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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

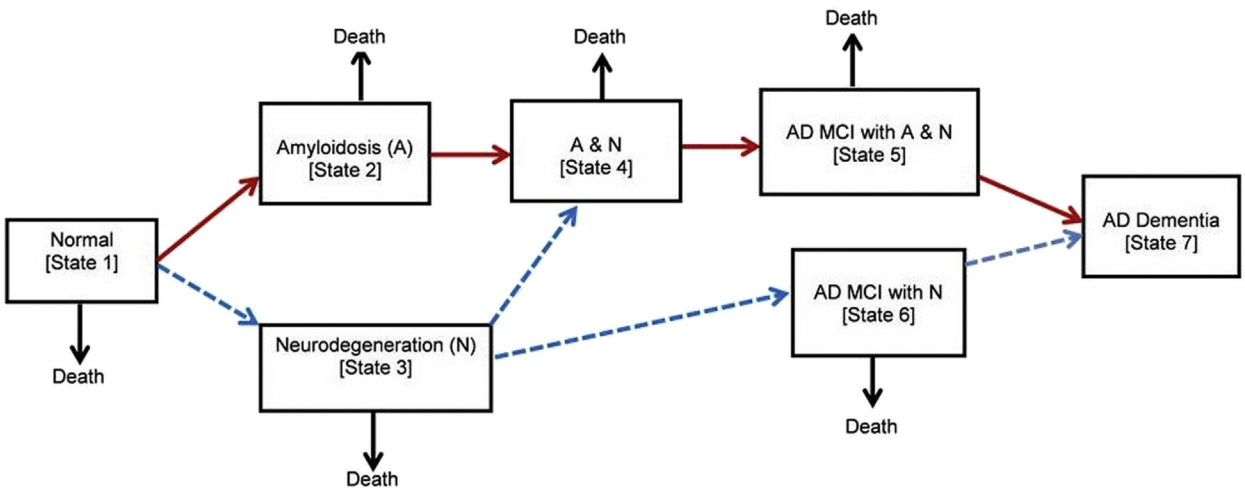

Fig. 1. The multistate model used to estimate lifetime risks of AD dementia. Abbreviations: AD, Alzheimer's disease; MCI, mild cognitive impairment.

that was based on 13 cohorts in Europe and the United States reported on the rates of progression from MCI to AD dementia and included at least 3 years of follow-up on 353 persons with MCI and both amyloidosis and neurodegeneration and another 222 persons with MCI and neurodegeneration [15]. We have previously described the use of these epidemiological cohort studies for estimating each of the transition rates in the multistate model [14].

We used US 2014 death rates by age and gender for persons in the preclinical states 1 through 4 and assumed those death rates remained constant into the future [16]. Recent studies have indicated that persons with MCI are at an increased risk of death compared with those without MCI [17–21]. A study from the population-based Mayo Clinic Study of Aging reported that the hazard ratio of death for persons with amnestic MCI before the onset of dementia relative to cognitively normal persons was 1.65 [17]. Similar hazard ratios have been reported in other studies [18–21]. We multiplied the background death rates by the factor 1.65 to obtain the death rates for persons with MCI in states 5 and 6.

2.3. Lifetime risk estimation

The lifetime risk is the probability of developing AD dementia during one's lifetime. We calculated lifetime risks accounting for preclinical or clinical disease state (states 1–6), age, and gender. Gender is factored into the calculations because death rates depend on gender. Age is factored in because death rates and transition rates between states depend on age. In addition, we calculated 10-year (absolute) risks which are the probabilities of developing AD dementia over the next 10 years. The 10-year risks (also called the absolute risk) are the probabilities of developing a clinical condition over a restricted time period (e.g., 10 years), whereas the lifetime risk is that probability over the entire remaining lifespan [22,23]. The Supplementary Material provides the equations that were used to calculate the lifetime and 10-year risks. In brief, first, we calculated the probability that a person in disease state i at age a develops AD dementia (state 7) at age $a+n$. We calculated that probability by multiplying one-step transition matrices n times (Supplementary Material). Second, we calculated the 10-year risk of AD dementia by summing those probabilities for each of the next 10 years (i.e., for $n = 1, 2\ldots, 10$). The lifetime risk was obtained by summing those probabilities of the occurrence of AD dementia at each age from age $a+1$ until age 109 (the maximal lifespan was assumed to be 109).

