The development of a stochastic mathematical model of Alzheimer's disease to help improve the design of clinical trials of potential treatments

Christoforos Hadjichrysanthou[1]*, Alison K. Ower[1], Frank de Wolf[1,2], Roy M. Anderson[1], for the Alzheimer's Disease Neuroimaging Initiative[¶]

1 Department of Infectious Disease Epidemiology, School of Public Health, Imperial College London, London, United Kingdom, **2** Janssen Prevention Center, Leiden, The Netherlands

¶ Membership of the Alzheimer's Disease Neuroimaging Initiative is provided in the Acknowledgments.
* c.hadjichrysanthou@imperial.ac.uk

Abstract

Alzheimer's disease (AD) is a neurodegenerative disorder characterised by a slow progressive deterioration of cognitive capacity. Drugs are urgently needed for the treatment of AD and unfortunately almost all clinical trials of AD drug candidates have failed or been discontinued to date. Mathematical, computational and statistical tools can be employed in the construction of clinical trial simulators to assist in the improvement of trial design and enhance the chances of success of potential new therapies. Based on the analysis of a set of clinical data provided by the Alzheimer's Disease Neuroimaging Initiative (ADNI) we developed a simple stochastic mathematical model to simulate the development and progression of Alzheimer's in a longitudinal cohort study. We show how this modelling framework could be used to assess the effect and the chances of success of hypothetical treatments that are administered at different stages and delay disease development. We demonstrate that the detection of the true efficacy of an AD treatment can be very challenging, even if the treatment is highly effective. An important reason behind the inability to detect signals of efficacy in a clinical trial in this therapy area could be the high between- and within-individual variability in the measurement of diagnostic markers and endpoints, which consequently results in the misdiagnosis of an individual's disease state.

Introduction

Alzheimer's disease (AD) is a neurodegenerative disorder which is characterised by progressive accumulation of amyloid-beta (Aβ) peptides, forming senile plaques in the brain, and neurofibrillary tangles of hyperphosphorylated tau, followed by progressive neuronal and synaptic loss. It has long preclinical and prodromal stages and affects memory, thinking, behaviour, daily functional abilities, and emotion. Alzheimer's disease may account for approximately 60–80% of dementia cases [1]. The worldwide prevalence of dementia was estimated to be over 46 million people, with studies suggesting that the number of cases is rising exponentially

with age and that the above estimate will almost triple by 2050 [2–4]. Apart from the health and social problems, Alzheimer's, and dementias in general, have huge economic impact, with the estimated worldwide cost of dementia approaching USD 818 billion [4–6]. Thus, drugs are urgently needed to improve therapies of AD and dementia.

There are two competing models proposed to explain the hallmarks of AD: the amyloid hypothesis (the neuron-centric model) [7, 8] and the Inverse Warburg hypothesis (the neuron-astrocytic model) [9, 10]. The neuron-centric model suggests that a mutation in the nuclear genome induce overproduction of Aβ and tau that become toxic to neurons. The neuron-astrocytic model contends that the progression of AD is triggered by defects in the normal energy transduction process, a condition induced by mitochondrial dysregulation. Although some clinical trials of metabolic interventions have shown promising results for the improvement of cognitive performance [11, 12], clinical trials of disease-modifying treatments have consistently failed. A recent study reviewed 413 clinical trials (124 Phase 1 trials, 206 Phase 2 trials, and 83 Phase 3 trials) of AD drug candidates that have been conducted between 2002 and 2012 [13]. The study reported that 99.6% of the trials failed or had been discontinued. No cure or other treatments that prevent, halt or reverse the underlying pathology of established AD have been approved as yet. Available treatments, such as the cholinesterase inhibitors tacrine (1993), donepezil (1996), rivastigmine (1998) and galantamine (2001), are approved for mild to moderate AD and can provide only temporary improvement in cognitive and behavioural symptoms, and at best a temporary impact on the progression of the underlying pathology of the disease [14].

The failure rate of AD clinical trials is far higher than that of trials in other therapy areas, and information on the reasons of trial failure or discontinuation is limited [13, 15]. Some of the reasons of high trial failure include the poorly understood nature of AD pathogenesis and progression and poor trial design. For example, the wrong choice of clinical endpoints and markers used as clinical trial entry criteria, as well as the selection of unsuitable individuals for enrolment in the trial. The retention of participants due to the long duration of the AD trials is also an important problem to overcome in the design of successful clinical trials in the AD area [15]. The high failure rate of clinical trials can also be attributed to the inability to detect signals of efficacy, even if the treatment is safe and effective. This could be due to the administration of the drug at a relatively late stage of the disease, at which time the condition of the patient may be irreversible, or due to the high variability in the measurements of different biochemical and cognitive markers that are used as diagnostic markers and endpoints.

Mathematical modelling of AD progression and the development of clinical trial simulations are essential tools for exploring the reasons why a clinical trial can fail and for the improvement of the design of clinical trials. The poorly understood nature of AD pathogenesis and progression limits the possibilities of developing robust mechanistic models for the accurate prediction of disease progression. However, a few attempts have been made to develop models that describe the development of AD at the molecular level (e.g. [16–20]). Published mathematical models also include semi-mechanistic models developed to describe longitudinal changes in measures of cognition, as assessed by errors in various cognitive tests designed for the assessments of the cognitive capabilities of the patients, such as the Modified Mini-Mental State Examination (MMSE) and the Alzheimer's Disease Assessment Scale (ADAS-cog) [21–25]. In general, published research on the mathematical modelling of AD has mainly focused on: (1) the study of the epidemiology of AD (e.g. [26, 27]); (2) the investigation of the progression of the disease based on changes in the cognitive status (e.g. [21–25]); (3) on defining the order of the various biomarkers of the disease in predicting progression (e.g. [28–40]), and (4) on the description of the pathogenesis and evolution of the disease at the molecular level (e.g. [16–20]). Most of the models developed so far are stochastic in nature [41]. Such

models permit variability in the model parameters and chance elements in AD disease progression.

In this study we develop and analyse a simple stochastic model to predict AD progression in a clinical trial. In particular, we define a discrete-time Markov model to describe the movement of individuals through a finite sequence of distinct health and disease states over time (distinct time points at which the state of the individuals is assessed). Markov models are ideal for the modelling of AD, as this disorder can be described as a multi-state disease process, and due to the observational nature of studies of AD in which the condition of individuals is assessed at periodic visits. These are also useful tools for the estimation of the impact of risk factors on the transitions between the states and can easily include reversible states that have been observed in many AD cohort studies. This modelling framework can contribute to the improved design of future clinical trials by providing insights into what to measure, the importance of measurement error in determining efficacy, sample size selection, duration of the trial and other important factors such as demographic characteristics of the sample. Markov models have also been purposed in previous studies for the estimation of the probabilities of transitioning between different stages of AD severity, and the investigation of potential covariates that can influence these probabilities [14, 41–51]. In this study, we use this framework to develop tools for the assessment and evaluation of the impact of receiving a hypothetical preventative treatment of varying efficacy, at different stages of disease progression, and illustrate the potential problems detecting significant differences between treated and untreated individuals. The specific action of the treatments in the model is irrelevant; the treatments are assumed to reduce the probability of transitioning to a more severe stage of the disease, which consequently slows the development and progression of the disease.

The transition probability distributions of the Markov model we describe are estimated using a particular longitudinal cohort dataset provided by the Alzheimer's Disease Neuroimaging Initiative (ADNI, adni.loni.usc.edu).

Material and methods

The model

The development and progression of AD in a clinical trial was assumed to be a stochastic process. In particular, we developed a discrete-time Markov chain in a random environment defined on a finite state space, with the property that for all states the probability of moving from the current state to the next state is independent of the past. Individuals were classified according to their disease status. In particular, based on a set of criteria individuals were categorised as Cognitively Normal (CN), with Mild Cognitive Impairment (MCI) and with AD. The criteria are based on the level or presence of a number of markers, including but not limited to memory complaints, logical memory II subscale, MMSE, CDR, and NINCDS/ADRDA criteria for probable AD [52]. The states are distinct and do not overlap.

In each (discrete) time step of the process, individuals can either withdraw from the study, for example due to death or personal reasons, remain at the same state or move to a different state with some probability (transition probability). Based on the information obtained from the ADNI dataset, transitions are allowed between the states CN and MCI in both directions (i.e. recovery to normal cognition is also allowed) and from the MCI to the AD state. Back-transitions may be due to either measurement error or a genuine ability in some patients to show cognitive improvement (e.g. due to cognitive reserve). In the ADNI dataset, a small number of transitions from AD back to MCI is also observed (a total of 17 transitions in yearly assessments across the ten-year cohort). Some reverse transitions from AD to MCI, as well as from MCI back to CN, have also been recorded in other longitudinal studies [50, 53–56].

