing findings is that the drugs were administered too late in the disease course [9]. The development of prevention interventions is a rapidly evolving field especially with increased understanding of biomarkers and the preclinical course of AD.

Forecasts of preclinical and clinical disease stages are important from a number of perspectives. First, the resources needed to care for patients vary considerably by clinical stage. Second, prevalence estimates by disease stage are important for planning as they provide information about the numbers of persons who could benefit from potential primary and secondary preventions.

Two approaches have been described for estimating national AD prevalence [10]. The first approach is based on probability-based nationally representative prevalence surveys such as the Aging, Demographics and Memory Study [11]. The second approach, called forward calculation, uses AD incidence rates from epidemiological cohort (longitudinal) studies, mortality rates, and population projections in a multistate model to forecast AD prevalence and incidence numbers [12–14]. An advantage of the forward calculation method is that it can be used to evaluate the potential impact of preventive and therapeutic advances that delay progression of disease. Here, we generalize the forward calculation method to incorporate preclinical disease and MCI states into a multistate model. We use the model to forecast US prevalence of preclinical and clinical disease and to evaluate the potential impact of primary and secondary preventions on those forecasts.

## 2. Methods

### 2.1. Multistate model

An NIA-AA workgroup proposed a framework for the preclinical stages of AD [1]. The framework posits that the AD process typically begins with asymptomatic amyloidosis which refers to amyloid  $\beta$  ( $A\beta$ ) deposition which can be detected by specific biomarkers for  $A\beta$  accumulation such as positron emission tomography amyloid imaging or low  $A\beta$  42 in the cerebrospinal fluid. The framework postulates

that sometime after the onset of amyloidosis, the disease process advances to neurodegeneration which can be detected by biomarkers including elevated cerebrospinal fluid tau, neuronal dysfunction based on fluorodeoxyglucose positron emission tomography, or hippocampal atrophy/cortical thinning on volumetric magnetic resonance imaging. Neurodegeneration is followed by subtle cognitive decline, onset of MCI due to AD [2], and ultimately clinical AD [3].

We use a multistate model largely based on the NIA-AA framework for the preclinical stages of AD [1]. Our model includes nine states: eight preclinical or clinical disease states plus the death state (Fig. 1). Persons can die in any state. The model allows several pathways to AD. One pathway (red pathway in Fig. 1) assumes persons progress sequentially through the following: normal (state 1), preclinical amyloidosis (state 2), amyloidosis with neurodegeneration (state 4), MCI due to AD with both amyloidosis and neurodegeneration (state 5), early clinical AD (state 7), and late (or advanced) clinical AD (state 8). Persons in states 7 and 8 have reached the threshold for a clinical diagnosis of AD, that is, dementia due to AD. While the red pathway is the primary pathway posited by the NIA-AA working group and most consistent with the amyloid hypothesis of AD [15], evidence supporting the occurrence of AD in the absence of amyloidosis has also been described [16]. While such pathways have been termed suspected non-AD pathophysiology, there is controversy as to whether such pathways should or should not be considered part of the AD pathological processes [17,18]. Here we allow for such alternative pathways including occurrence of neurodegeneration before amyloidosis and occurrence of MCI due to AD in the presence of neurodegeneration but not amyloidosis (blue pathways in Fig. 1).

The model in Fig. 1 differs from the NIA framework in that we do not include a stage of amyloidosis and neurodegeneration with subtle cognitive decline (called stage 3 in [1]) because we do not believe there are adequate data at this time to provide reliable estimates of transition rates to and from that stage. Instead, this stage is subsumed into state 4 in Fig. 1. The model in Fig. 1 differs from the model of

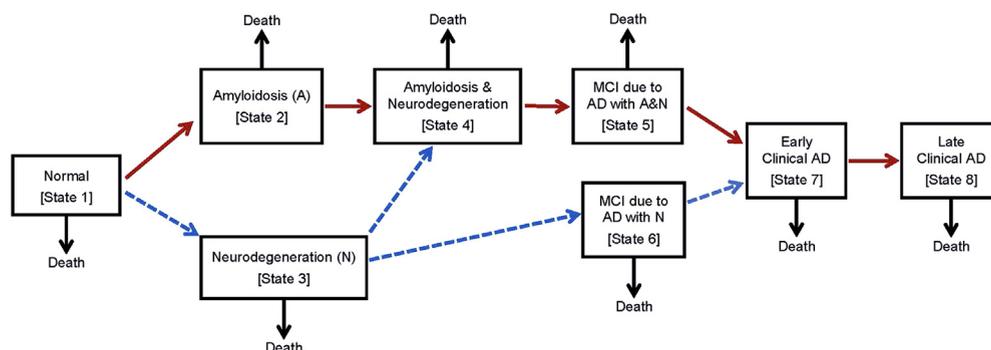


Fig. 1. Multistate model of the progression of Alzheimer's disease through preclinical and clinical disease states. Abbreviations: AD, Alzheimer's disease; MCI, mild cognitive impairment.

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