Journal of Alzheimer's Disease 89 (2022) 1143–1157
DOI 10.3233/JAD-220263
IOS Press

Personalized Prediction of Alzheimer's Disease and Its Treatment Effects by Donepezil: An Individual Participant Data Meta-Analysis of Eight Randomized Controlled Trials

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Handling Associate Editor: Elżbieta Kuźma

Accepted 25 July 2022
Pre-press 16 August 2022

Abstract.
Background: Patient characteristics may predict the progression of Alzheimer's disease (AD) and may moderate the effects of donepezil.
Objective: To build a personalized prediction model for patients with AD and to estimate patient-specific treatment effects of donepezil, using individual patient characteristics.
Methods: We systematically searched for all double-masked randomized controlled trials comparing oral donepezil and pill placebo in the treatment of AD and requested individual participant data through its developer, Eisai. The primary outcome was cognitive function at 24 weeks, measured with the Alzheimer's Disease Assessment Scale-cognitive component (ADAS-cog). We built a Bayesian meta-analytical prediction model for patients receiving placebo and we performed an individual patient data meta-analysis to estimate patient-level treatment effects.

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ISSN 1387-2877/$35.00

Results: Eight studies with 3,156 participants were included. The Bayesian prediction model suggested that more severe cognitive and global function at baseline and younger age were associated with worse cognitive function at 24 weeks. The individual participant data meta-analysis showed that, on average, donepezil was superior to placebo in cognitive function (ADAS-cog scores, –3.2; 95% Credible Interval (CrI) –4.2 to –2.1). In addition, our results suggested that antipsychotic drug use at baseline might be associated with a lower effect of donepezil in ADAS-cog (2.0; 95%CrI, –0.02 to 4.3).
Conclusion: Although our results suggested that donepezil is somewhat efficacious for cognitive function for most patients with AD, use of antipsychotic drugs may be associated with lower efficacy of the drug. Future research with larger sample sizes, more patient covariates, and longer treatment duration is needed.

Keywords: Alzheimer's disease, cognition, donepezil, effect modifier, meta-analysis, prognosis

INTRODUCTION

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by increasing aggravation of memory and other cognitive functions [1]. AD is the most common cause of dementia accounting for 60 to 80% of the cases worldwide, while it affects 10% of the population aged 65 or older [2]. There are limited therapeutics approved for the treatment of AD and specific patient factors contributing to treatment efficacy are not well understood.

Donepezil, an acetylcholinesterase inhibitor (AChEI), is the first approved drug currently available to treat AD, thus has accumulated the most abundant evidence. Donepezil is a widely standard treatment for the entire spectrum of AD. A recent systematic review of donepezil shows small efficacy of donepezil for AD in cognitive function, global clinical states rated by a clinician, and activities of daily living, compared to placebo [3]. Other AChEIs, such as rivastigmine and galantamine, were approved for mild and moderate stages, while the N-methyl-D-aspartate receptor antagonist, memantine, was for moderate to severe stages. In June 2021, a new drug, aducanumab, was granted by the US Food and Drug Administration expedited approval. However, none of these therapeutic drugs are expected to cure AD [2], and there has been no breakthrough medication for AD for the past two decades.

The efficacy of donepezil may be different for different types of patients. Personalized medicine (also known as "stratified" or "precision medicine") aims to find the best treatment for each patient, given the patient's individual characteristics [4]. This approach may lead to better patient outcomes. For example, personalized medicine can target providing beneficial interventions to treatment-sensitive patients and avoid specific treatments to treatment-resistant or harm-sensitive patients. To predict outcomes at the patient level, identification of both prognostic factors (i.e., characteristics that predict an outcome independent of the treatment) and effect modifiers (i.e., characteristics that predict differential response to alternative treatments) is needed. A previous observational study of patients with AD prescribed AChEI treatments showed that younger age, lower instrumental activities of daily living (IADLs), concomitant use of antipsychotic drugs, non-steroidal anti-inflammatory drugs, acetylsalicylic acid, solitary living, higher education, and lower mean dose of AChEIs may decrease the response to AChEIs for moderate AD [5]. These characteristics may be potential prognostic factors and/or effect modifiers. Previous randomized controlled trials (RCTs) have also identified potential effect modifiers. For example, one RCT did not find evidence of an effect of donepezil on cognitive impairment in people with AD and comorbid depression [6]. Another randomized controlled pilot trial indicated an association between olfactory deficits and the better efficacy of donepezil on cognitive function for those with depression and cognitive impairment [7].

Although there are several models available for predicting general dementia risk according to individual patient characteristics [8, 9], there are few studies on the prognosis of AD, and none have predicted the relative treatment effect. A recent study developed a prediction model for the prognosis of cognitive function in AD using the data of The Alzheimer's Disease Prediction of Longitudinal Evolution (TADPOLE). However, except for age and education, the covariates used are not readily available in usual clinical practice (e.g., neuroimaging, biomarkers, and genetic factors) [10]. In addition, prediction models based on observational studies are not able to accurately predict the relative treatment effect compared to no treatment because of existing confounders. Although the RCT is a strong study design to estimate treatment effects with reduced bias due to confounding factors, RCTs are commonly powered to detect average treatment effects. This means that a single RCT will usually lack the statistical power needed to accurately estimate

personalized treatment effects. Individual participant data meta-analysis (IPD-MA) of several RCTs can both increase the power to identify effect modifiers and predict relative treatment effects simultaneously by combining information from multiple patient-level datasets [11]. However, in the previous IPD-MA of donepezil for AD, only the mean treatment effect size was estimated, and patient-level treatment effects were not estimated [12]. Another study analyzed IPD from several double-masked RCTs to predict factors associated with rapid or slow cognitive decline, but the effect modification in the treatment of AD by donepezil was not examined [13].

The aim of the current study is therefore dual. We aimed to utilize easily accessible patient-level characteristics 1) to build a prediction model for the placebo response, i.e., to allow us to predict the natural course of the disease progression of AD, and 2) to estimate relative treatment effects of donepezil at an individual patient level. Thus, this study aims to provide tools for everyday clinical practice, by mapping the patient-specific natural disease progression and quantifying the expected benefit from donepezil at the patient level. Findings may guide both individual personalized treatment and future development of AD medications.

METHODS

This systematic review has been registered in PROSPERO (registry ID: CRD42019149573). We followed the PRISMA-IPD statement [14] and the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) statement [15].

Eligibility criteria and search strategy

The eligibility criteria for the current IPD-MA were as follows: double-masked RCT; treatment of AD diagnosed according to standard international operationalized diagnostic criteria (e.g., NINCDS-ADRDA criteria); oral donepezil as monotherapy for 24 weeks or longer, delivered daily in dose ranging between 5 and 23 mg as licensed in the USA, EU, or Japan; control condition was pill placebo; cognitive function was assessed by a validated psychometric test (e.g., ADAS-cog); the studies were conducted by Eisai, the developer of donepezil. We had planned to include multi-arm RCTs so long as donepezil and placebo were compared and crossover trials in which the data of the first phase were available, but we found no such studies meeting the eligibility criteria. We set no limitation of language and publication year. We searched articles published by August 9th, 2021, in the Cochrane CENTRAL, Medline, and WHO ICTRP. The detail of the search terms is described in the appendix (Supplementary Table 11). Two independent researchers (KY and YL) identified the eligible studies.

Data collection

We requested the IPD including the pre-specified variables (see below, outcomes and candidate covariates) and study protocols of the identified studies through ClinicalStudyDataRequest.com (https://www.clinicalstudydatarequest.com). We checked the obtained data by comparing the summary statistics in the publications of each study.

Risk of bias of individual studies

Two independent raters (KY and YL) assessed the risk of bias with regard to the primary outcome (cognitive function at 24 weeks, see below) for each study with a revised Cochrane risk-of-bias tool for randomized trials (RoB2) where the following domains were assessed as high risk, some concerns or low risk: randomization process, deviations from the intended interventions, missing outcome data, measurement of the outcome and selection of the reported result [16]. Any disagreement was resolved by discussion and, when necessary, consultation with the other review team members.

Data availability bias of individual studies

We assessed data availability bias by comparing the combined standardized mean difference (SMD) in the change of the primary outcome (cognitive function, see below) within 24 weeks between the analyzed studies and the other eligible studies of which we could not obtain the IPD. We used the software Review Manager version 5.4.1 for the calculation of the combined SMD.

Outcomes

For all the outcomes, we used measurements at 24 weeks after the initiation of the treatment.

Primary outcome

The primary outcome was cognitive function, as measured with the total score of the 11-item

Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog) [17, 18], the Severe Impairment Battery (SIB) [19, 20], or the Mini-Mental State Examination (MMSE) [21]. When only SIB or MMSE was assessed, we transformed the SIB (preferred) or the MMSE total scores to the ADAS-cog total scores according to the conversion table based on an equipercentile linking study of the three cognitive scales [22]. ADAS-cog is the most widely used cognitive scale in clinical trials for dementia. It consists of 11 items: word recall, word recognition, constructional praxis, orientation, naming objects and fingers, commands, ideational praxis, remembering test instruction, spoken language, word-finding, comprehension. The ADAS-cog total score ranges from 0 to 70 with the higher score representing more impaired cognitive function.

Secondary outcomes

We had pre-specified two secondary outcomes. One was the global assessment as measured using the Clinician's Interview-Based Impression of Change Plus Caregiver Input (CIBIC-Plus) [18, 23] or the Clinical Dementia Rating Sum of Boxes (CDR-SB) [24]. CDR-SB is the sum of the component scores in CDR, ranging from 0 to 18 with the higher score representing the more severe dementia [25]. When CIBIC-Plus was not administered but the data for CDR-SB scores were available, we transformed the change of CDR-SB scores from baseline to the CIBIC-Plus score according to the conversion table based on an equipercentile linking study for global assessment scales [26]. CIBIC-Plus is a standard global change rating scale for global function in the clinical trial for dementia. The score is derived from a semi-structured interview with patients and their caregivers. CIBIC-Plus score ranges from 1 to 7 with 1 corresponding to "markedly improved" and 7 corresponding to "markedly worse".

Another secondary outcome was all-cause dropouts, which was assessed by withdrawals from the trial in the 24-week treatment period. We adopted this outcome as a surrogate outcome for the acceptability of the treatment.