However, due to the progressive nature of AD and the fact that AD diagnosis cannot be confirmed until an autopsy is performed, in the theoretical model that we developed we do not allow transitions from AD back to MCI state, i.e. once patients reach the AD state their condition cannot improve. Even in the presence of candidate treatments that could potentially reverse the pathology at a stage of AD (e.g. [57, 58]), there is no sufficient evidence that the cognitive functions and clinical outcome of AD individuals can be improved. Due to the stochastic nature of the model, allowing both an MCI to CN and an AD to MCI transition would even mean that there will always be a chance of patients becoming fully recovered from AD, i.e. returning to a cognitively normal state, an outcome that cannot be supported at present. However, it should be noted that incorporating an AD to MCI transition in the model would have a negligible effect on the output due to the small chance of this transition happening. A small number of patients in ADNI also transitioned from CN directly to AD (3 patients in yearly assessments across the ten-year cohort). These transitions have also been attributed to potential misclassifications of patients and not been incorporated into the model (see [59]). A schematic diagram of the model developed is presented in Fig 1.
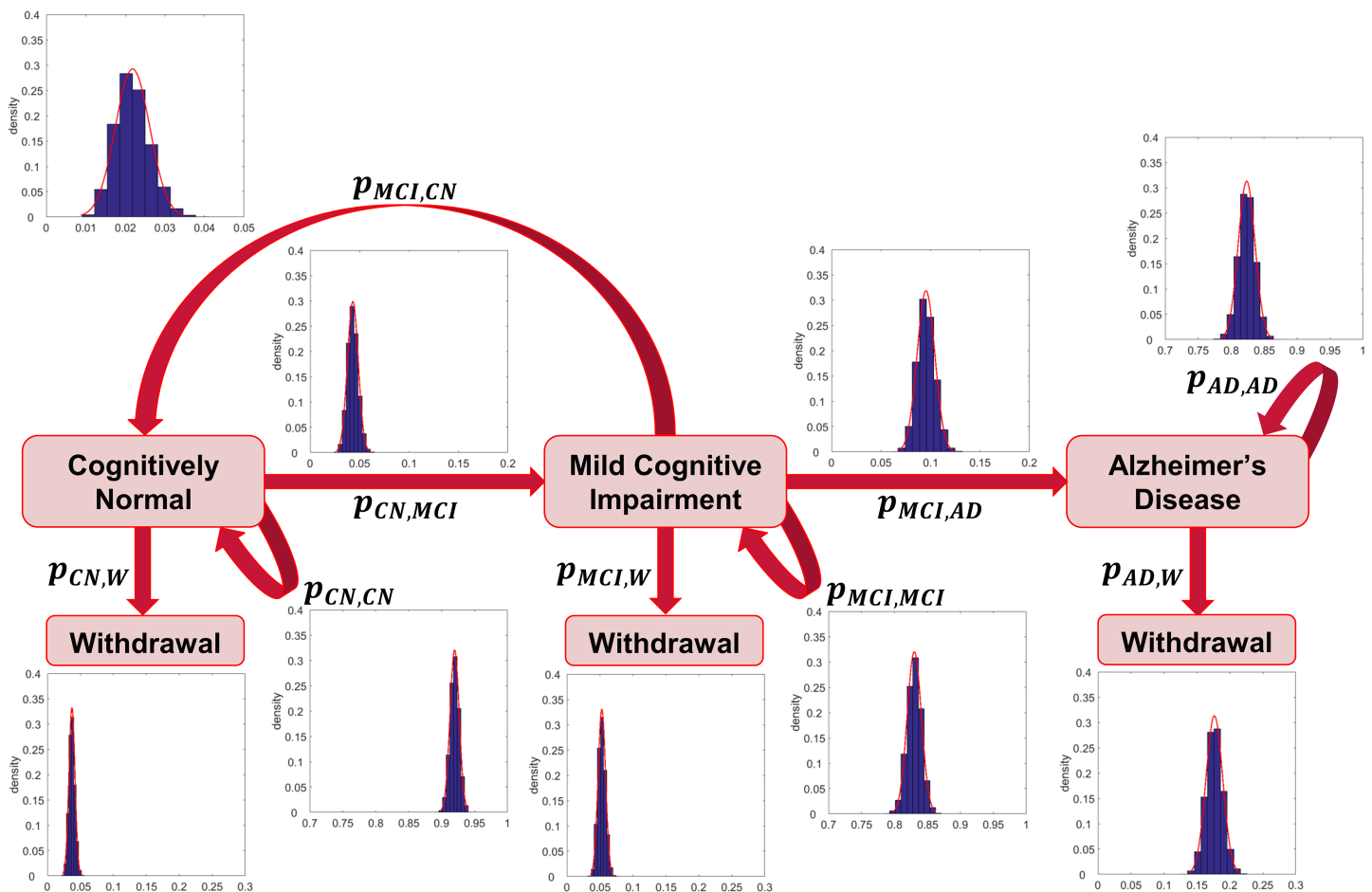
Fig 1. Flow diagram of possible transitions between the different states of the Markov model. Individuals can be in one of the following states: Cognitively Normal, Mild Cognitive Impairment, Alzheimer's Disease and Withdrawal. Arrows indicate possible transitions between the states. $p_{A,B}$ represents the probability of moving from state A to state B. The estimated distributions of the average one-year transition probabilities from the ADNI cohort dataset are presented.

Transition probabilities

For the estimation of the transition probabilities between the different states we followed a piecewise approach. We divided the observation period into one-year intervals and calculated the transition probabilities in each of these intervals (in ADNI, data exists for a total of 10 years). The probabilities of transitioning between states were estimated independently for each time interval, and it was assumed that the process is temporarily homogeneous within these intervals, i.e. the transition probabilities were assumed constant within each of the time intervals.

Let $p_{S_i,S_j}(t)$ be the transition probability to state S_j at time t given that at time $t-1$ the state is S_i, where $i, j \in \{1, 2, \ldots, K\}$ and $S_i, S_j \in S$. S is the state space of the Markov Chain and K is the number of states. The maximum likelihood estimate of the transition probability $p_{S_i,S_j}(t)$ is given by

$$p_{S_i,S_j}(t) = \frac{\tau_{S_i,S_j}(t)}{\sum_{l=1}^{K} \tau_{S_i,S_l}(t)}, \tag{1}$$

where $\tau_{S_i,S_j}(t)$' is the number of transitions from S_i (at time $t-1$) to S_j (at time t). $\sum_{j=1}^{K} p_{S_i,S_j} = 1$ for all i.

In order to assess the uncertainty of estimates of each transition probability we used the bootstrap method [60, 61]. With this method, a number of possible cohort datasets are generated to develop a range of possible transition matrices. Specifically, for each time interval new sets of transitions are generated by sampling with replacement from the original set of transitions (the number of transitions in the generated samples is the same as the total number of transitions in the observational study). Combining all the bootstrapped transition matrices we derive an approximation of the sampling distribution [61]. To smooth the distributions of the transition probabilities we fitted a Normal-distribution using the maximum likelihood estimation method.

The accurate estimation of transition probabilities is particularly challenging, mainly due to the heterogeneity of the data, the infrequent observations on the same patient, and missing data points [62]. It should be noted that although the total number of individuals in the study that we used is relatively large (1624 individuals, see subsection 'Dataset used'), this number decreases significantly over follow-up, either because individuals die or are lost to follow-up. It is also important to note that our analysis uses follow-up time as opposed to chronological time, such that those subjects recruited later (into the newer ADNI-GO or ADNI-2 cohorts, see subsection 'Dataset used') will have inherently less follow-up time than those enrolled initially into the study (ADNI-1). Thus, we naturally lose depth in the number of subjects at later follow-up times due to recruitment date.

Stochastic simulation

Within the modelling framework described, we numerically simulated the time progression of the disease in a sample of individuals in a clinical trial. As an example, in this preliminary study the development and progression of the disease was simulated in a general population of 1000 individuals for duration of up to 10 years. The trial duration was discretised into uniform steps. The time-step was defined to be one-month. At the beginning of each simulation, a value for each transition probability was assigned to each individual in the trial. The value was drawn at random from the respective distribution of the average one-year transition probability. In each time-step in the simulation (same for all individuals), each individual moved independently from one state to another state with the defined transition probability. The state of

each individual was updated synchronously. For each numerical simulation we performed 10^4 realisations. We focused on the proportion of AD cases over time. We are mainly interested in the effect of potential preventative treatments, before the occurrence of AD clinical symptoms. For this reason, we considered optimistic treatments focusing on the case where at the beginning of the process all individuals are cognitively normal. The other extreme where all individuals are initially at the MCI state was also considered. It should be noted that, given the assumption that AD is a progressive disorder, and thus AD is an irreversible state, including a number of AD individuals in the initial population would have the same effect as removing these individuals completely from the process.

The simulator was developed in MATLAB (R2017b). The computer code can be obtained from the authors upon request.