2.4. Sensitivity analyses and comparison with other approaches

We performed a sensitivity analysis of the lifetime and 10-year risk estimates to the transition rates. We calculated ranges that resulted from using a high and low series of transition rates. The high and low series of transition rates were based on the limits of the 95% confidence intervals for each transition rate.

We sought to determine if our estimates of lifetime risks could be corroborated by other independent data sources and methods. Unfortunately, there have been no previous studies of lifetime risks of AD dementia which account for preclinical disease state using biomarkers. AD dementia lifetime risks reported from the Framingham Heart Study, which were based on observations of AD dementia diagnoses and mortality during longitudinal follow-up, accounted for age and gender but did not account for biomarkers or preclinical disease states [5,6]. Thus, to make comparisons, we needed to calculate weighted averages of our multistate model lifetime risk estimates averaging over the six preclinical and clinical disease states where the weights were based on the prevalence rates of each of the states by age and gender (Supplementary Material). We also compared these estimates with lifetime risks for all-cause dementia from three studies: a study [24] using data from the Rotterdam Study, which is a community-based prospective cohort study in the Netherlands [25]; a study [26] using data from the Aging Demographics and Memory Study, which is a nationally representative US longitudinal study [27]; and a study [28] using data from the Canadian Study of Health and Aging [29]. Finally, we discuss results from studies that estimated the proportions of deaths in the United States either attributable to AD dementia or with AD dementia present at death [30,31] in relation to the lifetime risk estimates reported here.

3. Results

Table 1 shows the lifetime risks of AD dementia for females by preclinical or clinical disease state and age based on the multistate model. We found that the lifetime risks at each age increase in the following order by disease state: normal (state 1), neurodegeneration (state 3), amyloidosis (state 2), amyloidosis and neurodegeneration (state 4), MCI with neurodegeneration (state 6), and MCI with amyloidosis and neurodegeneration (state 5). We also observe in Table 1 that the lifetime risks generally decrease with age for persons in any given disease state. The explanation for the decreasing trend of lifetime risks with age within each disease state in Table 1 is that the expected remaining lifetime, in which AD dementia progresses, decreases with advancing age.

The lifetime risks mentioned in Table 1 vary considerably by age and disease state. For example, the lifetime risks for a 75-year-old female are 13.8% in the normal state, 23.5% with amyloidosis, 35.9% with amyloidosis and neurodegeneration, and 84.7% with MCI in the presence of both amyloidosis and neurodegeneration. We find that presence of preclinical disease does not necessarily signal a high likelihood of AD dementia. For example, a 90-year old with amyloidosis (state 2) has a lifetime risk of AD dementia of only 8.4% compared with a 65-year-old female with

Table 1
Lifetime risks (%) of AD dementia for females based on screening for amyloidosis (A), neurodegeneration (N), and mild cognitive impairment (MCI) by age