Candidates for prognostic factors and effect modifiers

We collected the data of the following characteristics as pre-specified potential prognostic and/or effect modifiers based on the literature and clinical expertise:

Demographics: Age [5, 13] and Sex; Life and social history: Education [5, 27], Marital status, Solitary living [5], History of alcohol use, Instrumental ADL [5]; Psychiatric history and symptomatology: Age at onset, Baseline severity [13], Baseline depression [6], Comorbid alcohol and other substance abuse; Physical history and symptomatology: Baseline body weight/BMI, Physical activity, Physical comorbidity including metabolic syndrome [5], Auditory sense [28], Olfactory sense [7]; Therapeutic process: Concomitant use of antipsychotics [5]; Brain physiology and genotype: Hippocampal volume [29], Apolipoprotein E (*APOE*) and other genotypes.

Regarding baseline severity, when CDR-SB was not administered at baseline but CIBIS-Plus (Clinician's Interview-Based Impression of Severity Plus Caregiver Input) was available, CIBIS-Plus scores were transformed to CDR-SB according to the conversion table based on an equipercentile linking study for global assessment scales [26].

Statistical analysis

Overview

For each outcome, we first developed a meta-analytical prediction model using only data from trial participants randomized to placebo. Next, we conducted an IPD-MA to estimate the relative treatment effects of donepezil over placebo as a function of patient characteristics. These two models combined can provide information about the expected natural progression of the disease (i.e., in the placebo arm), as well as the expected benefit due to drug therapy for each patient. We used this two-fold modelling strategy to best leverage the evidence provided by the studies to answer our research questions, without breaking randomization in the data.

Handling of missing data

Patients with missing covariates were excluded from the analyses because there were very few instances (15 patients, 0.5%). For partial missing in the items of ADAS-cog, SIB, MMSE, and CDR-SB, we used the ipsative mean imputation method assuming the average score of the remaining items when 20% or less of the data of the items were missing [30]. For the prediction model, we excluded patients with missing outcomes since we could not use them for assessing model performance (see below). Conversely, for the IPD-MA model we imputed missing outcomes assuming that they were missing at random.

For imputations, we used multilevel joint modeling multiple imputation, where between-study heterogeneity was modeled by random effects [31]. The imputation model included all the predictors, treatment indicator, treatment-covariate interactions, and outcome measurements prior to week 24 (weeks 4, 6, 8, 12, 16, 18, and 20).

Prediction model for placebo response

We built a set of competing prediction models for each outcome of our interest using only data from patients on placebo. We explored the following competing modeling strategies: simple linear (logistic) regression; frequentist and Bayesian (generalized) linear mixed-effects model with random effects placed on the study intercept; ridge regression; random forest; gradient boosting machines; and support vector machines. We selected the final model for each outcome after evaluating each models' performance using an internal-external cross-validation method (i.e., leave-one-study-out cross-validation) [32]. In this approach, each study was removed from the dataset, and the model was developed in the remaining studies. Then the model was evaluated in the left-out study. Finally, we cycled through all studies. As for measures of predictive performance, for continuous outcomes, we used the mean squared error (MSE) and coefficient of determination (R-squared) for observed versus predicted outcomes [32]. For binary outcome (i.e., all-cause dropouts), we used Area Under the Receiver Operating Characteristic Curve as a discrimination metric. After selecting the final models, we refitted using the whole dataset (i.e., all placebo patients from all studies).

Estimation of relative treatment effects (difference between outcomes with donepezil and placebo) through IPD-MA

For each outcome, we fitted a one-stage random effects IPD-MA model in the whole dataset [33]. The models included all aforementioned predictors as prognostic factors as well as treatment-covariate interactions. We used a linear mixed-effects model for the continuous outcomes (ADAS-cog and CIBIC-Plus) and a generalized linear mixed-effects model for the binary outcome (all-cause dropouts). We used informative prior distributions for the heterogeneity of the treatment effects (log odds ratios) in binary outcomes as provided in [34], for mental health indicator outcomes. Following recent recommendations [35], we incorporated shrinkage on all effect modifiers through a Bayesian LASSO. All covariates were standardized prior to fitting the models. After fitting the models, we reported the posterior estimates after reverting them to the original scale of the predictors, so that results were interpretable. Finally, using the developed models we estimated patient-specific treatment effects for all included participants as the sum of effect modification and average treatment effect [35]. We then generated histograms, to allow a visual inspection of the treatment effect heterogeneity in the included population. We assessed heterogeneity of the treatment effect among the included studies with τ^2, which represents the estimated between-study variance of underlying true effects across studies.

Implementation details

We used the statistical software R version 3.4.3 for all the analyses. We fit all Bayesian models using the R package rjags 4.1.0 [36]. For multiple imputation, we used the R package jomo 2.7.1. The code used to perform the analyses is available at https://github.com/MikeJSeo/phd/tree/master/donepezil

When fitting both the prognostic as well as the IPD-MA models, we used five imputed datasets and ran three chains of 10,000 iterations each, with 1000 burn-in. We assessed convergence using the Gelman-Rubin diagnostics [37]. For all models, we used a vague prior distribution for the precision of continuous outcomes, i.e., $\Gamma(0.001,\ 0.001)$. For regression coefficients, we used a $Normal(0, \sigma^2 = 1000)$ distribution. When applying Bayesian LASSO, a vague prior distribution was placed on variance parameter for Laplace prior, i.e., $U(0, 5)$.

RESULTS

Included studies

The initial literature search identified 1,219 published articles and trial registries that were screened as potential candidates meeting the eligibility criteria (Supplementary Figure 1). Seventy full texts were checked for eligibility, 13 RCTs ($n = 4{,}003$) of which were deemed relevant for the current study. Of these, we obtained the IPD of 3,156 participants (1,838 with donepezil, 1,318 with placebo) from eight studies through ClinicalStudyDataRequest.com [38–45]. In one study [41], there were no data provided for the 23 patients who discontinued the trial before the trial period. The reasons for not providing data for the remaining five studies were as follows: trials conducted by another pharmaceutical company collaborating with Eisai at that time [46, 47], the dif-

ferent focus of the study aim (i.e., neuroimaging and neuronal markers) [48, 49], and limited to only early-stage AD [50]. We also obtained the protocols of six studies [39, 40, 42–45]. The study duration was 24 weeks in seven studies [38–43, 45] and 54 weeks in one study [44] in which cognitive and global function was assessed also at 24 weeks. We used IPD of all the eight studies for the analyses of cognitive function outcome and global rating assessment outcome, and seven 24-week trials for the analyses of the all-cause dropout outcome.

All studies administered 5 mg/day or 10 mg/day of oral donepezil, usually with a dose-titration period in the intervention arms. Concomitant antipsychotic drug use was not allowed in four studies [38–40, 44] but allowed in the other four studies [41–43, 45]. The former studies included mild to moderately severe AD, while the latter included more severe cases. The SIB total scores in three studies [41, 42, 45] and the MMSE total scores in two studies [43, 44] were transformed to the ADAS-cog total scores. Change of the CDR-SB scores from baseline in three studies [38, 43, 44] was transformed to CIBIC-Plus scores. Regarding covariates, the CIBIS-Plus scores at baseline in three trials [41, 42, 45] were transformed to the CDR-SB scores. The covariates which were available across all the included studies were age, sex, weight, concomitant antipsychotic drug use, concomitant medication other than antipsychotic drugs, ADAS-cog score, and CDR-SB score. Table 1 shows the baseline characteristics for each study.

Risk of bias of individual studies

Supplementary Table 1 shows the risk of bias assessment of the included studies. All but two trials were rated at low risk of bias for all domains. Two trials [38, 41] were rated at some concerns in risk of bias due to baseline imbalance in dementia severity.

Data availability bias of individual studies

The point estimate for the SMD in cognitive function within 24 weeks in the analyzed eight studies (–0.43 in IPD-MA and also in aggregate data meta-analysis) [38–45] was almost identical to that in the other five eligible studies (–0.42 in aggregate data meta-analysis) [46–50], suggesting no data availability bias.

Primary outcome: Cognitive function measured with ADAS-cog

The proportion of randomized participants with missing outcome data for the ADAS-cog total score at 24 weeks was 24%.

Prediction model for patients in placebo

We started by fitting all competing prediction models using the leave-one-study-out analysis. Results are shown in Supplementary Table 2. The linear mixed-effects model and the Bayesian linear mixed-effects model were the best-performing methods, with an MSE, 60.4 and R-squared of 0.69. Among the two, and in order to be consistent with the IPD-MA model, we selected the Bayesian prediction model as the final model for this outcome. We then refitted the selected model in all placebo patients. Table 2 shows the estimated coefficients of each. Most predictive covariates were baseline measurements for ADAS-cog (coefficient, 0.95, meaning 0.95 ADAS-cog points increase at 24 weeks per one ADAS-cog point increase at baseline; 95% credible interval (CrI), 0.91 to 0.99), baseline CDR-SB (0.36; 95%CrI, 0.16 to 0.55), and age (–0.11; 95%CrI, –0.17 to –0.05).

Relative treatment effects: IPD-MA

Table 3 shows the estimates of each covariate (prognostic factor) and each treatment-by-covariate interaction (effect modifier) in the IPD-MA for the ADAS-cog total score. The average treatment effect of donepezil compared to placebo was –3.15 (95%CrI, –4.20 to –2.14). The most important potential effect modifier was concomitant antipsychotic drug use at baseline (2.00, meaning 2.00 ADAS-cog points increase at 24 weeks when taking donepezil compared to placebo; 95%CrI, –0.02 to 4.26), estimating an average lower treatment effect of donepezil, albeit with some uncertainty. Supplementary Figure 2 provides the distribution of patient-specific treatment effects in ADAS-cog scores among the analyzed participants, representing the estimated relative treatment effect by comparing donepezil to placebo for each participant. The distribution ranged from –5.18 to –0.04 (median, –3.19), indicating that donepezil was beneficial for cognitive function to some extent for the majority of patients. For some patients, donepezil was estimated to offer little benefit or even no benefit at all.

