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Featured Article

Estimation of lifetime risks of Alzheimer's disease dementia using biomarkers for preclinical disease

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Abstract

Introduction: Lifetime risks are the probabilities of progressing to Alzheimer's disease (AD) dementia during one's lifespan. Here, we report the first estimates of the lifetime and ten-year risks of AD dementia based on age, gender, and biomarker tests for preclinical disease.
Methods: We used a multistate model for the disease process together with US death rates.
Results: Lifetime risks of AD dementia vary considerably by age, gender, and the preclinical or clinical disease state of the individual. For example, the lifetime risks for a female with only amyloidosis are 8.4% for a 90-year old and 29.3% for a 65-year old. Persons younger than 85 years with mild cognitive impairment, amyloidosis, and neurodegeneration have lifetime risks of AD dementia greater than 50%.
Discussion: Most persons with preclinical AD will not develop AD dementia during their lifetimes. Lifetime risks help interpret the clinical significance of biomarker screening tests for AD.

Keywords: Alzheimer's disease; Lifetime risks; Preclinical; Prediction

1. Introduction

Considerable advances have been made in identifying biomarkers that detect preclinical Alzheimer's disease (AD) [1–3]. Biomarkers are central to current research on AD pathophysiology although their use in routine clinical care is less clear for several reasons. First, the biomarkers that are currently in use are based on imaging or cerebrospinal fluids and are either expensive, invasive, or both. Second, even if a preclinical disease is detected, there are no interventions strongly supported by the scientific evidence to slow the onset of dementia although cognitive training, blood pressure management, and physical activity may provide some benefit [4]. Third, persons with a preclinical disease may never actually experience any clinical symptoms during their lifetimes because of the long preclinical period of AD and the high mortality rates in elderly populations.

The lifetime risk is the probability that an individual experiences a clinical condition before death [5]. Lifetime risks for AD dementia have been based on longitudinal follow-up of cohorts as in the Framingham study [6]. To date, no lifetime risk estimates for AD dementia have been reported which account for biomarkers of preclinical conditions. Lifetime risk estimates address a critical question for clinicians, patients, and their families as to the likelihood that a preclinical condition detected by biomarker screening will ever actually manifest itself with clinical symptoms during a person's natural lifespan.

Here, we report estimates of the lifetime and ten-year risks of AD dementia based on age, gender, and biomarker tests for preclinical disease. The estimates are based on a multistate model for the progression of AD through preclinical and clinical disease states.

2. Methods

In this section, we provide an overview of the methods including the multistate model and transition rates used in the model. The Supplementary Material provides technical

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details including definitions and cutoffs of biomarker-defined states and the estimating equations.

2.1. Multistate model

We used a multistate model for the progression of AD through preclinical and clinical disease states to estimate lifetime risks of AD dementia. The model is based on the National Institute on Aging-Alzheimer's Association framework for the preclinical stages of AD [1]. The National Institute of Aging-Alzheimer's Association framework of preclinical disease postulates that the AD pathophysiology typically begins with a state of asymptomatic amyloidosis, that is, amyloid β deposition, that can be detected by specific biomarkers for amyloid β accumulation, such as positron emission tomography amyloid imaging or low amyloid β 42 in the cerebrospinal fluid. The disease process advances to neurodegeneration which can be detected using biomarkers including elevated cerebrospinal fluid tau, neuronal dysfunction based on fluorodeoxyglucose positron emission tomography or hippocampal atrophy/cortical thinning on volumetric magnetic resonance imaging. Subsequently, clinical signs and symptoms emerge including subtle cognitive decline, onset of mild cognitive impairment (MCI) due to AD, and ultimately AD dementia [7,8].