Age	Normal state 1	A state 2	N state 3	A & N state 4	MCI & A & N state 5	MCI & N state 6
60	20.1 (10.6–34.0)	31.0 (20.7–42.4)	30.3 (15.9–53.2)	41.9 (31.2–52.7)	95.6 (94.8–96.3)	78.1 (70.9–84.9)
65	18.7 (9.7–32.0)	29.3 (19.4–40.5)	27.6 (14.5–48.0)	40.8 (30.3–51.4)	93.6 (92.3–94.5)	71.4 (63.7–79.2)
70	16.6 (8.4–29.0)	26.9 (17.6–37.6)	24.5 (12.9–42.3)	38.9 (28.7–49.3)	90.1 (88.2–91.4)	63.0 (55.1–71.6)
75	13.8 (6.8–24.9)	23.5 (15.1–33.4)	20.8 (10.8–36.0)	35.9 (26.2–45.8)	84.7 (82.1–86.7)	53.2 (45.5–62.1)
80	10.4 (4.9–19.5)	19.1 (12.0–27.8)	16.5 (8.5–29.0)	31.2 (22.4–40.3)	76.2 (72.8–78.9)	42.0 (35.1–50.5)
85	7.1 (3.2–13.7)	13.8 (8.4–20.6)	11.9 (6.0–21.2)	24.7 (17.4–32.5)	63.8 (59.7–67.2)	30.3 (24.8–37.5)
90	4.1 (1.8–8.4)	8.4 (4.9–13.0)	7.3 (3.6–13.4)	16.9 (11.6–22.6)	46.7 (42.7–50.2)	19.1 (15.4–24.3)

Abbreviation: AD, Alzheimer's disease.
NOTE. Lower and upper bounds are given in brackets.

amyloidosis who has a lifetime risk of 29.3%. The lower lifetime risk for the 90-year old versus the 65-year old is explained by the shorter life expectancy of the 90-year old than that of the 65-year old. MCI in the presence of both amyloidosis and neurodegeneration confers a lifetime risk of at least 50% for all ages less than or equal to 85 years.

Table 2 shows the 10-year absolute risks of AD dementia for females according to disease state and age. The 10-year risks are useful for identifying which persons are most likely to progress to AD dementia in the near term and for whom prevention interventions to delay disease progression are especially urgent. Ten-year (or shorter term) risks provide a time perspective on lifetime risks and aid in assessing health-care and resource needs in the short term. The 10-year (or shorter term) risks also aid in designing clinical trials by identifying the persons at the highest risk of progression to the primary clinical endpoints (e.g., AD dementia) to increase statistical power and to identify those persons for whom there is significant potential benefit from trial enrollment [23]. The 10-year risks are necessarily less than lifetime risks, and the differences between them can vary considerably. For example, a 65-year-old female with amyloidosis (state 2) has a 10-year risk of AD dementia of 2.5% but a lifetime risk of 29.3%. In contrast, the 10-year risk for a 90-year old with amyloidosis (8.2%) is essentially indistinguishable from her lifetime risk (8.4%). Those findings are explained by the shorter life expectancy (less than 10 years) for 90-year olds than that for 65-year olds.

Table 3 shows the lifetime risks of AD dementia for males by preclinical and clinical disease state and age. The lifetime risks of males are less than the lifetime risks of females because mortality rates are higher for males than females. For example, the lifetime risks for a 75-year-old male and female with amyloidosis (state 2) are 17.2% and 23.5%, respectively. Generally, the trends and patterns of lifetime risks with age and disease state for males are similar to those observed with females. Table 4 shows the 10-year absolute risks of AD dementia for males. The 10-year risk of AD dementia for a male with amyloidosis (state 2) is less than 10% for all ages.

Table 5 compares lifetime risk estimates of AD dementia by age and gender (but not biomarker preclinical state) obtained from the multistate model with those of several other studies. The Framingham Study reported lifetime risks of AD dementia by age and gender. The Framingham estimates are lower than the estimates from the multistate model, especially for males, although the ranges overlapped. For example, the lifetime risks for males at age 75 years were 21.1% (range, 11.2%–34.8%) and 10.2% (95% CI, 7.9%–12.5%) based on the multistate model and Framingham study, respectively. A possible explanation [26] for the lower risks in Framingham is that death rates were generally higher during the follow-up period of the Framingham Study (which was centered approximately around the year 1985) than US death rates in 2014, which was what was used in the multistate model. If death rates are higher, then lifetime risks of AD dementia will be lower. Table 5 also shows lifetime risks for all-cause dementia based on data from the Rotterdam study [24] and the Aging Demographics and Memory Study [26]. The lifetime risks of all-cause dementia