Table 1
Study characteristics of the eight included studies at baseline

	Dose of donepezil (mg/day)	Number of randomized patients	Number allocated to placebo	Trial duration, week	Countries	Age, y (mean, SD)†	Sex, female (%)	Weight, kg (mean, SD)‡	Concomitant antipsychotic drug use (%)	Concomitant medication other than antipsychotic drugs (%)	Baseline cognitive function, ADAS-cog (mean, SD)	Baseline global function, CDR-SB (mean, SD)
Homma et al., 2000 [38]	Placebo, 5 mg	268	132 (49%)	24	Japan	70.5 (7.2)	179 (67%)	50.5 (8.7)	0 (0%)	134 (50%)	24.9 (9.4)	7.5 (2.4)
Rogers et al., 1998 [39]	Placebo, 5 mg, 10 mg	473	162 (34%)	24	US	73.5 (7.2)	293 (62%)	68.5 (14.2)	2 (0.4%)	358 (76%)	27.1 (11.5)	7.1 (2.4)
Burns et al., 1999 [40]	Placebo, 5 mg, 10 mg	818	274 (33%)	24	Australia, Belgium, Canada, France, Germany, Ireland, New Zealand, South Africa, UK	71.6 (7.4)	470 (57%)	65.9 (12.4)	0 (0%)	471 (58%)	24.5 (10.0)	6.5 (2.0)
Homma et al., 2008 [41]	Placebo, 5 mg, 10 mg	302 *	105 (35%)	24	Japan	78.4 (7.7)	242 (80%)	46.6 (8.1)	52 (17%)	46 (15%)	51.8 (12.1)§	12.2 (2.7)¶
Black et al., 2007 [42]	Placebo, 10 mg	343	167 (49%)	24	US, Canada, France, UK, Australia	78.1 (7.6)	241 (70%)	64.2 (13.2)	48 (14%)	288 (84%)	48.5 (14.3)§	10.8 (2.7)¶
Tariot et al., 2001 [43]	Placebo, 10 mg	208	105 (50%)	24	US	84.8 (6.0)	172 (83%)	61.3 (11.6)	38 (18%)	202 (97%)	38.1 (13.8)‖	11.0 (3.9)
Mohs et al., 2001 [44]	Placebo, 10 mg	431	217 (50%)	54	US	75.6 (8.0)	271 (63%)	66.6 (14.6)	28 (6%)	378 (88%)	30.7 (6.8)‖	6.8 (2.1)
Jia et al., 2017 [45]	Placebo, 10 mg	313	156 (50%)	24	China	71.3 (8.2)	203 (65%)	56.0 (10.1)	32 (10%)	169 (54%)	50.2 (11.8)§	12.1 (2.2)¶

SD, standard deviation; ADAS-cog, Alzheimer's Disease Assessment Scale-Cognitive Subscale; CDR-SB, Clinical Dementia Rating Sum of Boxes. Quantitative data are given as mean (SD); categorical data are given as number (%). *There were no data provided for 23 patients who discontinued the trial before the trial period although 325 patients initially enrolled. †In the dataset, age ranged from 60 to 90 years, where less than 60 and over 90 years were recorded as 60 and 90 respectively. ‡In the dataset, weight ranged from 35kg to 115kg where less than 35kg and over 115kg were given as 35kg and 115kg respectively. §ADAS-cog total score was transformed from Severe Impairment Battery (SIB) total score. ‖ADAS-cog total score was transformed from Mini-Mental State Examination (MMSE) total score. ¶CDR-SB score was transformed from Clinician's Interview-Based Impression of Severity plus caregiver input (CIBIS-Plus) score.

Table 2
Estimated parameters of the prediction model for placebo response in Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-cog) at 24 weeks

Parameter	Posterior Estimates (95% Credible Interval)
Main Effects (Prognostic Factors)	
Age, y	–0.11 (–0.17 to –0.05)
Female Sex	–0.84 (–1.87 to 0.18)
Weight, kg	0.00 (–0.04 to 0.04)
Concomitant antipsychotic drug use	–0.84 (–2.56 to 0.88)
Concomitant medication other than antipsychotic drug	–0.84 (–1.85 to 0.16)
Baseline cognitive function severity, ADAS-cog	0.95 (0.91 to 0.99)
Baseline global function severity, CDR-SB	0.36 (0.16 to 0.55)

ADAS-cog, Alzheimer's Disease Assessment Scale-Cognitive Subscale; CDR-SB, Clinical Dementia Rating Sum of Boxes.

Table 3
Estimated parameters from the individual participant data meta-analysis model regarding relative treatment effects (donepezil versus placebo) in Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-cog) at 24 weeks

Parameter	Posterior Estimates (95% Credible Interval)
Average treatment effect of donepezil	–3.15 (–4.20 to –2.14)
Main Effects (Prognostic Factors)	
Age, y	–0.10 (–0.14 to –0.05)
Female Sex	–0.63 (–1.50 to 0.17)
Weight, kg	–0.02 (–0.05 to 0.01)
Concomitant antipsychotic drug use	–0.06 (–1.67 to 1.50)
Concomitant medication other than antipsychotic drug	–0.72 (–1.61 to 0.10)
Baseline cognitive function severity, ADAS-cog	0.95 (0.92 to 0.99)
Baseline global function severity, CDR-SB	0.41 (0.26 to 0.56)
Treatment-by-Covariate Interaction (Effect Modifiers)	
Age, y	0.04 (–0.01 to 0.10)
Female Sex	0.45 (–0.39 to 1.52)
Weight, kg	0.00 (–0.03 to 0.03)
Concomitant antipsychotic drug use	2.00 (–0.02 to 4.26)
Concomitant medication other than antipsychotic drug	0.63 (–0.25 to 1.75)
Baseline cognitive function severity, ADAS-cog	–0.02 (–0.07 to 0.01)
Baseline global function severity, CDR-SB	0.01 (–0.13 to 0.18)

ADAS-cog, Alzheimer's Disease Assessment Scale-Cognitive Subscale; CDR-SB, Clinical Dementia Rating Sum of Boxes. Heterogeneity (τ^2), 1.07 (95%CrI 0.15 to 2.50).

Secondary outcome: Global function measured with CIBIC-Plus

The proportion of randomized participants with missing outcome data for the CIBIC-Plus score at 24 weeks was 24%.

Prediction model for patients in placebo

We found that all competing prediction models for this outcome performed poorly. The R-squared was negative, implying that the model prediction of the outcome was worse than a simple average of the outcome for each study (Supplementary Table 2). Thus, we deemed that these prediction models were not usable for this outcome, and we did not pursue them further.

Relative treatment effect: IPD-MA

Table 4 shows the estimated coefficients of all model parameters for the IPD-MA model for the CIBIC-Plus score. The average treatment effect of donepezil versus placebo was –0.42 (95%CrI, –0.54 to –0.30). The most important potential effect modifier was concomitant antipsychotic drug use at baseline (0.29; 95%CrI, –0.02 to 0.64), albeit with uncertainty. Supplementary Figure 3 shows the distribution of patient-specific treatment effects in CIBIC-Plus scores among the analyzed participants, ranging between –0.70 and 0.01 (median: –0.39). This means that although the treatment was beneficial for most, for some patients, donepezil did not improve CIBIC-Plus scores.

Table 4
Estimated parameters from the individual participant data meta-analysis model regarding relative treatment effects (donepezil versus placebo) in Clinician's Interview-Based Impression of Severity Plus Caregiver Input (CIBIC-Plus) at 24 weeks

Parameter	Posterior Estimates (95% Credible Interval)
Average treatment effect of donepezil	–0.42 (–0.54 to –0.30)
Main Effects (Prognostic Factors)	
Age, y	0.00 (–0.01 to 0.01)
Female Sex	–0.05 (–0.20 to 0.09)
Weight, kg	0.00 (0.00 to 0.01)
Concomitant antipsychotic drug use	–0.20 (–0.45 to 0.04)
Concomitant medication other than antipsychotic drug	0.01 (–0.11 to 0.14)
Baseline cognitive function severity, ADAS-cog	0.02 (0.01 to 0.02)
Baseline global function severity, CDR-SB	–0.01 (–0.04 to 0.01)
Treatment-by-Covariate Interaction (Effect Modifiers)	
Age, y	0.00 (–0.01 to 0.00)
Female Sex	0.18 (0.00 to 0.37)
Weight, kg	0.00 (–0.01 to 0.00)
Concomitant antipsychotic drug use	0.29 (–0.02 to 0.64)
Concomitant medication other than antipsychotic drug	0.00 (–0.13 to 0.14)
Baseline cognitive function severity, ADAS-cog	0.00 (0.00 to 0.01)
Baseline global function severity, CDR-SB	–0.01 (–0.04 to 0.01)

ADAS-cog, Alzheimer's Disease Assessment Scale-Cognitive Subscale; CDR-SB, Clinical Dementia Rating Sum of Boxes. Heterogeneity (τ^2), 0.10 (95%CrI 0.00 to 0.27).

Secondary outcome: All-cause dropouts

We excluded one 54-week study [44] from the analysis for all-cause dropouts at 24 weeks because dropout at 24 weeks was not recorded in the study. The proportion of randomized participants with missing outcome data for the all-cause dropouts total score at 24 weeks was 0.2% (7 participants).

Prediction model for patients in placebo

As in CIBIC-Plus, we found that all prediction models performed poorly. For example, the leave-one-study-out gave an Area Under the Receiver Operating Characteristic Curve of only 0.53 (Supplementary Table 2). Similar to the case of CIBIC-Plus, we decided that our prediction models were not useful for this outcome.

Relative treatment effect: IPD-MA

Supplementary Table 8 (standardized covariate results) and Supplementary Table 9 (reverting standardized covariates to original scale) show the coefficient estimates of model parameters for all-cause dropouts IPD-MA. The average treatment effect in an odds ratio was estimated at 1.03 (95%CrI, 0.59 to 1.75). Supplementary Figure 4 shows the distribution of patient-specific treatment effects in all-cause dropouts among the analyzed participants ranged between 0.78 and 1.24 (median: 1.03) in the odds ratio scale. We did not find evidence of strong effect modifications for this outcome, and all estimated treatment effects were very uncertain.