Impact of interventions

Interventions were applied at different time points of the process. In our analysis we focused on treatments that, irrespective of their specific action, reduce the probability of transitioning from state X to a more severe state Y by a proportion $E_{X,Y} \in (0,1)$. Despite the nature of the dataset we used, we focused on preventative treatments that are administered to a sample of cognitively normal individuals in order to reduce the probability of transitioning to MCI and later from MCI to AD. The same treatments were also assessed in a sample consisting of only MCI individuals. We also simulated clinical trials to evaluate the effect of treatments that are administered to a sample of only cognitively normal individuals, but the treatment becomes effective only at the MCI state and reduces the probability of developing AD. The effect of a treatment that reduces the probability of transitioning from CN to MCI has a negligible effect when administered to individuals that have already reached the MCI state. To investigate the impact of treatments that might not be effective beyond a point, as may happen, for example, due to severe neuronal degeneration, we also considered treatments that are administered before the MCI onset to reduce only the probability of developing MCI, i.e. they are no longer effective beyond the MCI state. Indeed, the model also allows the consideration of the effectiveness of treatments that might vary with time, but we did not consider this scenario in the current study. All the treatment effects were assumed to be homogeneous between individuals. We focused on the ideal scenario where treatments have an immediate effect, but we also considered cases where there are time delays, which may refer either to delays in the administration of treatments that are immediately effective or delays before treatments that are administered at the beginning of the trial start to be effective. Indeed, if a clinical trial involving ideal treatments which have an immediate effect and their effectiveness is not reduced over time is unsuccessful, we expect that clinical trials of less effective treatments (example, clinical trials of treatments which have delayed and/or time-decaying effects) will also be unsuccessful. We assessed the impact of interventions on the proportion of AD cases over time. The effect of a treatment at a specific time point is defined as the mean difference between the proportion of AD cases in the untreated and treated groups. Other potential endpoints that could be studied using the model include the incidence proportion of AD cases, the expected time spent in a disease state, and the expected time and probability to reach a specific state from any other state. Information for each of these endpoints is generated in the simulation.

For every simulation output we present the predicted value of the proportion of AD cases at the end of a 5- and a 10-year trial under different intervention scenarios. We calculated the 95% credible interval of the distribution of the proportion of AD cases and the standard deviation. Although outside the scope of the current study, it should be noted that the results of such simulation exercises could also be used as prior information required for sample size

calculations before the conduct of a clinical trial. For every case, we performed a hypothesis test for the equality of two binomial proportions, the proportions of AD cases in the treated and untreated groups, i.e. we tested whether the difference of the two proportions is equal to 0. A two-tailed test was performed and statistical significance was calculated using a 95% confidence level.

Dataset used

For the development of the Markov model and the estimation of the model parameters we used data obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu, last downloaded 2016/10/31). The ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early Alzheimer's disease (AD). For up-to-date information, see www.adni-info.org.

The dataset used is a longitudinal observational study consisting of 1737 individuals (from the ADNI-1, ADNI-GO, and ADNI-2 protocols), 106 of which were categorised as 'Significant Memory Concern' (SMC) at baseline and excluded from our analysis. In addition, there were 7 individuals that had only a screening visit and they were also excluded. Therefore, in the present study, we analysed data from 1624 participants. The characteristics of the individuals in the dataset considered are presented in Supporting Information, S1 Table. The maximum duration for which a participant in the study has been followed up is 10 years. It should be noted that in the original dataset, individuals in the MCI state are further classified as 'Early MCI' (EMCI) and 'Late MCI' (LMCI). However, in this analysis we combined the two MCI subtypes.

The status of individuals was assessed only at the distinct time points considered in the model. The number of transitions between the states of the Markov model at each time point is presented in Supporting Information, S2 Table.

Results

Fig 1 illustrates the distributions of the average one-year transition probabilities (for the parameters of the fitted Normal distributions see Table 1). Fig 2, Fig 3 and S1 Fig show the output of stochastic simulations (expected proportion of AD cases over time in a general population of 1000 individuals) in the untreated and treated groups under different intervention scenarios. In all the examples presented in these figures we assumed that individuals are initially at the CN state. S2 Fig shows the output of simulations for the case where treatments reduce the probability of transitioning from CN to MCI and from MCI to AD, and all

Table 1. Fitted normal distributions for the average one-year transition probabilities between the states of the Markov model. SD: standard deviation.

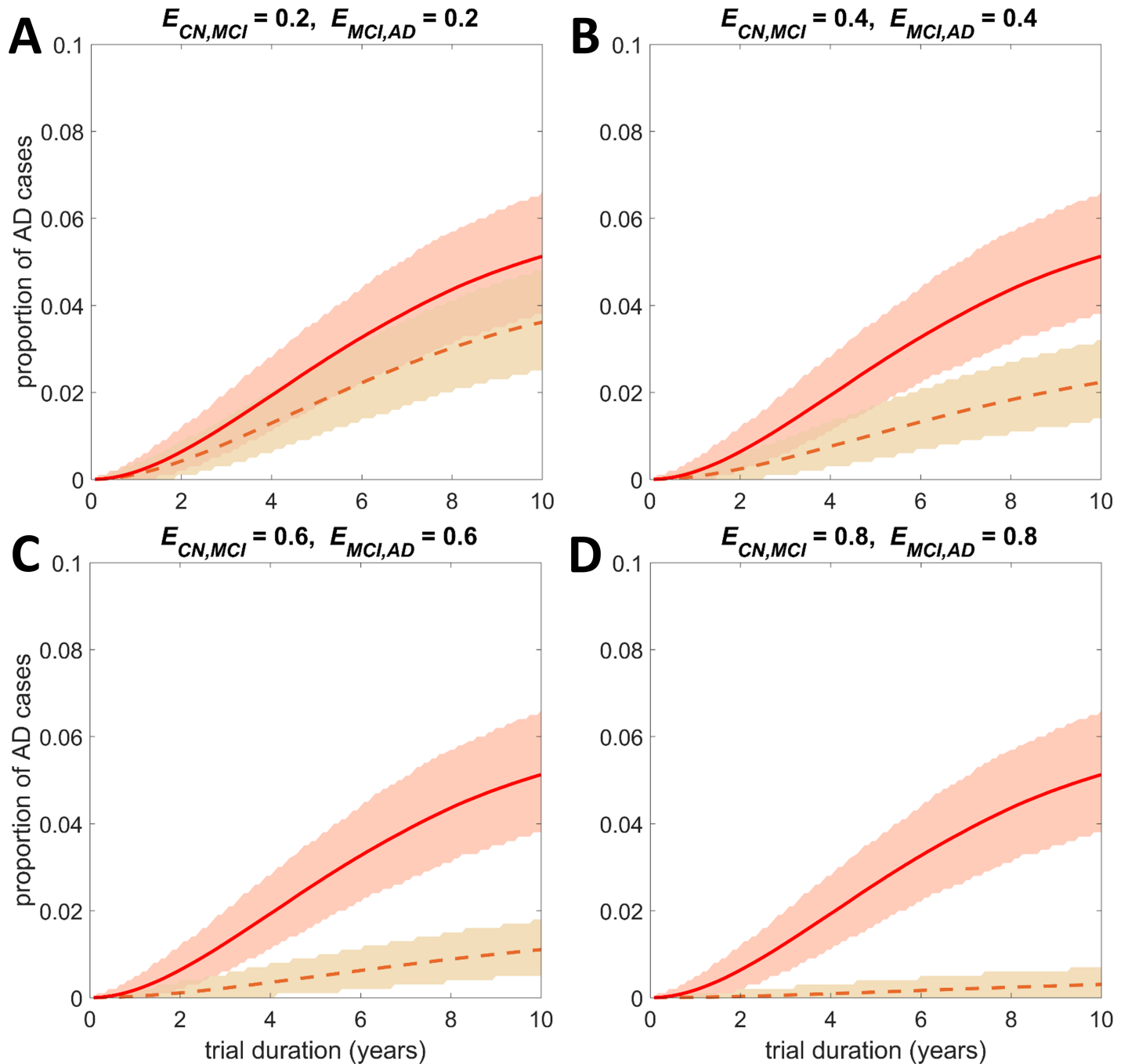| Average one-year transition probabilities	CN→MCI	MCI→CN	MCI→AD
	mean = 0.0432, SD = 0.0055	mean = 0.0218, SD = 0.0044	mean = 0.0954, SD = 0.0090
	CN→Withdrawal	MCI→Withdrawal	AD→Withdrawal
	mean = 0.0372, SD = 0.0046	mean = 0.0528, SD = 0.0057	mean = 0.1765, SD = 0.0127
	CN→CN	MCI→MCI	AD→AD
	mean = 0.9197, SD = 0.0070	mean = 0.8300, SD = 0.0108	mean = 0.8235, SD = 0.0127

Fig 2. Output of stochastic simulations: The expected proportion of AD cases over time and the effect of treatments that reduce the transition probabilities $p_{CN,MCI}$ **and** $p_{MCI,AD}$ **in a sample of CN individuals.** The expected proportion of AD cases over time in the untreated group is presented by the solid line. The expected proportions after the administration of potential treatments that reduce the transition probabilities $p_{CN,MCI}$ and $p_{MCI,AD}$ by a proportion $E_{CN,MCI}$ and $E_{MCI,AD}$, respectively, are presented by the dashed lines. (A) $E_{CN,MCI}$ = 0.2, $E_{MCI,AD}$ = 0.2, (B) $E_{CN,MCI}$ = 0.4, $E_{MCI,AD}$ = 0.4, (C) $E_{CN,MCI}$ = 0.6, $E_{MCI,AD}$ = 0.6, (D) $E_{CN,MCI}$ = 0.8, $E_{MCI,AD}$ = 0.8. The value of E can be interpreted as the efficacy of the candidate treatment, with $E = 0$ implying no efficacy and $E = 1$ a 100% efficacy which stops progression. The 'shaded area' represents the 95% credible interval of the distribution of the proportion of AD cases. At the beginning of the trial all individuals are at the CN state. The population size in each group is $N = 1000$.