Table 2
Ten-year risks (%) of AD dementia for females based on screening for amyloidosis (A), neurodegeneration (N), and mild cognitive impairment (MCI) by age

Age	Normal state 1	A state 2	N state 3	A & N state 4	MCI & A & N state 5	MCI & N state 6
60	0.2 (0.06–0.8)	1.3 (0.6–2.5)	3.6 (1.1–14.2)	7.1 (4.5–10.9)	93.5 (91.1–95.0)	57.2 (48.2–67.9)
65	0.5 (0.14–1.8)	2.5 (1.2–4.9)	4.3 (1.4–15.0)	10.7 (6.8–16.2)	91.7 (89.2–93.5)	55.4 (46.6–65.8)
70	1.1 (0.34–3.5)	4.7 (2.4–8.7)	5.5 (2.0–16.6)	15.5 (10.0–22.8)	88.6 (85.8–90.6)	52.2 (43.8–62.4)
75	2.2 (0.74–6.5)	7.8 (4.1–14.0)	7.3 (2.9–19.0)	20.8 (13.7–29.7)	83.8 (80.7–86.2)	47.4 (39.6–57.0)
80	3.7 (1.3–9.8)	11.1 (6.0–18.7)	9.3 (3.9–20.9)	24.4 (16.4–33.8)	75.8 (72.2–78.7)	40.0 (33.1–48.6)
85	4.7 (1.8–11.0)	11.5 (6.5–18.5)	9.7 (4.3–19.3)	23.1 (15.8–31.2)	63.7 (59.6–67.2)	30.0 (24.5–37.2)
90	3.8 (1.5–8.2)	8.2 (4.7–12.9)	7.1 (3.3–13.3)	16.8 (11.5–22.6)	46.7 (42.7–50.2)	19.1 (15.3–24.3)

Abbreviation: AD, Alzheimer's disease.
NOTE. Lower and upper bounds are given in brackets.

Table 3
Lifetime risks (%) of AD dementia for males based on screening for amyloidosis (A), neurodegeneration (N), and mild cognitive impairment (MCI) by age

Age	Normal state 1	A state 2	N state 3	A & N state 4	MCI & A & N state 5	MCI & N state 6
60	13.9 (6.9–25.1)	23.1 (14.9–33.0)	23.1 (11.4–44.3)	33.6 (24.4–43.5)	92.9 (91.7–93.9)	71.7 (64.3–79.2)
65	12.9 (6.3–23.6)	21.9 (13.9–31.4)	20.8 (10.3–39.4)	32.9 (23.8–42.7)	90.4 (88.6–91.7)	64.9 (57.1–73.2)
70	11.3 (5.4–21.2)	19.9 (12.5–29.0)	18.2 (9.0–34.0)	31.3 (22.5–40.7)	86.0 (83.6–87.8)	56.3 (48.6–65.0)
75	9.3 (4.3–17.8)	17.2 (10.6–25.4)	15.2 (7.5–28.2)	28.6 (20.3–37.5)	79.5 (76.5–82.0)	46.6 (39.4–55.2)
80	6.8 (3.0–13.5)	13.6 (8.2–20.6)	11.7 (5.7–21.9)	24.5 (17.1–32.5)	69.9 (66.1–73.0)	36.0 (29.8–43.8)
85	4.4 (1.9–9.2)	9.5 (5.6–14.8)	8.1 (3.9–15.5)	18.9 (13.0–25.5)	56.7 (52.6–60.2)	25.3 (20.6–31.7)
90	2.4 (1.0–5.2)	5.4 (3.1–8.8)	4.7 (2.2–9.2)	12.4 (8.3–17.0)	40.2 (36.4–43.5)	15.6 (12.5–20.0)

Abbreviation: AD, Alzheimer's disease.
NOTE. Lower and upper bounds are given in brackets.

from these studies are higher than those for AD dementia from either the multistate model or Framingham Study. Another study of lifetime risks of all-cause dementia risks [28] was based on the Canadian Study of Health and Aging and reported even higher estimates than those based on Aging Demographics and Memory Study and Rotterdam. The Canadian study reported lifetime risks of all-cause dementia (not stratified by gender) at ages 65, 75, and 85 years of 42.4%, 47.3%, and 58.5%, respectively [28].