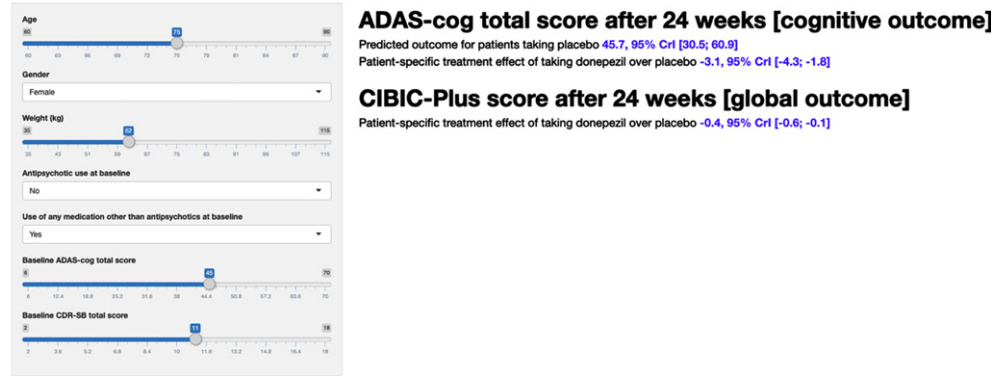
Sensitivity analysis

We were unable to conduct the pre-specified sensitivity analysis because no included studies were rated as high risk in the overall risk of bias assessment (Supplementary Table 1). We compared predictions obtained from the different models (Bayesian linear mixed-effects, frequentist linear mixed-effects, and ridge regression models) and found very good agreement (Supplementary Figures 5 and 6). In addition, we only used the three studies where ADAS-cog was not transformed to fit a linear mixed-effects model and obtain predictions for this outcome and compared them with the predictions obtained from the full dataset. Results were broadly consistent (Supplementary Figure 7). We did not conduct a sensitivity analysis of these three studies to fit an IPD-MA model because patients in these studies had nearly no patients with concomitant antipsychotic drug use. Likewise, we only used the five studies where CIBIC-Plus was not transformed to fit an IPD-MA model. Results were consistent with the analysis obtained from the full dataset (Supplementary Table 10).

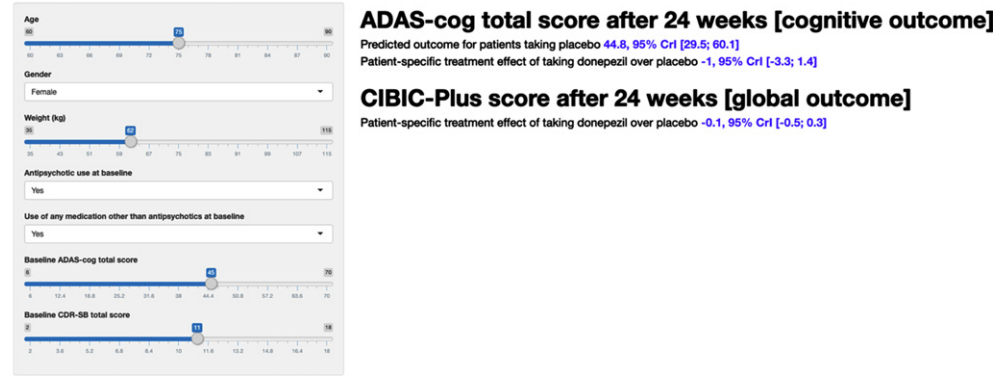
Interactive web application

To facilitate the use of our results in clinical practice, we developed an interactive web applica-

A



B



C

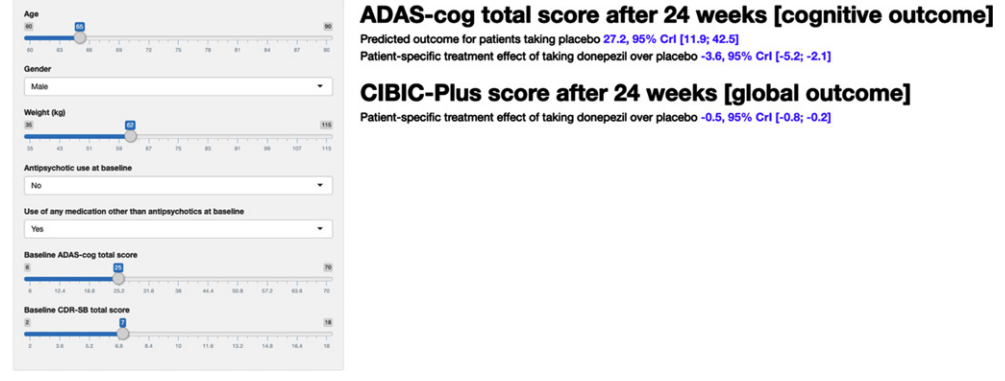


Fig. 1. Interactive web application for individual prediction and treatment effect estimation of cognitive function and global function severity. A) For a typical patient: 75-year-old woman with baseline ADAS-cog of 45.0 and baseline CDR-SB of 11 without antipsychotic drug use at baseline. B) For a patient with antipsychotic use at baseline: 75-year-old woman with baseline ADAS-cog of 45.0 and baseline CDR-SB of 11 with antipsychotic drug use at baseline. C) For a younger male patient with milder dementia: 65-year-old man with baseline ADAS-cog of 25.0 and baseline CDR-SB of 7 without antipsychotic drug use at baseline. In examples A through C, other factors are set to Weight, 62.0 kg, Use of any medication other than antipsychotics at baseline = Yes.

tion (https://cinema.ispm.unibe.ch/shinies/donepezil/). This allows users to make predictions of absolute outcomes and patient-specific treatment effect for different combinations of baseline characteristics. More specifically, the application demonstrates the prediction for the ADAS-cog in placebo and provides an estimate of the relative treatment effect of donepezil over placebo. It also estimates the relative treatment effect in terms of CIBIC-Plus. We only included the prediction model for the ADAS-cog outcome because the prediction models for CIBIC-Plus and dropout performed poorly. In addition, we did not include the estimated treatment effects for dropout, since these were estimated with large uncertainty. The default baseline characteristics are set to the median covariate values of the patients. Figure 1 further illustrates three hypothetical cases, for a 75-year-old woman (Fig. 1A), for a woman taking an antipsychotic drug (Fig. 1B), and for a younger man with milder dementia (Fig. 1C).

DISCUSSION

This study analyzed the IPD from more than 3,000 patients with AD who participated in double-masked RCTs comparing donepezil and placebo. For our primary outcome, cognitive function measured in ADAS-cog, we first developed a Bayesian model to predict placebo response, and then we estimated patient-level treatment effects of donepezil using an IPD-MA. Our prediction model for placebo response identified that baseline cognitive function, global functioning, and age are prognostic factors for cognitive function. Our IPD-MA results suggested that for most patients, donepezil is expected to yield some benefit in cognitive and global functioning, as compared to placebo. Conversely, for a minority of patients, our models suggested no benefit from donepezil. While we could not identify definitive evidence for heterogeneous effects of donepezil for AD in all outcomes, our results suggested that concomitant antipsychotic drug use at treatment initiation may be associated with a reduced effect of donepezil for cognitive and global function.

Prognostic factors associated with worse cognitive function after 24 weeks included more severe baseline cognitive and global function, and younger age. These findings were consistent with a previous study where the outcome was the change in cognitive function and dichotomized [13]. Our result that younger age for the same dementia severity predicted worse cognitive function was concordant with other previous findings [5, 51].

Regarding relative treatment effects of donepezil on cognitive function, although the magnitude of the clinically meaningful difference between the treatment arms has not been defined, the average between-group difference of ADAS-cog (–3.15 point in our analysis) may be clinically meaningful when accounting for the minimal clinically important change in the ADAS-cog total score is approximately three [52]. The magnitude of the treatment effect in our analysis was a little larger compared to that reported in the most recent Cochrane review (–2.02 in 5 mg and –2.81 in 10 mg of donepezil) [3] and a previous IPD-MA (–2.0 in 5 mg and –3.1 in 10 mg of donepezil) [12]. The differences may be due to differences in the included studies and the statistical methods used (e.g., handling of missing data). Cognitive function in five out of eight studies was not originally measured with ADAS-cog but transformed from SIB (three studies) or MMSE (two studies) to ADAS-cog using equipercentile linking [22]. We also used joint modeling multiple imputation for missing outcome data at 24 weeks in the same way across studies.

Potential effect modification by antipsychotic drug use, which was suggested in our analyses, is important because antipsychotic drugs are often prescribed off-label in clinical settings to deal with behavioral and neuropsychiatric symptoms such as agitation/aggression, delusion, and hallucination, which are frequently occurring in people with AD [53–55]. However, no antipsychotic drugs have been approved for the treatment of behavioral and psychological symptoms secondary to AD by the US Food and Drug Administration because of their serious side effects such as stroke and death [56]. Our findings of a smaller treatment effect on cognitive function for patients with concomitant antipsychotic drug use was in line with the secondary analysis of one RCT (the Clinical Antipsychotic Trials of Intervention Effectiveness–Alzheimer's Disease study: CATIE-AD study) [57]. In this study, in which 64% of patients were taking AChEIs, atypical antipsychotic drugs were associated with greater deteriorated cognitive function compared to placebo. Another mixed-effects model analysis in an observational study of patients with AD prescribed AChEI treatment also reported that concomitant antipsychotic drug use predicted negative treatment response for AD with a 1.99 point lower MMSE total score [5]. A detailed neurobiological mechanism has not been identified, but the

potential antipsychotic drug use effect modification may be because of the drug interaction between antipsychotics and AChEIs. This could be explained by the opposite influences of cholinergic and anticholinergic drug effects [58]. We should also interpret the results carefully with the consideration of confounding variables. For example, a decreased effect of donepezil may not be due to antipsychotic drug use itself, but rather due to concurrent behavioral and neuropsychiatric symptoms of AD. Previous studies showed the association between those symptoms and rapid cognitive decline in people with AD [55, 59], but potential effect modification by such symptoms on donepezil for AD is unclear. Future research is necessary to elucidate whether a potentially reduced effect of donepezil for AD was due to antipsychotic drug use itself or due to some underlying confounding factor.

Regarding relative treatment effects of donepezil on all-cause dropouts, one of our secondary outcomes was a surrogate outcome for the acceptability of the treatment. We could not identify evidence of treatment effect modification, which were estimated with large uncertainty. However, donepezil should be used for AD after due consideration of both risks and benefits to maximize the treatment effect because some side effects have been reported more frequently in patients taking donepezil compared to those taking placebo, although most of them are mild, such as nausea, vomiting, and diarrhea commonly [3].