https://doi.org/10.1371/journal.pone.0190615.g002

individuals are initially at the MCI state. In each of the above figures, the uncertainty in the output of the stochastic simulations in both the treated and untreated groups is also illustrated.
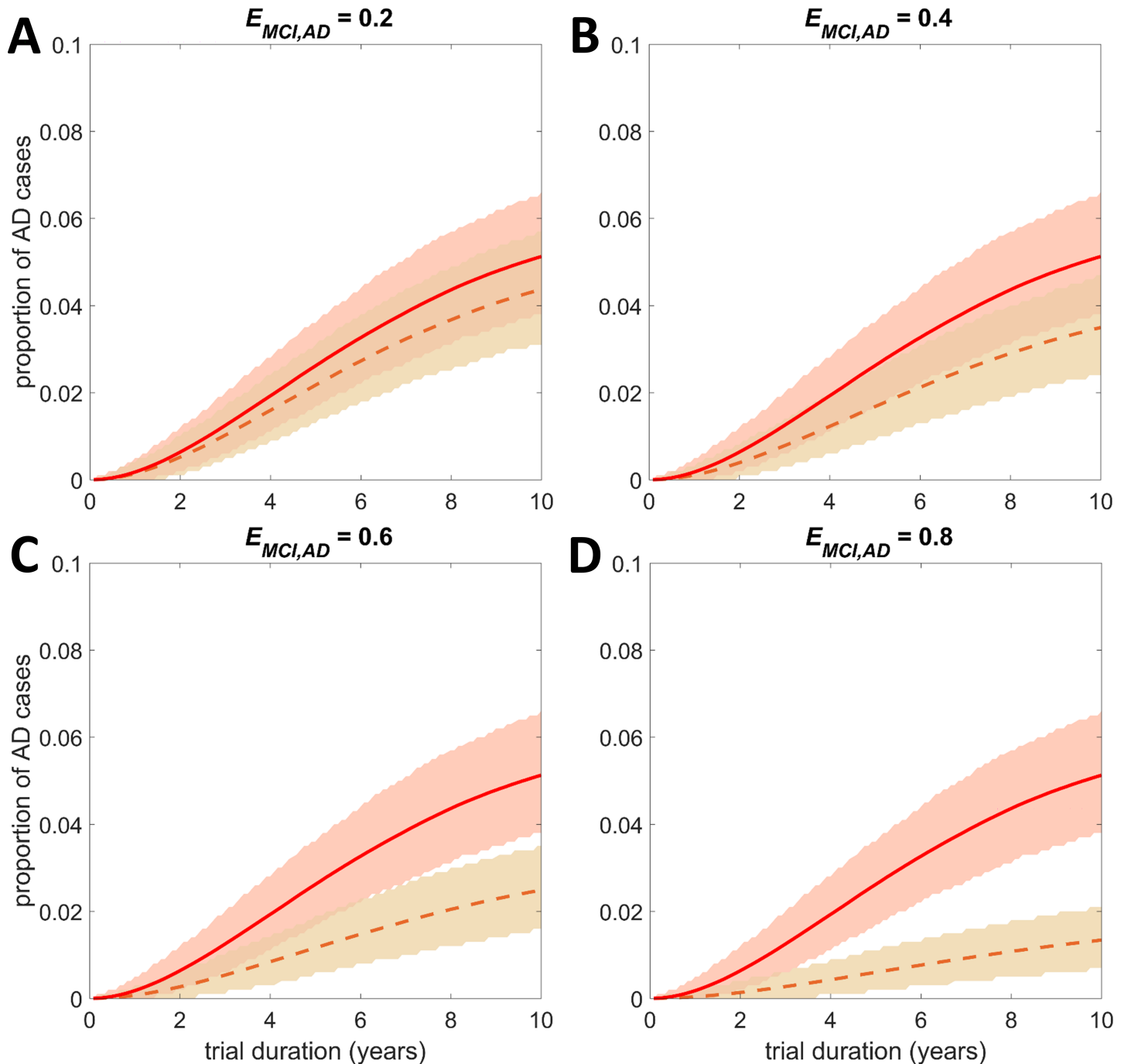
Fig 3. Output of stochastic simulations: The expected proportion of AD cases over time and the effect of treatments that reduce the transition probability $p_{MCI,AD}$ in a sample of CN individuals. The expected proportion of AD cases over time in the untreated group is presented by the solid line. The expected proportions after the administration of potential treatments that reduce the transition probability $p_{MCI,AD}$ by a proportion $E_{MCI,AD}$ are presented by the dashed lines. (A) $E_{MCI,AD}$ = 0.2, (B) $E_{MCI,AD}$ = 0.4, (C) $E_{MCI,AD}$ = 0.6, (D) $E_{MCI,AD}$ = 0.8. The value of E can be interpreted as the efficacy of the candidate treatment, with $E = 0$ implying no efficacy and $E = 1$ a 100% efficacy which stops progression. The 'shaded area' represents the 95% credible interval of the distribution of the proportion of AD cases. At the beginning of the trial all individuals are at the CN state. The population size in each group is $N = 1000$.

https://doi.org/10.1371/journal.pone.0190615.g003

The expected values of the proportion of AD cases at the end of a 5- and a 10-year simulated trial where all individuals are initially cognitively normal are provided in S3 Table. In S4 Table

we present the results obtained at the end of a 5-year simulated trial for the cases where all individuals are initially at the MCI state. For each case, the 95% credible interval and the standard deviation are also presented. In S5 and S6 Tables we present the *p*-values of the hypothesis tests for the equality of the proportions of AD cases in the untreated and treated groups under the different intervention scenarios that have been investigated.

It is observed that although treatments might be effective in reducing the chance of developing AD, due to the high uncertainty it might be difficult to assess their real effectiveness in a clinical trial. In particular, it is remarkable that in the sample of cognitively normal individuals alone, the simulation suggests that in a clinical trial of duration of five years, it is likely that the true efficacy of a treatment will not be detected even if the treatment has moderate efficacy (Fig 2, S3 and S5 Tables). As expected, if all the participants are initially at the CN state, a difference between the untreated and the treated group becomes even more challenging if the treatment is effective only when individuals are at the MCI state (Fig 3, S3 and S5 Tables). In particular, in a sample of cognitively normal individuals, treatments that reduce both the transition probability of moving from CN to MCI and the probability of moving from MCI to AD are the most effective, followed by treatments that reduce only the probability of transitioning from CN to MCI and then the treatments that reduce the probability of developing AD from the MCI state. Increasing the duration of the trial and the population size improves the chances of clinical success in all cases (see for example S3 and S5 Tables). The efficacy of a treatment that reduces the probability of transitioning to more severe states may be more likely to be detected in a trial where all individuals are initially at the MCI state (S2 Fig, S4 and S6 Tables). However, the proportion of AD cases at the end of such a trial is much higher. As mentioned earlier, in the analysis performed we showed that the effect of a treatment that reduces the probability of moving from CN to MCI state is negligible when it is administered to MCI individuals.

Fig 4 illustrates the impact of time delays, before the treatment starts to be effective, on the proportion of AD cases at the end of a 5-year simulated trial. The treatment is administered to reduce the probabilities of transitioning to more severe states ($p_{CN,MCI}$ only, $p_{MCI,AD}$ only,
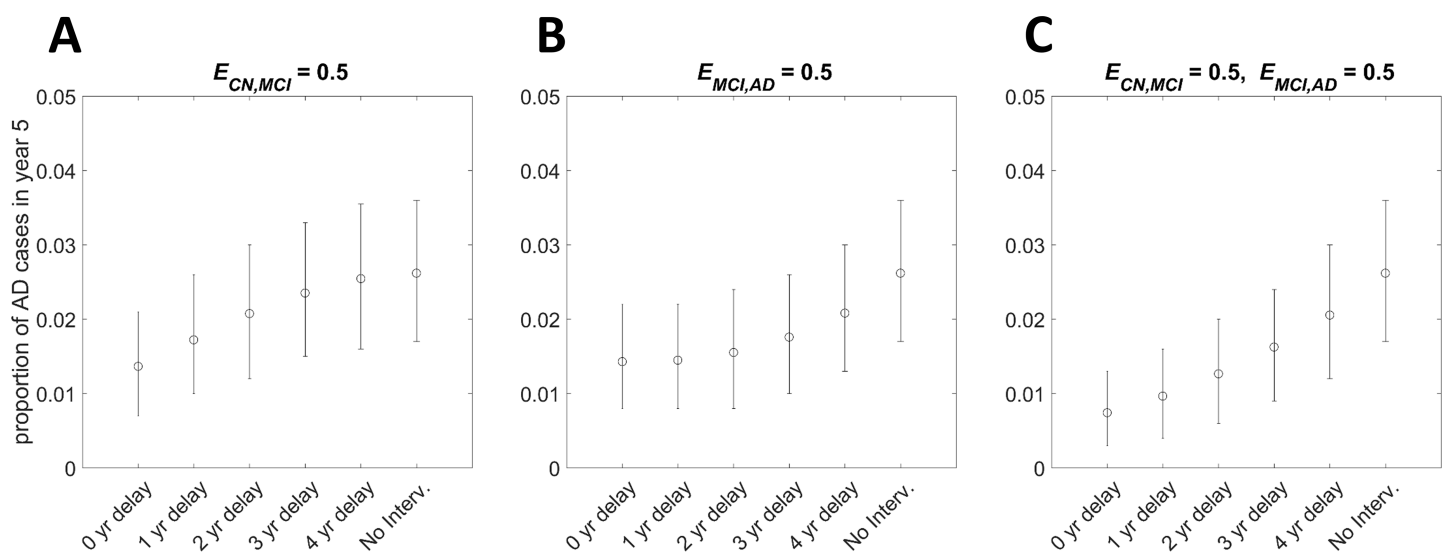