Two other studies on AD and mortality are relevant to the question at hand although these studies did not directly estimate lifetime risks [30,31]. One study based on data from the Chicago Health and Aging Project found that approximately 600,000 deaths in the US occurred among persons over the age of 65 years with AD in 2010, which represented approximately 32% of all US deaths over the age of 65 years [30,32]. A second study using data from multiple sources including Chicago Health and Aging Project, the Rush Memory and Aging Project, and the Religious Order Study concluded that approximately 503,400 deaths in the US among persons aged 75 years and older were attributable to AD dementia in 2010, which represents approximately 36% of deaths over the age of 75 years [31,32]. The results from these two studies [30,32] suggested that AD dementia is identified in well over 30% of US deaths among elderly persons, a percentage that is higher than any of the multistate model lifetime risk or Framingham estimates in Table 5. To summarize, compared with the lifetime risk of AD dementia from the multistate model reported here, two mortality studies [30,31] suggested higher risks, whereas the Framingham study [5,6] suggested lower risks.

4. Discussion

The prevalence of preclinical AD in the United States has been estimated to be approximately 46.7 million persons [14]. Tables 1 and 3 show that most persons with preclinical disease will not develop AD dementia during their lifetimes. We find that the lifetime risks for AD dementia vary considerably by age, gender, and preclinical disease state. If interventions could slow disease progression rates even modestly, lifetime risks of AD dementia could be appreciably reduced [33].

Lifetime risks are useful from a number of perspectives. Lifetime risk calculations can provide guidance as to whether biomarker screening would provide clinically useful prognostic information. For example, the lifetime risks of AD dementia for 90-year males and females who do not have cognitive impairment are less than 12.4% and 16.9%, respectively. Thus, 90-year olds who do not have cognitive impairment are unlikely to develop AD dementia during their lifetime regardless of their current preclinical state, and thus, biomarker screening would not yield much additional prognostic information. In some situations, lifetime risks may allay some anxiety about the meaning of a particular positive screening test with regard to the likelihood of developing AD dementia. For example, the lifetime risk of AD dementia of a 60-year-old male with amyloidosis is only 23%, and thus, he is considerably more likely to not develop AD dementia. Lifetime risks also explain some discordance between clinical and pathological studies. Some studies have reported persons with AD brain pathology who do not have AD dementia at the time of death. Lifetime risks can help explain that discordance. For example,

Table 4
Ten-year risks (%) of AD dementia for males based on screening for amyloidosis (A), neurodegeneration (N), and mild cognitive impairment (MCI) by age

Age	Normal state 1	A state 2	N state 3	A & N state 4	MCI & A & N state 5	MCI & N state 6
60	0.2 (0.05–0.8)	1.2 (0.6–2.4)	3.4 (1.0–13.5)	6.7 (4.3–10.4)	91.1 (88.5–92.8)	54.9 (46.2–65.3)
65	0.4 (0.13–1.6)	2.3 (1.2–4.5)	4.0 (1.3–14.1)	10.1 (6.4–15.2)	88.8 (86.1–90.8)	52.6 (44.1–62.7)
70	1.0 (0.3–3.2)	4.2 (2.1–7.9)	5.0 (1.8–15.1)	14.2 (9.2–21.0)	84.9 (81.9–87.2)	48.7 (40.7–58.4)
75	1.9 (0.6–5.5)	6.8 (3.5–12.1)	6.4 (2.5–16.6)	18.4 (12.0–26.4)	79.0 (75.5–81.6)	43.0 (35.8–52.0)
80	2.9 (1.0–7.7)	8.9 (4.8–15.1)	7.5 (3.1–17.1)	20.4 (13.6–28.5)	69.7 (65.8–72.9)	34.9 (28.8–42.8)
85	3.3 (1.2–7.8)	8.4 (4.7–13.8)	7.1 (3.1–14.6)	18.1 (12.2–24.9)	56.6 (52.5–60.2)	25.2 (20.5–31.6)
90	2.3 (0.9–5.1)	5.4 (3.0–8.7)	4.6 (2.1–9.2)	12.4 (8.3–17.0)	40.2 (36.4–43.5)	15.6 (12.5–20.0)