The multistate model we used is illustrated in Fig. 1. The model postulates that one pathway that leads to AD dementia (red pathway in Fig. 1), which is consistent with the amyloid hypothesis of AD [9], is sequential progression through the following states: normal (state 1), asymptomatic amyloidosis (state 2), amyloidosis and neurodegeneration (state 4), MCI due to AD with both amyloidosis and neurodegeneration (state 5), and AD dementia (state 7). Evidence supporting alternative pathways leading to AD dementia has also been described, including the occurrence of Alzheimer's dementia in the absence of amyloidosis or with neurodegeneration arising before amyloidosis [10]. We allow for these alternative pathways (blue pathways in Fig. 1) although we recognize there is controversy as to whether such pathways should or should not be considered as part of the AD pathological processes [11,12]. Persons are at risk of death in any preclinical or clinical disease state. The multistate model in Fig. 1 differs from the National Institute of Aging-Alzheimer's Association framework, in which we do not include a stage of amyloidosis and neurodegeneration with subtle cognitive decline because we do not believe there are adequate data to provide reliable estimates of transition rates to and from that stage and instead that stage is included in state 4 in Fig. 1. The model also differs from the multistate model used by Jack et al. [13] to estimate transition rates, in which we included an AD MCI state with both amyloidosis and neurodegeneration (state 5) and an MCI state with only neurodegeneration (state 6). The model in Fig. 1 is similar to a model we previously used for obtaining population forecasts for preclinical and clinical disease states [14] with the difference being that for the purpose of estimating lifetime risks, we modeled only the disease process up to the onset of AD dementia and not its subsequent clinical course.

The multistate model is a discrete time Markov model in which the transition rates from one state to the next are allowed to depend on a person's current age but not on the duration of time that a person has already spent in the state. Transitions are assumed to occur at the end of each chronological year of age.

2.2. Transition rates and death rates

The transition rates we used in the multistate model are based on two large published epidemiological cohort studies that measured biomarkers for amyloidosis and neurodegeneration. One study, The Mayo Clinic Study of Aging analyzed 1541 participants and reported preclinical transition rates between biomarker states [13]. The second study

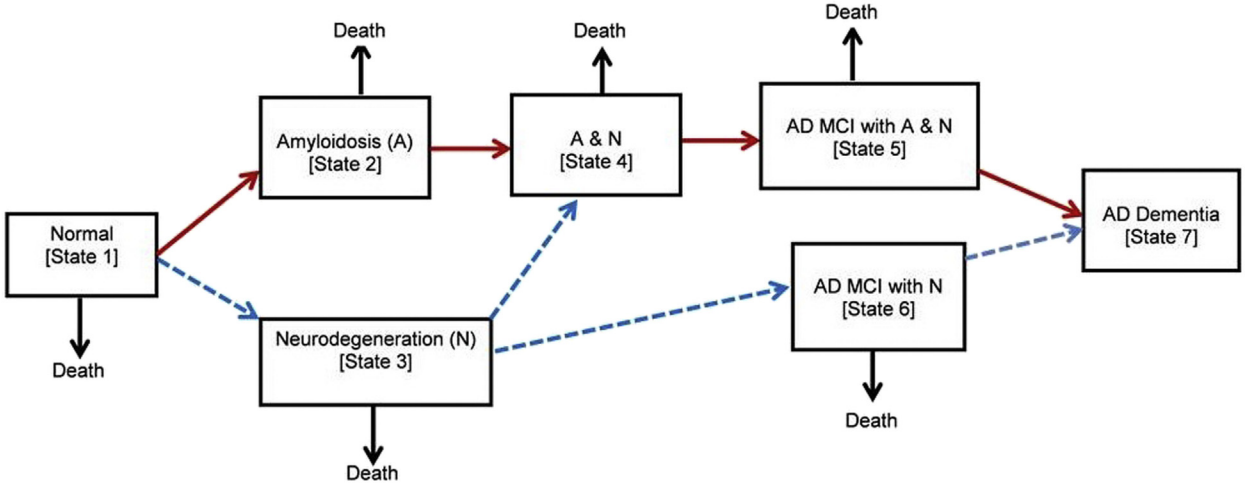

Fig. 1. The multistate model used to estimate lifetime risks of AD dementia. Abbreviations: AD, Alzheimer's disease; MCI, mild cognitive impairment.