Fig 4. The expected proportion of AD cases at the end of a 5-year trial and the impact of time delays in the activation of various treatments in a sample of CN individuals. Treatments that reduce the transition probabilities (A) $p_{CN,MCI}$ only, (B) $p_{MCI,AD}$ only, (C) $p_{CN,MCI}$ and $p_{MCI,AD}$, by a proportion 0.5 are effective after some time delay. Circles represent the expected proportion of AD cases at the end of a 5-year trial and the error bars the 95% credible interval. At the beginning of the trial all individuals are at the CN state. The population size in each group is $N = 1000$.

https://doi.org/10.1371/journal.pone.0190615.g004

$p_{CN,MCI}$ and $p_{MCI,AD}$). The impact of such delays on the proportion of AD cases at the end of a 10-year trial in the same scenario is illustrated in S3 Fig. In both Fig 4 and S3 Fig all individuals are initially cognitively normal. S4 Fig shows the impact of time delays on the effect of a treatment that reduces the transition probabilities from CN to MCI and from MCI to AD when the initial population consists of only MCI individuals. Fig 4, as well as S3 and S4 Figs, can also be thought of as the case where there is a period of delay before the administration of treatments that are immediately effective. Such delays influence the population distribution at the time of treatment administration; the initial number of CN individuals decreases and the number of MCI and AD individuals increases. It is shown that treatments administered to CN individuals are likely to be more effective in slowing AD progression if they are administered at the beginning of the study ($t = 0$) to reduce the probabilities of moving to MCI and later to AD state (see Fig 4, S3 and S5 Tables). However, the impact of time delays is more pronounced in the cases where treatments given to CN individuals reduce their chance of transitioning to the MCI state (but see S4 Fig). This is partly due to the fact that delays in the 'activation' of the treatment result in a reduction in the number of CN individuals who can benefit from the treatment, as a consequence of disease development between the initiation of the study and treatment activation. Consequently, after some delay, treatments administered to CN individuals to reduce the probability of developing AD from the MCI state may be more effective than treatments administered to CN individuals to reduce only the probability of moving to the MCI state. Hence, in a clinical trial the specific time of intervention is crucial.

Discussion

Using the ADNI dataset, we developed a basic framework for the simulation of the development and progression of AD in a clinical trial to facilitate the assessment of the effect of potential candidate treatments. Treatments slow the transition to a more severe state, and thus disease progression. This reduction in the progression rate of the disease can be associated with a significant decrease in the incidence of AD, increase in the duration of individuals' independence and the time until institutionalisation, and concomitantly a significant decrease in the costs of care. It is interesting to note that if such interventions could delay both disease onset and disease progression by even one year, the global prevalence of AD could decrease by almost 9.2 million, by the year 2050 [3].

It has been demonstrated that the chance of identifying the true treatment effect may be challenging due to the high uncertainty in the clinical trial outcome, even if the treatment has high efficacy. This can be one of the dominant causes of trial failure of AD treatments. The high uncertainty, which can be illustrated by the output of the simulations, can be attributed partly to the sparsity and heterogeneity of the available data, and the high variance in the measurements of markers that have been used for the classification of individuals in the different disease states. The simple criteria used for the classification of individuals, such as the performance on cognitive tests, and potential associated measurement error, may influence the correct diagnosis and could be an important reason of the presence of the high variability. Other reasons that can introduce variability in the measurements, both within and between individuals, and influence the diagnosis of the actual clinical stage include underlying medical conditions such as the presence of depression or psychosis, inter-clinician differences in application of diagnostic criteria, and resistance to cognitive decline due to cognitive reserve [42, 47, 63–65]. As some of these factors can significantly contribute to variance in the model parameters representing disease progression, they should potentially be considered as covariates in extended models.

It should be noted that, due to the nature of the ADNI data used in this study, our outputs may not reflect the progression and impact of the disease in the general population, and indeed

the output in prevention clinical trials considered here. Participants in this dataset have been selected to mimic that of a population that would be recruited for a clinical trial of a potential AD-drug, such as from memory assessment clinics [66, 67]. For example, as observed in Supporting Information, S1 Table, in the dataset used in this study there is a high proportion of ApoE ε4 carriers, which is a significant genetic risk factor of AD. Thus, these individuals are at higher risk of developing the disease, creating significant selection bias issues. In addition, in the model we assumed long preclinical and prodromal AD stages and ADNI dataset is not sufficient to support this silent 'incubation period'. Due to the nature of the data, we also believe that the real effect of hypothetical preventative treatments, as assessed in the current study, is underestimated, as CN individuals in ADNI move faster to the MCI state than expected in the general population. However, all this should not limit the applicability of the model and the major outputs of this work which illustrate the usefulness of clinical trial simulations in AD therapy area, and how the high variability in measurements could mask the true efficacy of potential AD treatments.

Despite the nature of AD and problems with the available data, the Markov model is a powerful tool for predicting the development and progression of the disease and the assessment of the impact of potential treatments in clinical trials. Ideally, the model described in this paper should be extended so that there are more disease states, given there is enough information for the derivation of reliable estimates of the model parameters. The model should also be extended for the estimation of covariate effects of risk factors on transitions among states and concomitantly on disease progression. Such covariates could include age, genetic background (for example presence/absence of the apolipoprotein ε4 (APOE ε4) genotype), gender and education, all of which are important risk factors for AD. Other factors, such as family history, capability, lifestyle (e.g. alcohol consumption), social status, health and environment can also be influential [68]. Adding such heterogeneity will be described in a subsequent publication. It would also be interesting to incorporate into the model changes in cognitive markers and biomarkers, such as beta-amyloid and total-tau [69], as well as MRI markers, even though the precise estimates of the transition probabilities over time, conditional on the levels of these markers, might be difficult using the current data.

Clinical trials are difficult to conduct and very expensive if carried out in large samples of patients observed over many years. Modelling and simulating AD trials are relatively low cost activities and they can be a powerful tool for improving the design of the actual clinical trials and increase the chances of the accurate assessment of treatment efficacy [70]. Improving the quality of the data is clearly essential for the determination of the importance of variance in clinical trials. The reduction of the variance in currently employed measures (whether biomarkers, brain scans or cognitive scores) will improve trial design, facilitate detecting a signal in the trial, shorten the trial times and reduce the number of patients enrolled. Ideal datasets should include frequent sampling and repeated assessments for the same individual [71]. Utilising the growing number of available AD datasets from many different countries, and performing systematic and standardised analyses, it should be possible to provide substantial information for improving clinical trial design [72]. However, extra caution will be needed when working with the different datasets. Among the available studies there is a variation in the diagnostic tools, in the markers measured and measurement methods used. There is also a little agreement on the definition of the disease states and selection criteria as well as the size and demographic characteristics of the samples. Pooling and standardisation of clinical trial data, as well as standardisation of the methods employed in future studies, will facilitate better prediction of disease course and allow for better interpretation of model predictions. It will help in the identification of the sources of variance, and consequently it will facilitate progress towards the precise assessment of new prophylactic and therapeutic treatments of AD.