Our study has limitations of note. First, we could not obtain the IPD from all the studies meeting the eligibility criteria but analyzed the IPD from eight (total $n = 3,156$) out of 13 eligible studies (total $n = 4,003$) in the comprehensive literature search. However, data availability bias was deemed small, as suggested by the similar SMD in cognitive function between the analyzed studies and the other eligible studies. Second, we included only studies conducted by Eisai co. Ltd, the manufacturer of donepezil. However, a previous study found no evidence suggesting a difference in the treatment effects of donepezil between pharmaceutical-company-sponsored studies and others [60]. Third, although we listed several potential prognostic factors and effect modifiers *a priori*, only a few variables were available for our analyses. This limitation is often seen in meta-analysis in practice, as studies usually collect different sets of covariates. Future research should examine the impact of those factors that we could not include on the prognosis of AD and the treatment effect of donepezil such as *APOE* $\varepsilon 4$ allele. We could not build prediction models for our secondary outcomes (global function measured with CIBIC-Plus and all-cause dropouts) because of poor model performance. It may be because we could not include important predictors in the models. Fourth, we could not perform the analysis considering the specific type of concomitant antipsychotic or non-antipsychotic drugs because the dataset did not provide relevant information. Any medication other than antipsychotic drugs may have included drugs for physical or psychiatric symptoms. Future research is needed to elucidate which medication or comorbidities influence the treatment effect of donepezil for AD. Fifth, the condition of concomitant medication was different across the included studies. In particular, antipsychotic drugs were mainly used in the studies targeting patients with more severe AD. Future research should confirm the role of concomitant antipsychotic drug use as a potential effect modifier, especially in relation to AD severity. Finally, our 24-week cognitive outcome may be comparatively short for the chronic progression of AD. For example, the European Alzheimer's disease consortium recommended an 18-month follow-up period for disease-modifying trials [61]. Future research is necessary to examine longer outcomes.

Notwithstanding the limitations, our study has several important strengths. First, this study analyzed IPD from over 3,000 patients with AD who participated in several double-masked RCTs comparing donepezil and placebo. Jointly analyzing the data from all these studies was achieved by linking three cognitive function scales and two global function scales through equipercentile linking. Furthermore, IPD-MA of double-masked RCTs allowed us to estimate relative treatment effect estimates without compromising randomization. Second, since this is an analysis based on IPD instead of aggregate-level data, we applied the same statistical method for all studies in the sample, including imputation for missing data. Moreover, the proportion of missing covariates was small. Third, we used an internal-external cross-validation method, to assess the generalizability of our findings in new settings. Following this procedure, we decided not to present prediction models for the secondary outcomes, but we found that the prediction model for the primary outcome had acceptable performance. Additionally, we developed an interactive web application (https://cinema.ispm.unibe.ch/shinies/donepezil/) to quantitatively demonstrate the prediction for cognitive function in placebo after 24 weeks. This accounts for the relative treatment effect of donepezil

over placebo, based on individual patient characteristics, which would be useful in clinical settings for patients and clinicians to discuss their treatment options.

Conclusions

Our analyses of individual participant data from eight RCTs of donepezil for AD suggests that donepezil is beneficial for cognitive and global function for most patients with AD. Importantly, the efficacy of the drug may be different for different patient characteristics. Concomitant use of antipsychotic drugs may be associated with reduced efficacy of donepezil for AD in both cognitive and global function. Whether this reduction is due to the antipsychotic drugs or due to some confounding factor associated with taking antipsychotics (e.g., agitation/aggression) remains to be seen. Further studies with larger sample sizes, collecting more patient covariates such as *APOE* ε4 allele, with longer treatment duration, are needed to predict more precisely the natural disease course and the relative treatment effects of donepezil at the patient-level.

ACKNOWLEDGMENTS

We acknowledge Eisai Co. Ltd for providing us with the study data. Eisai Co. Ltd did not provide study design or critical input for the study. We acknowledge http://www.clinicalstudydatarequest.com for hosting the study data.

This study was supported in part by JSPS Grant-in-Aid for Scientific Research (Grant Number 22K19688) to Furukawa.

Cipriani is supported by the National Institute for Health Research (NIHR) Oxford Cognitive Health Clinical Research Facility, by an NIHR Research Professorship (grant RP-2017-08-ST2-006), by the NIHR Oxford and Thames Valley Applied Research Collaboration and by the NIHR Oxford Health Biomedical Research Centre (grant BRC-1215-20005). The views expressed are those of the authors and not necessarily those of the UK National Health Service, the NIHR, or the UK Department of Health.

Efthimiou is supported by project grant No.180083 from the Swiss National Science Foundation (SNSF).

This study did not receive any other specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Authors' disclosures available online (https://www.j-alz.com/manuscript-disclosures/22-0263r1).

DATA AVAILABILITY STATEMENT

Data access made available upon request to http://www.clinicalstudydatarequest.com.

SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: https://dx.doi.org/10.3233/JAD-220263.

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Supplementary Material

Personalized Prediction of Alzheimer's Disease and Its Treatment Effects by Donepezil: An Individual Participant Data Meta-Analysis of Eight Randomized Controlled Trials

Supplementary Table 1. Risk of bias assessment of the cognitive function outcome in the included studies

Study	Original measurement scale for cognitive function*	Domain 1: Randomization process	Domain 2: Deviations from the intended interventions	Domain 3: Missing outcome data	Domain 4: Measurement of the outcome	Domain 5: Selection of the reported result	Overall risk-of-bias judgement
Homma et al., 2000 [1]	ADAS-cog	Some concerns[†]	Low risk	Low risk	Low risk	Low risk	Some concerns
Rogers et al., 1998 [2]	ADAS-cog	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Burns et al., 1999 [3]	ADAS-cog	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Homma et al., 2008 [4]	SIB	Some concerns[‡]	Low risk	Low risk	Low risk	Low risk	Some concerns
Black et al., 2007 [5]	SIB	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Tariot et al., 2001 [6]	MMSE	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Mohs et al., 2001 [7]	MMSE	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Jia et al., 2017 [8]	SIB	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

ADAS-cog, Alzheimer's Disease Assessment Scale-Cognitive Subscale; SIB, Severe Impairment Battery; MMSE, Mini-Mental State Examination.

*Measurement scale for cognitive function which was transformed to ADAS-cog in the current study when ADAS-cog was not assessed in the original study.

[†]Baseline ADAS-cog total mean score was 23.0 in the donepezil arm and 27.0 in the placebo arm.

[‡]Baseline transformed ADAS-cog total mean score was 53.2 in the donepezil arm and 49.3 in the placebo arm.

Supplementary Table 2. Prediction model performance

ADAS-cog outcome

	Linear model	Linear mixed effects model	Ridge regression model	Bayesian linear mixed effects model	Random-forest model	Gradient boosting machine model	Support Vector Machine model
MSE	64.60	**60.40**	60.47	60.44	66.33	72.01	64.80
R-squared	0.672	0.688	0.687	0.688	0.659	0.672	**0.696**

CIBIC-Plus outcome

	Linear model	Linear mixed effects model	Ridge regression model	Bayesian linear mixed effects model	Random-forest model	Gradient boosting machine model	Support Vector Machine model
MSE	1.23	1.23	**1.23**	1.23	1.26	1.30	1.33
R-squared	-0.10	-0.09	-0.10	-0.09	0.01	**0.02**	0.02

All-cause dropout outcome

	Linear model	Linear mixed effects model	Ridge regression model	Bayesian linear mixed effects model	Random-forest model	Gradient boosting machine model	Support Vector Machine model
AUC	0.525	0.525	**0.552**	0.529	0.527	0.521	0.494

ADAS-cog, Alzheimer's Disease Assessment Scale-Cognitive Subscale; CIBIC-Plus, Clinician's Interview-Based Impression of Change Plus Caregiver Input; MSE, mean squared error; R-squared, coefficient of determination; AUC, Area Under the Receiver Operating Characteristic Curve. MSE and R-squared are for cross validating the prediction models.

Supplementary Table 3. Estimated parameters of the prediction model for placebo response in Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-cog) at 24 weeks (standardized covariate results)

Parameter	Posterior Estimates (95% Credible Interval)
Main Effects (Prognostic Factors)	
Age, y	-0.92 (-1.39 to -0.44)
Female Sex	-0.40 (-0.89 to 0.09)
Weight, kg	-0.05 (-0.61 to 0.51)
Concomitant antipsychotic drug use	-0.20 (-0.62 to 0.21)
Concomitant medication other than antipsychotic drug	-0.40 (-0.88 to 0.08)
Baseline cognitive function severity, ADAS-cog	14.74 (14.07 to 15.41)
Baseline global function severity, CDR-SB	1.20 (0.54 to 1.86)

ADAS-cog, Alzheimer's Disease Assessment Scale-Cognitive Subscale; CDR-SB, Clinical Dementia Rating Sum of Boxes.

Supplementary Table 4. Estimated parameters from the individual participant data meta-analysis model regarding relative treatment effects (donepezil versus placebo) in Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-cog) at 24 weeks (standardized covariate results)

Parameter	Posterior Estimates (95% Credible Interval)
Average treatment effect of donepezil	-3.15 (-4.20 to -2.14)
Main Effects (Prognostic Factors)	
Age, y	-0.80 (-1.22 to -0.42)
Female Sex	-0.30 (-0.71 to 0.08)
Weight, kg	-0.33 (-0.75 to 0.10)
Concomitant antipsychotic drug use	-0.01 (-0.41 to 0.36)
Concomitant medication other than antipsychotic drug	-0.34 (-0.77 to 0.05)
Baseline cognitive function severity, ADAS-cog	14.77 (14.24 to 15.33)
Baseline global function severity, CDR-SB	1.39 (0.89 to 1.88)
Treatment-by-Covariate Interaction (Effect Modifiers)	
Age, y	0.32 (-0.10 to 0.84)
Female Sex	0.21 (-0.18 to 0.72)
Weight, kg	-0.03 (-0.49 to 0.42)
Concomitant antipsychotic drug use	0.49 (-0.01 to 1.04)
Concomitant medication other than antipsychotic drug	0.30 (-0.12 to 0.83)
Baseline cognitive function severity, ADAS-cog	-0.33 (-1.04 to 0.17)
Baseline global function severity, CDR-SB	0.05 (-0.43 to 0.60)

ADAS-cog, Alzheimer's Disease Assessment Scale-Cognitive Subscale; CDR-SB, Clinical Dementia Rating Sum of Boxes. Heterogeneity (τ^2), 1.07 (95%CrI 0.15 to 2.50).