Abbreviation: AD, Alzheimer's disease.
NOTE. Lower and upper bounds are given in brackets.

Table 5
Comparison of lifetime risks of AD dementia (%) by age and gender based on the multistate model (ranges) and the Framingham Study (95% confidence intervals) [5].

Age	Multistate (AD)	Framingham (AD)	Rotterdam (all dementia)	ADAMS (all dementia)
Female				
60	24.4 (13.1–39.8)	N.R.	N.R.	N.R.
65	25.2 (13.7–40.9)	17.2 (15.0–19.4)	34.5	N.R.
70	26.2 (14.3–41.9)	N.R.	N.R.	34.7
75	27.3 (15.1–42.6)	18.5 (16.2–20.9)	35.4	34.1
80	27.7 (15.7–42.1)	N.R.	N.R.	32.9
85	26.8 (15.7–39.5)	20.3 (17.0–23.6)	32.7	31.2
90	23.2 (14.0–33.2)	N.R.	N.R.	29.3
Male				
60	17.6 (9.0–30.8)	N.R.	N.R.	N.R.
65	18.7 (9.6–32.3)	9.1 (7.2–11.1)	16.0	N.R.
70	19.9 (10.3–33.7)	N.R.	N.R.	26.9
75	21.1 (11.2–34.8)	10.2 (7.9–12.5)	18.0	27.1
80	21.8 (11.9–34.7)	N.R.	N.R.	26.7
85	21.2 (12.0–32.5)	12.1 (8.2–15.9)	12.3	25.7
90	18.2 (10.6–27.0)	N.R.	N.R.	24.7

Abbreviations: AD, Alzheimer's disease; ADAMS, Aging Demographics and Memory Study; N.R., not reported.

NOTE. Also shown are lifetime risks for all-cause dementia based on the Rotterdam Study [24] and the ADAMS Study [26].

although 23% of 60-year-old males with amyloidosis will ultimately develop AD dementia, the flip side is that 67% of 60-year olds with amyloidosis will die before onset of AD dementia.

Key sources of uncertainty in our results are the transition rates between disease states. The transition rates were based on some of the largest longitudinal studies available to date which have measured biomarkers. We provided ranges for the lifetime risks based on confidence intervals for the transition rates. However, we recognize that there are important potential sources of bias that may not be accounted for by these ranges. For example, although the Mayo Clinic Study of Aging is a population-based cohort study, it is not ethnically diverse. Furthermore, vascular risk factors and pathology in the presence of AD pathology may increase the transition to AD dementia, and thus, the transition rates we used may not be applicable to other populations with different levels of vascular pathology. Future studies of transition rates in more ethnically diverse populations that also account for education and other sociodemographic characteristics with varying prevalence rates of vascular pathology will be important. We also acknowledge that the preclinical transition rates depend on the specific biomarkers and cut points used in defining the preclinical states. It is reassuring that one study suggested that results are not sensitive to the definitions of the states of amyloidosis and neurodegeneration [34]. Furthermore, it is reassuring that AD incidence rates produced by the multistate model were consistent with a worldwide systematic review of clinical AD dementia incidence based on 27 cohorts from around the world (see figure 4 in [14]).