Supporting information

S1 Table. Characteristics at baseline of the ADNI dataset that has been used in the current study.
(DOCX)

S2 Table. Number of transitions between the states of the Markov model at each time step in ADNI dataset.
(DOCX)

S3 Table. Expected proportion of AD cases (AD) at the end of the trial under different intervention scenarios in the case where at the beginning of the trial all individuals are at the CN state. Credible intervals (CI) and standard deviations (SD) are presented. The treatment is effective from the beginning of the trial, unless otherwise stated. The population size in each group is $N = 1000$.
(DOCX)

S4 Table. Expected proportion of AD cases (AD) at the end of the trial under different intervention scenarios in the case where at the beginning of the trial all individuals are at the MCI state. Credible intervals (CI) and standard deviations (SD) are presented. The treatment is effective from the beginning of the trial, unless otherwise stated. The population size in each group is $N = 1000$.
(DOCX)

S5 Table. *p*-values of the hypothesis tests for the equality of the expected proportions of AD cases in the untreated and treated groups under the different intervention scenarios in the case where at the beginning of the trial all individuals are at the CN state. The treatment is effective from the beginning of the trial, unless otherwise stated. The population size in each group is $N = 1000$.
(DOCX)

S6 Table. *p*-values of the hypothesis tests for the equality of the expected proportions of AD cases in the untreated and treated groups under the different intervention scenarios in the case where at the beginning of the trial all individuals are at the MCI state. The treatment is effective from the beginning of the trial, unless otherwise stated. The population size in each group is $N = 1000$.
(DOCX)

S1 Fig. Output of stochastic simulations: the expected proportion of AD cases over time and the effect of treatments that reduce the transition probability $p_{CN,MCI}$ in a sample of CN individuals. The expected proportion of AD cases over time in the untreated group is presented by the solid line. The expected proportions after the administration of potential treatments that reduce the transition probability $p_{CN,MCI}$ by a proportion $E_{CN,MCI}$ are presented by the dashed lines. (A) $E_{CN,MCI} = 0.2$, (B) $E_{CN,MCI} = 0.4$, (C) $E_{CN,MCI} = 0.6$, (D) $E_{CN,MCI} = 0.8$. The value of E can be interpreted as the efficacy of the candidate treatment, with $E = 0$ implying no efficacy and $E = 1$ a 100% efficacy which stops progression. The 'shaded area' represents the 95% credible interval of the distribution of the proportion of AD cases. At the beginning of the trial all individuals are at the CN state. The population size in each group is $N = 1000$.
(DOCX)

S2 Fig. Output of stochastic simulations: The expected proportion of AD cases over time and the effect of treatments that reduce the transition probabilities $p_{CN,MCI}$ and $p_{MCI,AD}$ in a sample of MCI individuals. The expected proportion of AD cases over time in the untreated

group is presented by the solid line. The expected proportions after the administration of potential treatments that reduce the transition probabilities $p_{CN,MCI}$ and $p_{MCI,AD}$ by a proportion $E_{CN,MCI}$ and $E_{MCI,AD}$, respectively, are presented by the dashed lines. (A) $E_{CN,MCI} = 0.2$, $E_{MCI,AD} = 0.2$, (B) $E_{CN,MCI} = 0.4$, $E_{MCI,AD} = 0.4$, (C) $E_{CN,MCI} = 0.6$, $E_{MCI,AD} = 0.6$, (D) $E_{CN,MCI} = 0.8$, $E_{MCI,AD} = 0.8$. The value of E can be interpreted as the efficacy of the candidate treatment, with $E = 0$ implying no efficacy and $E = 1$ a 100% efficacy which stops progression. The 'shaded area' represents the 95% credible interval of the distribution of the proportion of AD cases. At the beginning of the trial all individuals are at the MCI state. The population size in each group is $N = 1000$.
(DOCX)

S3 Fig. The expected proportion of AD cases at the end of a 10-year trial and the impact of time delays in the activation of various treatments in a sample of CN individuals. Treatments that reduce the transition probabilities (A) $p_{CN,MCI}$ only, (B) $p_{MCI,AD}$ only, (C) $p_{CN,MCI}$ and $p_{MCI,AD}$, by a proportion 0.5 are effective after some time delay. Circles represent the expected proportion of AD cases at the end of a 10-year trial and the error bars the 95% credible interval. At the beginning of the trial all individuals are at the CN state. The population size in each group is $N = 1000$.
(DOCX)

S4 Fig. The expected proportion of AD cases at the end of a 5-year trial and the impact of time delays in the activation of a treatment in a sample of MCI individuals. The treatment that reduces the transition probabilities $p_{CN,MCI}$ and $p_{MCI,AD}$ by a proportion 0.5 is effective after some time delay. Circles represent the expected proportion of AD cases at the end of a 5-year trial and the error bars the 95% credible interval. At the beginning of the trial all individuals are at the MCI state. The population size in each group is $N = 1000$.
(DOCX)

Author Contributions

Conceptualization: Christoforos Hadjichrysanthou.

Data curation: Christoforos Hadjichrysanthou, Alison K. Ower.

Formal analysis: Christoforos Hadjichrysanthou, Alison K. Ower.

Funding acquisition: Frank de Wolf, Roy M. Anderson.

Investigation: Christoforos Hadjichrysanthou.

Methodology: Christoforos Hadjichrysanthou.

Validation: Christoforos Hadjichrysanthou.

Visualization: Christoforos Hadjichrysanthou.

Writing – original draft: Christoforos Hadjichrysanthou.

Writing – review & editing: Christoforos Hadjichrysanthou, Alison K. Ower, Frank de Wolf, Roy M. Anderson.

References

1. Knopman DS. The initial recognition and diagnosis of dementia. The American journal of medicine. 1998; 104(4a):2S–12S; discussion 39S-42S. Epub 1998/06/09. PMID: 9617846.

2. Brookmeyer R, Evans DA, Hebert L, Langa KM, Heeringa SG, Plassman BL, et al. National estimates of the prevalence of Alzheimer's disease in the United States*. Alzheimer's & dementia: the journal of the Alzheimer's Association. 2011; 7(1):61–73. https://doi.org/10.1016/j.jalz.2010.11.007 PMID: 21255744

3. Brookmeyer R, Johnson E, Ziegler-Graham K, Arrighi HM. Forecasting the global burden of Alzheimer's disease. Alzheimers Dement. 2007; 3(3):186–91. Epub 2007/07/01. https://doi.org/10.1016/j.jalz.2007.04.381 PMID: 19595937.

4. Prince M, Comas-Herrera A, Knapp M, Guerchet M, Karagiannidou M. World Alzheimer Report 2016—Improving healthcare for people living with dementia: Coverage, quality and costs now and in the future: Alzheimer's Disease International; 2016.

5. Wimo A, Jonsson L, Winblad B. An estimate of the worldwide prevalence and direct costs of dementia in 2003. Dementia and geriatric cognitive disorders. 2006; 21(3):175–81. Epub 2006/01/13. https://doi.org/10.1159/000090733 PMID: 16401889.

6. Bloom BS, de Pouvourville N, Straus WL. Cost of Illness of Alzheimer's Disease: How Useful Are Current Estimates? The Gerontologist. 2003; 43(2):158–64. https://doi.org/10.1093/geront/43.2.158 PMID: 12677073

7. Hardy J, Selkoe DJ. The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. Science (New York, NY). 2002; 297(5580):353–6. Epub 2002/07/20. https://doi.org/10.1126/science.1072994 PMID: 12130773.

8. Hardy J. Alzheimer's disease: the amyloid cascade hypothesis: an update and reappraisal. Journal of Alzheimer's disease: JAD. 2006; 9(3 Suppl):151–3. Epub 2006/08/18. PMID: 16914853.

9. Demetrius LA, Magistretti PJ, Pellerin L. Alzheimer's disease: the amyloid hypothesis and the Inverse Warburg effect. Frontiers in Physiology. 2015; 5(522). https://doi.org/10.3389/fphys.2014.00522 PMID: 25642192

10. De Strooper B, Karran E. The Cellular Phase of Alzheimer's Disease. Cell. 2016; 164(4):603–15. Epub 2016/02/13. https://doi.org/10.1016/j.cell.2015.12.056 PMID: 26871627.

11. Winblad B, Amouyel P, Andrieu S, Ballard C, Brayne C, Brodaty H, et al. Defeating Alzheimer's disease and other dementias: a priority for European science and society. The Lancet Neurology. 2016; 15 (5):455–532. Epub 2016/03/19. https://doi.org/10.1016/S1474-4422(16)00062-4 PMID: 26987701.

12. Kivipelto M, Hakansson K. A Rare Success against Alzheimer's. Scientific American. 2017; 316(4):32–7. Epub 2017/03/16. https://doi.org/10.1038/scientificamerican0417-32 PMID: 28296841.

13. Cummings JL, Morstorf T, Zhong K. Alzheimer's disease drug-development pipeline: few candidates, frequent failures. Alzheimer's Research & Therapy. 2014; 6(4):1–7. https://doi.org/10.1186/alzrt269 PMID: 25024750

14. Budd D, Burns LC, Guo Z, L'Italien G, Lapuerta P. Impact of early intervention and disease modification in patients with predementia Alzheimer's disease: a Markov model simulation. ClinicoEconomics and outcomes research: CEOR. 2011; 3:189–95. Epub 2011/11/03. https://doi.org/10.2147/ceor.s22265 PMID: 22046104; PubMed Central PMCID: PMCPMC3202482.

15. Gauthier S, Albert M, Fox N, Goedert M, Kivipelto M, Mestre-Ferrandiz J, et al. Why has therapy development for dementia failed in the last two decades? Alzheimer's & Dementia. 2016; 12(1):60–4. http://dx.doi.org/10.1016/j.jalz.2015.12.003.