Supplementary Table 5. Estimated parameters from the individual participant data meta-analysis model regarding relative treatment effects (donepezil versus placebo) in Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-cog) at 24 weeks (reverting standardized covariates to original scale)

Parameter	Posterior Estimates (95% Credible Interval)
Average treatment effect of donepezil	-6.03 (-11.78 to -1.16)
Main Effects (Prognostic Factors)	
Age, y	-0.10 (-0.14 to -0.05)
Female Sex	-0.63 (-1.50 to 0.17)
Weight, kg	-0.02 (-0.05 to 0.01)
Concomitant antipsychotic drug use	-0.06 (-1.67 to 1.50)
Concomitant medication other than antipsychotic drug	-0.72 (-1.61 to 0.10)
Baseline cognitive function severity, ADAS-cog	0.95 (0.92 to 0.99)
Baseline global function severity, CDR-SB	0.41 (0.26 to 0.56)
Treatment-by-Covariate Interaction (Effect Modifiers)	
Age, y	0.04 (-0.01 to 0.10)
Female Sex	0.45 (-0.39 to 1.52)
Weight, kg	0.00 (-0.03 to 0.03)
Concomitant antipsychotic drug use	2.00 (-0.02 to 4.26)
Concomitant medication other than antipsychotic drug	0.63 (-0.25 to 1.75)
Baseline cognitive function severity, ADAS-cog	-0.02 (-0.07 to 0.01)
Baseline global function severity, CDR-SB	0.01 (-0.13 to 0.18)

ADAS-cog, Alzheimer's Disease Assessment Scale-Cognitive Subscale; CDR-SB, Clinical Dementia Rating Sum of Boxes. Heterogeneity (τ^2), 1.07 (95%CrI 0.15 to 2.50). Posterior estimates are reverting standardized covariates to their original scale.

Supplementary Table 6. Estimated parameters from the individual participant data meta-analysis model regarding relative treatment effects (donepezil versus placebo) in Clinician's Interview-Based Impression of Severity Plus Caregiver Input (CIBIC-Plus) at 24 weeks (standardized covariate results)

Parameter	Posterior Estimates (95% Credible Interval)
Average treatment effect of donepezil	-0.42 (-0.54 to -0.30)
Main Effects (Prognostic Factors)	
Age, y	-0.01 (-0.07 to 0.05)
Female Sex	-0.02 (-0.09 to 0.04)
Weight, kg	0.01 (-0.05 to 0.08)
Concomitant antipsychotic drug use	-0.05 (-0.11 to 0.01)
Concomitant medication other than antipsychotic drug	0.01 (-0.05 to 0.06)
Baseline cognitive function severity, ADAS-cog	0.24 (0.15 to 0.32)
Baseline global function severity, CDR-SB	-0.05 (-0.12 to 0.04)
Treatment-by-Covariate Interaction (Effect Modifiers)	
Age, y	-0.03 (-0.10 to 0.03)
Female Sex	0.09 (0.00 to 0.18)
Weight, kg	-0.02 (-0.10 to 0.05)
Concomitant antipsychotic drug use	0.07 (0.00 to 0.16)
Concomitant medication other than antipsychotic drug	0.00 (-0.06 to 0.07)
Baseline cognitive function severity, ADAS-cog	0.02 (-0.05 to 0.12)
Baseline global function severity, CDR-SB	-0.03 (-0.14 to 0.04)

ADAS-cog, Alzheimer's Disease Assessment Scale-Cognitive Subscale; CDR-SB, Clinical Dementia Rating Sum of Boxes. Heterogeneity (τ^2), 0.10 (95%CrI 0.00 to 0.27).

Supplementary Table 7. Estimated parameters from the individual participant data meta-analysis model regarding relative treatment effects (donepezil versus placebo) in Clinician's Interview-Based Impression of Severity Plus Caregiver Input (CIBIC-Plus) at 24 weeks (reverting standardized covariates to original scale)

Parameter	Posterior Estimates (95% Credible Interval)
Average treatment effect of donepezil	-0.20 (-0.91 to 0.65)
Main Effects (Prognostic Factors)	
Age, y	0.00 (-0.01 to 0.01)
Female Sex	-0.05 (-0.20 to 0.09)
Weight, kg	0.00 (0.00 to 0.01)
Concomitant antipsychotic drug use	-0.20 (-0.45 to 0.04)
Concomitant medication other than antipsychotic drug	0.01 (-0.11 to 0.14)
Baseline cognitive function severity, ADAS-cog	0.02 (0.01 to 0.02)
Baseline global function severity, CDR-SB	-0.01 (-0.04 to 0.01)
Treatment-by-Covariate Interaction (Effect Modifiers)	
Age, y	0.00 (-0.01 to 0.00)
Female Sex	0.18 (0.00 to 0.37)
Weight, kg	0.00 (-0.01 to 0.00)
Concomitant antipsychotic drug use	0.29 (-0.02 to 0.64)
Concomitant medication other than antipsychotic drug	0.00 (-0.13 to 0.14)
Baseline cognitive function severity, ADAS-cog	0.00 (0.00 to 0.01)
Baseline global function severity, CDR-SB	-0.01 (-0.04 to 0.01)

ADAS-cog, Alzheimer's Disease Assessment Scale-Cognitive Subscale; CDR-SB, Clinical Dementia Rating Sum of Boxes. Heterogeneity (τ^2), 0.10 (95%CrI 0.00 to 0.27). Posterior estimates are reverting standardized covariates to original scale.

Supplementary Table 8. Estimated parameters from the individual participant data meta-analysis model regarding relative treatment effects (donepezil versus placebo) in all-cause dropout at 24 weeks (standardized covariate results)

Parameter	Posterior Estimates (95% Credible Interval)
Average treatment effect of donepezil	0.03 (-0.53 to 0.56)
Main Effects (Prognostic Factors)	
Age, y	0.19 (0.05 to 0.31)
Female Sex	-0.02 (-0.16 to 0.11)
Weight, kg	-0.07 (-0.21 to 0.08)
Concomitant antipsychotic drug use	0.04 (-0.07 to 0.15)
Concomitant medication other than antipsychotic drug	-0.05 (-0.18 to 0.07)
Baseline cognitive function severity, ADAS-cog	0.10 (-0.07 to 0.28)
Baseline global function severity, CDR-SB	0.22 (0.05 to 0.40)
Treatment-by-Covariate Interaction (Effect Modifiers)	
Age, y	0.04 (-0.06 to 0.20)
Female Sex	0.04 (-0.06 to 0.20)
Weight, kg	0.00 (-0.14 to 0.12)
Concomitant antipsychotic drug use	-0.02 (-0.15 to 0.08)
Concomitant medication other than antipsychotic drug	0.02 (-0.09 to 0.16)
Baseline cognitive function severity, ADAS-cog	-0.04 (-0.23 to 0.07)
Baseline global function severity, CDR-SB	-0.03 (-0.21 to 0.09)

ADAS-cog, Alzheimer's Disease Assessment Scale-Cognitive Subscale; CDR-SB, Clinical Dementia Rating Sum of Boxes. Estimates are in logit scale. Heterogeneity (τ^2), 0.58 (95%CrI 0.20 to 1.36).

Supplementary Table 9. Estimated parameters from the individual participant data meta-analysis model regarding relative treatment effects (donepezil versus placebo) in all-cause dropout at 24 weeks (reverting standardized covariates to original scale)

Parameter	Posterior Estimates (95% Credible Interval)
Average treatment effect of donepezil	-0.18 (-1.92 to 1.14)
Main Effects (Prognostic Factors)	
Age, y	0.02 (0.01 to 0.04)
Female Sex	-0.04 (-0.34 to 0.23)
Weight, kg	0.00 (-0.02 to 0.01)
Concomitant antipsychotic drug use	0.16 (-0.29 to 0.63)
Concomitant medication other than antipsychotic drug	-0.10 (-0.37 to 0.15)
Baseline cognitive function severity, ADAS-cog	0.01 (0.00 to 0.02)
Baseline global function severity, CDR-SB	0.06 (0.02 to 0.12)
Treatment-by-Covariate Interaction (Effect Modifiers)	
Age, y	0.00 (-0.01 to 0.02)
Female Sex	0.08 (-0.13 to 0.43)
Weight, kg	0.00 (-0.01 to 0.01)
Concomitant antipsychotic drug use	-0.07 (-0.62 to 0.33)
Concomitant medication other than antipsychotic drug	0.04 (-0.18 to 0.33)
Baseline cognitive function severity, ADAS-cog	0.00 (-0.01 to 0.00)
Baseline global function severity, CDR-SB	-0.01 (-0.06 to 0.03)

ADAS-cog, Alzheimer's Disease Assessment Scale-Cognitive Subscale; CDR-SB, Clinical Dementia Rating Sum of Boxes. Estimates are in logit scale. Heterogeneity (τ^2), 0.58 (95%CrI 0.20 to 1.36). Posterior estimates are reverting standardized covariates to original scale.