The disease transition rates in our model were allowed to depend on chronological age, but they did not depend on calendar time. Recent reports have suggested that dementia prevalence and incidence rates have declined over the past three decades [35,36]. The disease transition rates we used were based on recent follow-up of cohorts and thus should reflect current AD dementia rates. However, if AD dementia incidence rates decline in the future, then the lifetime risks reported here would overestimate actual risks.

Important inputs into our calculations are the death rates. The lifetime risk estimates vary inversely with death rates; as death rates increase, the lifetime risks of AD dementia decrease [37]. Our lifetime and 10-year risk estimates are based on 2014 US mortality rates and as such may not be applicable to other populations. Furthermore, if mortality rates decline in the future, and all other factors remaining the same, then the lifetime risks reported here would underestimate actual risks. We adjusted for excess mortality in the MCI state, but if the adjustment factor (relative risk of 1.65) that we used was too high (low), then our lifetime AD dementia risks would be too low (high).

An important question is whether supplementary information on apolipoprotein (*APOE*) ε4 carrier status, in addition to that on preclinical biomarkers, would refine lifetime risk estimates. Some studies have suggested that *APOE* ε4 carriers are at increased risk of developing amyloidosis [38–41]. Consider the supposition that the effect of being an *APOE* ε4 carrier is to increase the rates of transition from normal (state 1) to amyloidosis (state 2) and from neurodegeneration (state 3) to amyloidosis and neurodegeneration (state 4), but to not alter any other transition rates in the multistate model. Under that supposition, information on *APOE* ε4 carrier status could be used to refine the lifetime risks in Tables 1 and 3 for persons without amyloidosis (persons in states 1, 3, and 6). Further studies are necessary to precisely quantify the impact of *APOE* ε4 status on each of the preclinical transition rates and to identify other risk factors that in combination with biomarkers of preclinical disease would yield more precise estimates of lifetime risk of AD dementia.

Pathologies related to non-AD dementias may coexist with AD pathologies. It is uncertain whether multiple mixed pathologies act independently or synergistically on risk of all-cause dementia. Extensions of the multistate model to include additional preclinical states that are either specific to AD (e.g., biomarkers for tau pathology [42]) or biomarkers related to other types of dementia would refine estimates of lifetime risks of AD dementia and all-cause dementia.

Guidelines for the appropriate clinical use of screening tests for preclinical AD and MCI will be increasingly important [43,44] as the sensitivity and specificity of biomarkers for preclinical AD improve and as intervention options to slow disease progression become

available. There are numerous critical factors [45,46] to consider in assessing the value of screening for AD biomarkers. Lifetime risks will aid in formulating screening guidelines by identifying groups of persons for whom screening for preclinical AD may be most useful and by helping interpret the clinical significance of biomarker screening tests for preclinical AD.

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Authors' contributions: R.B. conceived the study, developed the methods, interpreted the data, and drafted the manuscript. N.A. carried out statistical analyses, developed the computer software code, and critically revised the manuscript.

Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jalz.2018.03.005.

RESEARCH IN CONTEXT

1. Systematic review: The authors searched PubMed for articles on lifetime risks of Alzheimer's disease (AD) dementia. Lifetime risks are the probabilities that individuals progress to AD dementia during their natural lifespan. Here, we report the first estimates of lifetime and ten-year risks of AD dementia that account for age, gender, biomarker screening tests for preclinical disease including amyloidosis or neurodegeneration, and presence or absence of mild cognitive impairment.
2. Interpretation: We find that lifetime risks for AD dementia vary considerably by age, gender, and preclinical disease state. Most persons with preclinical AD will not develop AD dementia during their lifetimes.
3. Future directions: Persons with preclinical AD may never experience any clinical symptoms during their lifetimes because of its long and variable preclinical period and the high mortality rates in elderly populations. Lifetime risks assist in the interpretation of the clinical significance of biomarker screening tests for preclinical AD.

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