16. Helal M, Hingant E, Pujo-Menjouet L, Webb G. Alzheimer's disease: analysis of a mathematical model incorporating the role of prions. J Math Biol. 2014; 69(5):1207–35. https://doi.org/10.1007/s00285-013-0732-0 PMID: 24146290

17. Craft D, Wein L, Selkoe D. A mathematical model of the impact of novel treatments on the Aβ burden in the Alzheimer's brain, CSF and plasma. Bull Math Biol. 2002; 64(5):1011–31. https://doi.org/10.1006/bulm.2002.0304 PMID: 12391865

18. Bertsch M, Franchi B, Marcello N, Tesi MC, Tosin A. Alzheimer's disease: A mathematical model for onset and progression. arXiv:150304669v1. 2015.

19. Puri IK, Li L. Mathematical Modeling for the Pathogenesis of Alzheimer's Disease. PLoS ONE. 2010; 5 (12):e15176. https://doi.org/10.1371/journal.pone.0015176 PMID: 21179474

20. Proctor CJ, Boche D, Gray DA, Nicoll JAR. Investigating Interventions in Alzheimer's Disease with Computer Simulation Models. PLoS ONE. 2013; 8(9):e73631. https://doi.org/10.1371/journal.pone.0073631 PMID: 24098635

21. Ashford JW, Schmitt FA. Modeling the time-course of Alzheimer dementia. Current psychiatry reports. 2001; 3(1):20–8. Epub 2001/03/20. PMID: 11177755.

22. Mitnitski AB, Fallah N, Dean CB, Rockwood K. A multi-state model for the analysis of changes in cognitive scores over a fixed time interval. Statistical methods in medical research. 2011; 23(3):244–56. Epub 2011/09/23. https://doi.org/10.1177/0962280211406470 PMID: 21937474.

23. Ito K, Corrigan B, Zhao Q, French J, Miller R, Soares H, et al. Disease progression model for cognitive deterioration from Alzheimer's Disease Neuroimaging Initiative database. Alzheimers Dement. 2011; 7 (2):151–60. Epub 2010/09/03. https://doi.org/10.1016/j.jalz.2010.03.018 PMID: 20810324.

24. Samtani MN, Farnum M, Lobanov V, Yang E, Raghavan N, Dibernardo A, et al. An improved model for disease progression in patients from the Alzheimer's disease neuroimaging initiative. Journal of clinical pharmacology. 2012; 52(5):629–44. Epub 2011/06/11. https://doi.org/10.1177/0091270011405497 PMID: 21659625.

25. Rogers JA, Polhamus D, Gillespie WR, Ito K, Romero K, Qiu R, et al. Combining patient-level and summary-level data for Alzheimer's disease modeling and simulation: a beta regression meta-analysis. Journal of pharmacokinetics and pharmacodynamics. 2012; 39(5):479–98. Epub 2012/07/24. https://doi.org/10.1007/s10928-012-9263-3 PMID: 22821139.

26. Mar J, Soto-Gordoa M, Arrospide A, Moreno-Izco F, Martinez-Lage P. Fitting the epidemiology and neuropathology of the early stages of Alzheimer's disease to prevent dementia. Alzheimers Res Ther. 2015; 7(1):2. Epub 2015/02/26. https://doi.org/10.1186/s13195-014-0079-9 PMID: 25713598; PubMed Central PMCID: PMCPmc4338563.

27. Macdonald A, Pritchard D. A Mathematical Model of Alzheimer's Disease and the Apoe Gene. ASTIN Bulletin. 2000; 30(01):69–110. https://doi.org/10.2143/AST.30.1.504627

28. Aisen PS, Petersen RC, Donohue MC, Gamst A, Raman R, Thomas RG, et al. Clinical Core of the Alzheimer's Disease Neuroimaging Initiative: progress and plans. Alzheimers Dement. 2010; 6(3):239–46. Epub 2010/05/11. https://doi.org/10.1016/j.jalz.2010.03.006 PMID: 20451872; PubMed Central PMCID: PMCPmc2867843.

29. Frisoni GB, Fox NC, Jack CR, Scheltens P, Thompson PM. The clinical use of structural MRI in Alzheimer disease. Nature reviews Neurology. 2010; 6(2):67–77. https://doi.org/10.1038/nrneurol.2009.215 PMID: 20139996

30. Jack CR, Knopman DS, Jagust WJ, Shaw LM, Aisen PS, Weiner MW, et al. Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. Lancet neurology. 2010; 9(1):119. https://doi.org/10.1016/S1474-4422(09)70299-6 PMID: 20083042

31. Jack CR Jr., Holtzman DM. Biomarker modeling of Alzheimer's disease. Neuron. 2013; 80(6):1347–58. Epub 2013/12/24. https://doi.org/10.1016/j.neuron.2013.12.003 PMID: 24360540; PubMed Central PMCID: PMCPmc3928967.

32. Lo RY, Hubbard AE, Shaw LM, Trojanowski JQ, Petersen RC, Aisen PS, et al. Longitudinal change of biomarkers in cognitive decline. Archives of neurology. 2011; 68(10):1257–66. Epub 2011/06/15. https://doi.org/10.1001/archneurol.2011.123 PMID: 21670386.

33. Forster S, Grimmer T, Miederer I, Henriksen G, Yousefi BH, Graner P, et al. Regional expansion of hypo-metabolism in Alzheimer's disease follows amyloid deposition with temporal delay. Biological psychiatry. 2012; 71(9):792–7. Epub 2011/06/18. https://doi.org/10.1016/j.biopsych.2011.04.023 PMID: 21679929.

34. Landau SM, Mintun MA, Joshi AD, Koeppe RA, Petersen RC, Aisen PS, et al. Amyloid deposition, hypo-metabolism, and longitudinal cognitive decline. Annals of neurology. 2012; 72(4):578–86. Epub 2012/10/31. https://doi.org/10.1002/ana.23650 PMID: 23109153; PubMed Central PMCID: PMCPMC3786871.

35. Bateman RJ, Xiong C, Benzinger TLS, Fagan AM, Goate A, Fox NC, et al. Clinical and Biomarker Changes in Dominantly Inherited Alzheimer's Disease. New England Journal of Medicine. 2012; 367 (9):795–804. https://doi.org/10.1056/NEJMoa1202753 PMID: 22784036.

36. Buchhave P, Minthon L, Zetterberg H, Wallin AK, Blennow K, Hansson O. Cerebrospinal fluid levels of beta-amyloid 1–42, but not of tau, are fully changed already 5 to 10 years before the onset of Alzheimer dementia. Archives of general psychiatry. 2012; 69(1):98–106. Epub 2012/01/04. https://doi.org/10.1001/archgenpsychiatry.2011.155 PMID: 22213792.

37. Villemagne VL, Burnham S, Bourgeat P, Brown B, Ellis KA, Salvado O, et al. Amyloid beta deposition, neurodegeneration, and cognitive decline in sporadic Alzheimer's disease: a prospective cohort study. The Lancet Neurology. 2013; 12(4):357–67. Epub 2013/03/13. https://doi.org/10.1016/S1474-4422(13)70044-9 PMID: 23477989.

38. Young AL, Oxtoby NP, Daga P, Cash DM, Fox NC, Ourselin S, et al. A data-driven model of biomarker changes in sporadic Alzheimer's disease. Brain: a journal of neurology. 2014; 137(Pt 9):2564–77. Epub 2014/07/12. https://doi.org/10.1093/brain/awu176 PMID: 25012224; PubMed Central PMCID: PMCPmc4132648.

39. Young AL, Oxtoby NP, Ourselin S, Schott JM, Alexander DC. A simulation system for biomarker evolution in neurodegenerative disease. Medical image analysis. 2015; 26(1):47–56. Epub 2015/09/12. https://doi.org/10.1016/j.media.2015.07.004 PMID: 26356148.

40. Fonteijn HM, Modat M, Clarkson MJ, Barnes J, Lehmann M, Hobbs NZ, et al. An event-based model for disease progression and its application in familial Alzheimer's disease and Huntington's disease. NeuroImage. 2012; 60(3):1880–9. Epub 2012/01/28. https://doi.org/10.1016/j.neuroimage.2012.01.062 PMID: 22281676.

41. Green C, Shearer J, Ritchie CW, Zajicek JP. Model-based economic evaluation in Alzheimer's disease: a review of the methods available to model Alzheimer's disease progression. Value in health: the journal of the International Society for Pharmacoeconomics and Outcomes Research. 2011; 14(5):621–30. Epub 2011/08/16. https://doi.org/10.1016/j.jval.2010.12.008 PMID: 21839398.

42. Neumann PJ, Araki SS, Arcelus A, Longo A, Papadopoulos G, Kosik KS, et al. Measuring Alzheimer's disease progression with transition probabilities: estimates from CERAD. Neurology. 2001; 57(6):957–64. Epub 2001/09/26. PMID: 11571317.