Supplementary Table 10. Comparison of Bayesian LASSO individual participant data meta-analysis model regarding relative treatment effect (donepezil versus placebo) between full dataset (eight studies) and five studies where Clinician's Interview-Based Impression of Severity Plus Caregiver Input (CIBIC-Plus) was not transformed, for CIBIC-Plus at 24 weeks

	5 studies Posterior Estimates (95% CrI)	8 studies* Posterior Estimates (95% CrI)
Average treatment effect	-0.33 (-0.47 to -0.19)	-0.42 (-0.54 to -0.30)
Main Effects (Prognostic Factors)		
Age, y	0.00 (-0.01 to 0.01)	0.00 (-0.01 to 0.01)
Female Sex	-0.05 (-0.23 to 0.11)	-0.05 (-0.20 to 0.09)
Weight, kg	0.00 (-0.00 to 0.00)	0.00 (0.00 to 0.01)
Concomitant antipsychotic drug use	-0.14 (-0.43 to 0.12)	-0.20 (-0.45 to 0.04)
Concomitant medication other than antipsychotic drug	-0.08 (-0.22 to 0.05)	0.01 (-0.11 to 0.14)
Baseline cognitive function severity, ADAS-cog	0.02 (0.01 to 0.02)	0.02 (0.01 to 0.02)
Baseline global function severity, CDR-SB	0.02 (-0.00 to 0.05)	-0.01 (-0.04 to 0.01)
Treatment-by-Covariate Interaction (Effect Modifiers)		
Age, y	0.00 (-0.01 to 0.01)	0.00 (-0.01 to 0.00)
Female Sex	0.12 (-0.02 to 0.36)	0.18 (0.00 to 0.37)
Weight, kg	0.00 (-0.01 to 0.01)	0.00 (-0.01 to 0.00)
Concomitant antipsychotic drug use	0.12 (-0.11 to 0.50)	0.29 (-0.02 to 0.64)
Concomitant medication other than antipsychotic drug	0.02 (-0.10 to 0.17)	0.00 (-0.13 to 0.14)
Baseline cognitive function severity, ADAS-cog	0.00 (-0.01 to 0.00)	0.00 (0.00 to 0.01)
Baseline global function severity, CDR-SB	0.00 (-0.02 to 0.02)	-0.01 (-0.04 to 0.01)

ADAS-cog, Alzheimer's Disease Assessment Scale-Cognitive Subscale; CDR-SB, Clinical Dementia Rating Sum of Boxes. *Note that 8 studies estimates are same as Table 4.

Supplementary Table 11. Search sources and search strategies (last searched on August 9th, 2021)

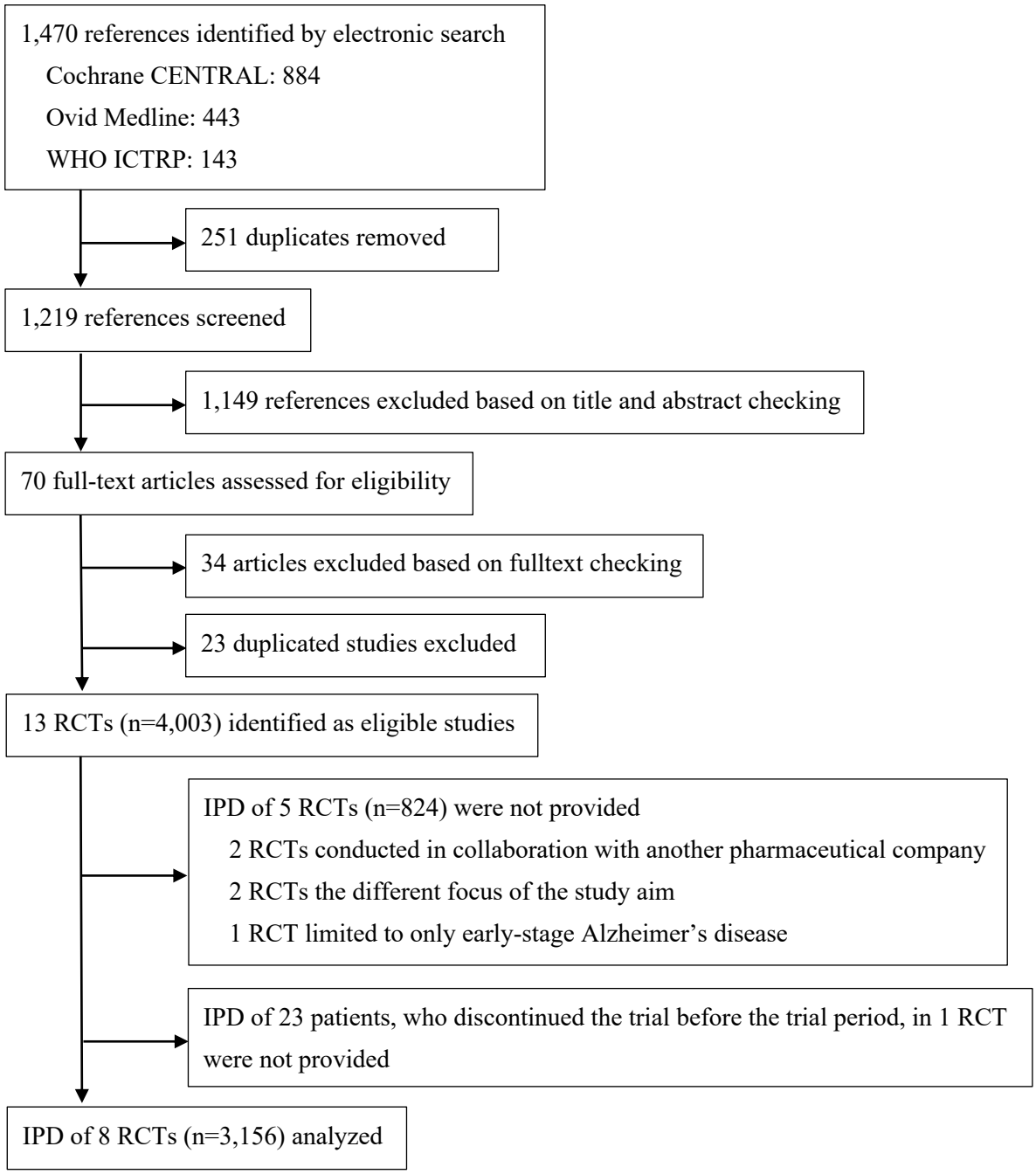
Source	Search strategy	Hits
Cochrane CENTRAL	**(**E2020 OR donepezil OR Aricept) AND (Alzheimer* OR dementia OR ((cognit* or memory* or mental*) and (declin* or impair* or los* or deteriorat*)) AND Placebo*	884
Medline (Ovid SP) Ovid Medline (R), In-Process & Other Non-Indexed Citations	1. donepezil.mp. 2. aricept*.mp. 3. donepezil.ti,ab 4. E2020 5. or/1-4 6. dement*.ti,ab 7. alzheimer*.ti,ab 8. exp Dementia 9. or/6-8 10. randomized controlled trial.pt. 11. controlled clinical trial.pt. 12. randomized.ab. 13. placebo.ab. 14. drug therapy.fs 15. randomly.ab. 16. trial.ab. 17. groups.ab. 18. or/10-17 19. 5 and 9 and 18 20. placebo*.ti,ab 21. 19 and 20	443
WHO ICTRP	(E2020 OR donepezil OR Aricept) AND (Alzheimer* OR dementia) AND Placebo*	143

Cochrane CENTRAL, Cochrane central register of controlled trial; WHO ICTRP, World Health Organization International Clinical Trials Registry Platform.

Supplementary Table 12. TRIPOD Checklist: Prediction Model Development and Validation

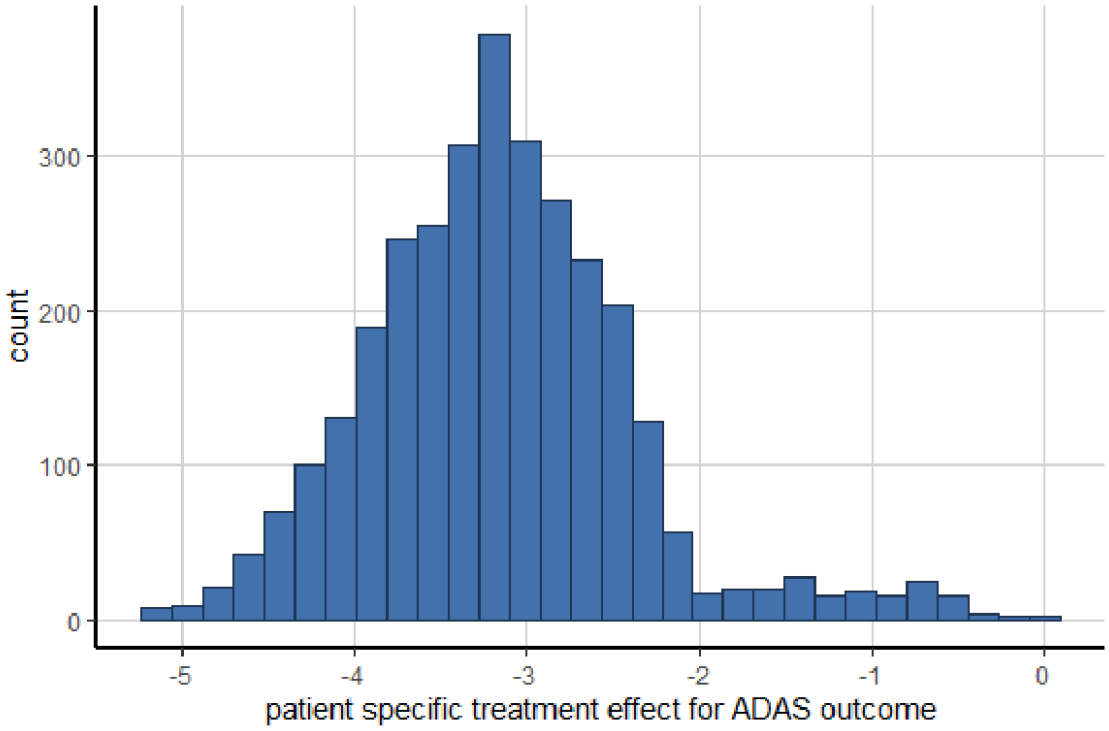
Section/Topic			Checklist Item	Page
Title and abstract				
Title	1	D;V	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.	1
Abstract	2	D;V	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	1
Introduction				
Background and objectives	3a	D;V	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	2, 3
	3b	D;V	Specify the objectives, including whether the study describes the development or validation of the model or both.	3
Methods				
Source of data	4a	D;V	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	3
	4b	D;V	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	3
Participants	5a	D;V	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centers.	3
	5b	D;V	Describe eligibility criteria for participants.	3
	5c	D;V	Give details of treatments received, if relevant.	3
Outcome	6a	D;V	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	3, 4
	6b	D;V	Report any actions to blind assessment of the outcome to be predicted.	3
Predictors	7a	D;V	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.	4
	7b	D;V	Report any actions to blind assessment of predictors for the outcome and other predictors.	3
Sample size	8	D;V	Explain how the study size was arrived at.	NA
Missing data	9	D;V	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	4, 5
Statistical analysis methods	10a	D	Describe how predictors were handled in the analyses.	5
	10b	D	Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.	5
	10c	V	For validation, describe how the predictions were calculated.	5
	10d	D;V	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	5
	10e	V	Describe any model updating (e.g., recalibration) arising from the validation, if done.	NA
Risk groups	11	D;V	Provide details on how risk groups were created, if done.	NA
Development versus validation	12	V	For validation, identify any differences from the development data in setting, eligibility criteria, outcome, and predictors.	3, 5
Results				
Participants	13a	D;V	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	5, 6, 8, 9
	13b	D;V	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	5-9
	13c	V	For validation, show a comparison with the development data of the distribution of important variables (demographics, predictors and outcome).	7
Model development	14a	D	Specify the number of participants and outcome events in each analysis.	NA
	14b	D	If done, report the unadjusted association between each candidate predictor and outcome.	NA
Model specification	15a	D	Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).	6, 8, 9
	15b	D	Explain how to the use the prediction model.	9-11
Model performance	16	D;V	Report performance measures (with CIs) for the prediction model.	6, 8, 9
Model-updating	17	V	If done, report the results from any model updating (i.e., model specification, model performance).	NA
Discussion				
Limitations	18	D;V	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	12
Interpretation	19a	V	For validation, discuss the results with reference to performance in the development data, and any other validation data.	12
	19b	D;V	Give an overall interpretation of the results, considering objectives, limitations, results from similar studies, and other relevant evidence.	11, 12
Implications	20	D;V	Discuss the potential clinical use of the model and implications for future research.	12, 13
Other information				
Supplementary information	21	D;V	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	9-13
Funding	22	D;V	Give the source of funding and the role of the funders for the present study.	13