43. Fuh JL, Pwu RF, Wang SJ, Chen YH. Measuring Alzheimer's disease progression with transition probabilities in the Taiwanese population. International journal of geriatric psychiatry. 2004; 19(3):266–70. Epub 2004/03/18. https://doi.org/10.1002/gps.1076 PMID: 15027042.

44. Kryscio RJ, Schmitt FA, Salazar JC, Mendiondo MS, Markesbery WR. Risk factors for transitions from normal to mild cognitive impairment and dementia. Neurology. 2006; 66(6):828–32. Epub 2006/03/29. https://doi.org/10.1212/01.wnl.0000203264.71880.45 PMID: 16567698.

45. Tyas SL, Salazar JC, Snowdon DA, Desrosiers MF, Riley KP, Mendiondo MS, et al. Transitions to mild cognitive impairments, dementia, and death: findings from the Nun Study. American journal of epidemiology. 2007; 165(11):1231–8. Epub 2007/04/14. https://doi.org/10.1093/aje/kwm085 PMID: 17431012; PubMed Central PMCID: PMCPMC2516202.

46. Spackman DE, Kadiyala S, Neumann PJ, Veenstra DL, Sullivan SD. Measuring Alzheimer disease progression with transition probabilities: estimates from NACC-UDS. Current Alzheimer research. 2012; 9 (9):1050–8. Epub 2011/12/20. PMID: 22175655; PubMed Central PMCID: PMCPMC3690579.

47. Abner EL, Kryscio RJ, Cooper GE, Fardo DW, Jicha GA, Mendiondo MS, et al. Mild Cognitive Impairment: Statistical Models of Transition Using Longitudinal Clinical Data. International Journal of Alzheimer's Disease. 2012; 2012:9. https://doi.org/10.1155/2012/291920 PMID: 22536535

48. Stewart A, Phillips R, Dempsey G. Pharmacotherapy for people with Alzheimer's disease: a Markov-cycle evaluation of five years' therapy using donepezil. International journal of geriatric psychiatry. 1998; 13(7):445–53. Epub 1998/08/08. PMID: 9695032.

49. Jones RW, McCrone P, Guilhaume C. Cost effectiveness of memantine in Alzheimer's disease: an analysis based on a probabilistic Markov model from a UK perspective. Drugs & aging. 2004; 21 (9):607–20. Epub 2004/07/21. PMID: 15260515.

50. Hubbard RA, Zhou XH. A comparison of non-homogeneous Markov regression models with application to Alzheimer's disease progression. Journal of applied statistics. 2011; 38(10):2313–26. Epub 2011/01/ 01. https://doi.org/10.1080/02664763.2010.547567 PMID: 22419833; PubMed Central PMCID: PMCPMC3299197.

51. Yesavage JA, O'Hara R, Kraemer H, Noda A, Taylor JL, Ferris S, et al. Modeling the prevalence and incidence of Alzheimer's disease and mild cognitive impairment. Journal of Psychiatric Research. 2002; 36(5):281–6. http://dx.doi.org/10.1016/S0022-3956(02)00020-1. PMID: 12127595

52. Alzheimer's Disease Neuroimaging Initiative. [http://adni.loni.usc.edu/wp-content/uploads/2008/07/ adni2-procedures-manual.pdf].

53. Ritchie K, Artero S, Touchon J. Classification criteria for mild cognitive impairment: a population-based validation study. Neurology. 2001; 56(1):37–42. Epub 2001/01/10. PMID: 11148233.

54. Gauthier S, Touchon J. Mild cognitive impairment is not a clinical entity and should not be treated. Archives of neurology. 2005; 62(7):1164–6; discussion 7. Epub 2005/07/13. https://doi.org/10.1001/ archneur.62.7.1164 PMID: 16009780.

55. Ganguli M, Dodge HH, Shen C, DeKosky ST. Mild cognitive impairment, amnestic type: an epidemio-logic study. Neurology. 2004; 63(1):115–21. Epub 2004/07/14. PMID: 15249620.

56. Jicha GA, Abner E, Schmitt FA, Cooper GE, Stiles N, Hamon R, et al. Clinical Features of Mild Cognitive Impairment Differ in the Research and Tertiary Clinic Settings. Dementia and geriatric cognitive disor-ders. 2008; 26(2):187–92. https://doi.org/10.1159/000151635 PMID: 18724049

57. Sevigny J, Chiao P, Bussière T, Weinreb PH, Williams L, Maier M, et al. The antibody aducanumab reduces Aβ plaques in Alzheimer's disease. Nature. 2016; 537(7618):50–6. https://doi.org/10.1038/ nature19323 http://www.nature.com/nature/journal/v537/n7618/abs/nature19323.html#supplementary-information. PMID: 27582220

58. The Lancet N. Solanezumab: too late in mild Alzheimer's disease? The Lancet Neurology. 2017; 16 (2):97. Epub 2017/01/20. https://doi.org/10.1016/S1474-4422(16)30395-7 PMID: 28102152.

59. Beach TG, Monsell SE, Phillips LE, Kukull W. Accuracy of the Clinical Diagnosis of Alzheimer Disease at National Institute on Aging Alzheimer's Disease Centers, 2005–2010. Journal of Neuropathology and Experimental Neurology. 2012; 71(4):266–73. https://doi.org/10.1097/NEN.0b013e31824b211b PMID: 22437338

60. Efron B, Tibshirani RJ. An Introduction to the Bootstrap: Taylor & Francis; 1994.

61. Craig BA, Sendi PP. Estimation of the transition matrix of a discrete-time Markov chain. Health econom-ics. 2002; 11(1):33–42. Epub 2002/01/15. PMID: 11788980.

62. Kryscio RJ, Abner EL. Are Markov and semi-Markov models flexible enough for cognitive panel data? Journal of biometrics & biostatistics. 2013; 4(1). Epub 2013/11/14. https://doi.org/10.4172/2155-6180. 1000e122 PMID: 24224120; PubMed Central PMCID: PMCPMC3820113.

63. Stern Y. The concept of cognitive reserve: a catalyst for research. Journal of clinical and experimental neuropsychology. 2003; 25(5):589–93. Epub 2003/06/20. https://doi.org/10.1076/jcen.25.5.589.14571 PMID: 12815497.

64. Mortimer JA. Brain reserve and the clinical expression of Alzheimer's disease. Geriatrics. 1997; 52 Suppl 2:S50–3. Epub 1997/10/06. PMID: 9307589.

65. Schmand B, Smit JH, Geerlings MI, Lindeboom J. The effects of intelligence and education on the development of dementia. A test of the brain reserve hypothesis. Psychological medicine. 1997; 27 (6):1337–44. Epub 1997/12/24. PMID: 9403905.

66. Weiner MW, Veitch DP, Aisen PS, Beckett LA, Cairns NJ, Green RC, et al. The Alzheimer's Disease Neuroimaging Initiative: a review of papers published since its inception. Alzheimers Dement. 2013; 9 (5):e111–94. Epub 2013/08/13. https://doi.org/10.1016/j.jalz.2013.05.1769 PMID: 23932184; PubMed Central PMCID: PMCPMC4108198.

67. Whitwell JL, Wiste HJ, Weigand SD, Rocca WA, Knopman DS, Roberts RO, et al. Comparison of imag-ing biomarkers in the Alzheimer Disease Neuroimaging Initiative and the Mayo Clinic Study of Aging. Archives of neurology. 2012; 69(5):614–22. Epub 2012/07/12. https://doi.org/10.1001/archneurol.2011. 3029 PMID: 22782510; PubMed Central PMCID: PMCPMC3569033.

68. Qiu C, Kivipelto M, von Strauss E. Epidemiology of Alzheimer's disease: occurrence, determinants, and strategies toward intervention. Dialogues in clinical neuroscience. 2009; 11(2):111–28. Epub 2009/07/ 10. PMID: 19585947; PubMed Central PMCID: PMCPMC3181909.

69. Ower AK, Hadjichrysanthou C, Gras L, Goudsmit J, Anderson RM, de Wolf F. Temporal association patterns and dynamics of amyloid-β and tau in Alzheimer's disease. European Journal of Epidemiology. 2017. https://doi.org/10.1007/s10654-017-0326-z PMID: 29071500

70. Spiegel R, Doody RS, Hendrix S, Kahle-Wrobleski K. Modeling the course of Alzheimer's disease to improve clinical trials: symposium report. Alzheimer's Research & Therapy. 2013; 5(3):1–5. https://doi.org/10.1186/alzrt183 PMID: 23767782

71. Schneider LS. The potential and limits for clinical trials for early Alzheimer's disease and some recommendations. The journal of nutrition, health & aging. 2010; 14(4):295–8. Epub 2010/03/23. PMID: 20305999; PubMed Central PMCID: PMCPMC3923577.

72. Chibnik LB, Wolters FJ, Bäckman K, Beiser A, Berr C, Bis JC, et al. Trends in the incidence of dementia: design and methods in the Alzheimer Cohorts Consortium. European Journal of Epidemiology. 2017; 32(10):931–8. https://doi.org/10.1007/s10654-017-0320-5 PMID: 29063414