TRIPOD, Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis; NA, Not applicable.

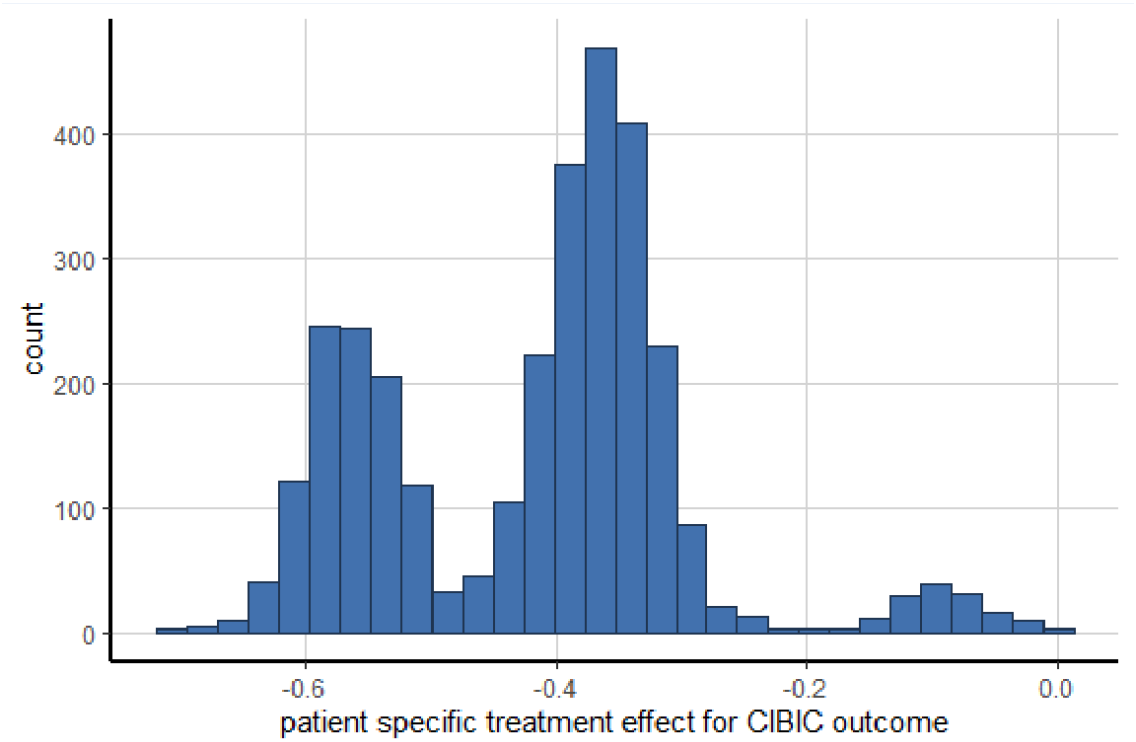


Supplementary Figure 1. PRISMA flow diagram for selection of studies

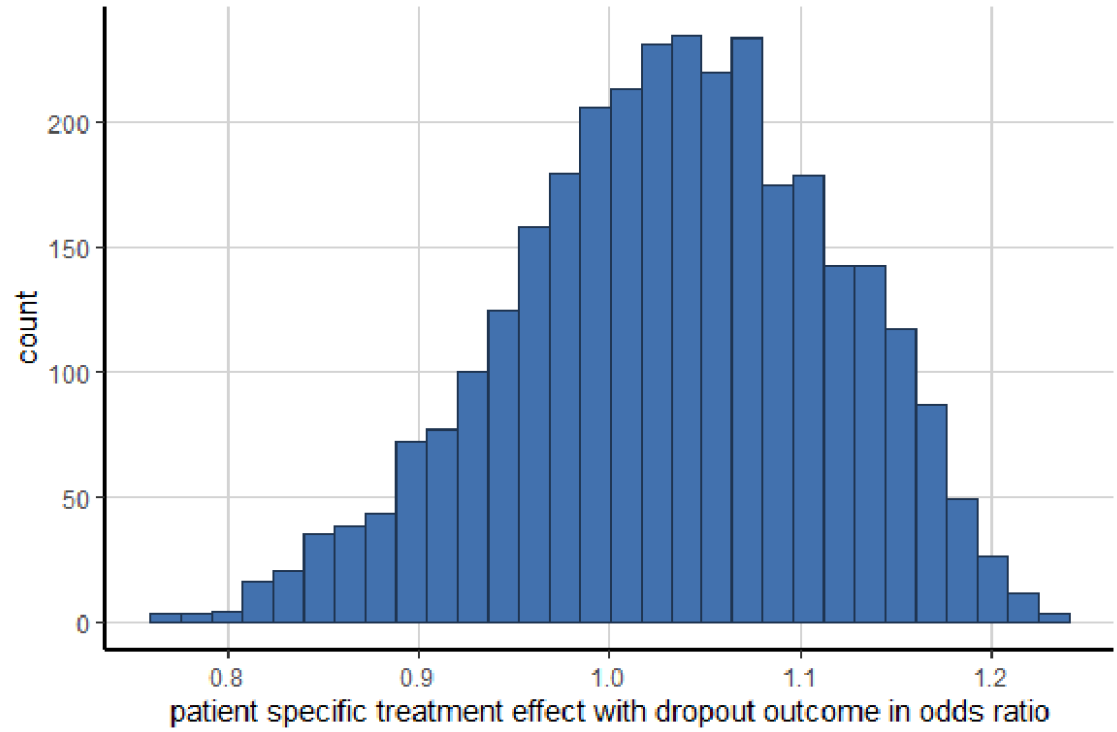
RCT, randomized controlled trial; IPD, individual participant data.



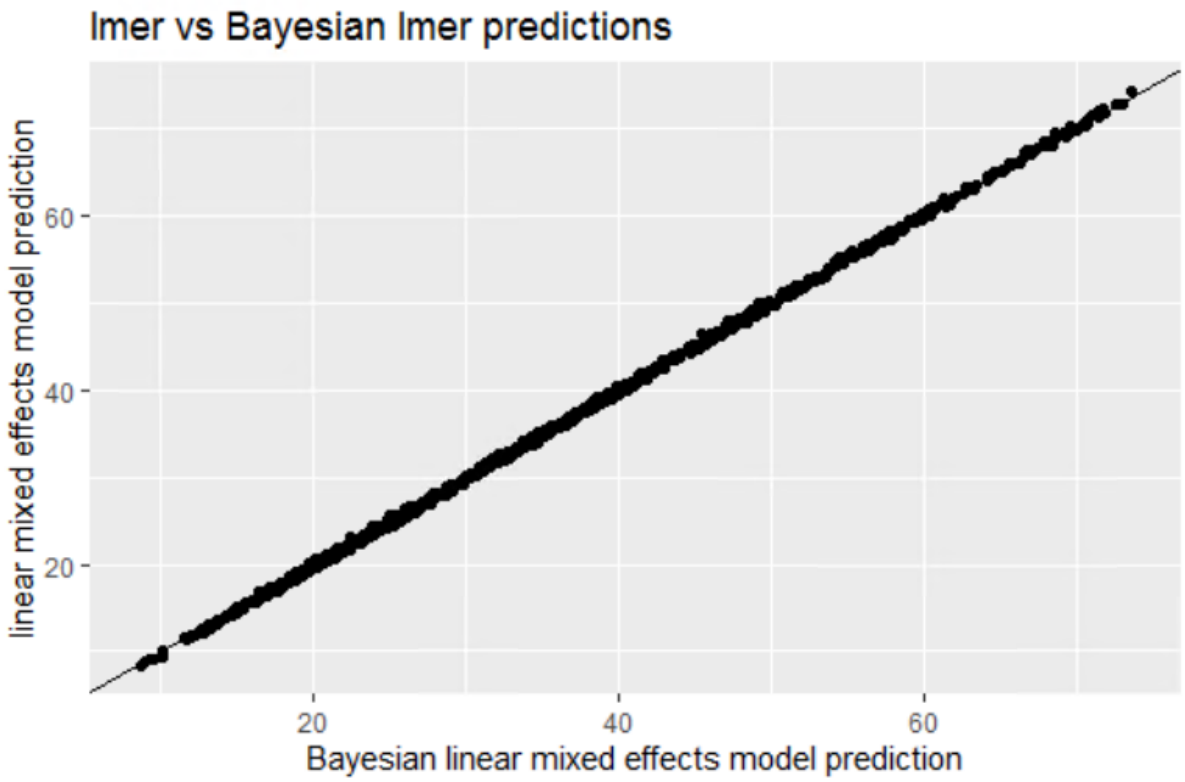
Supplementary Figure 2. Patient-specific treatment effect for Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-cog) outcome



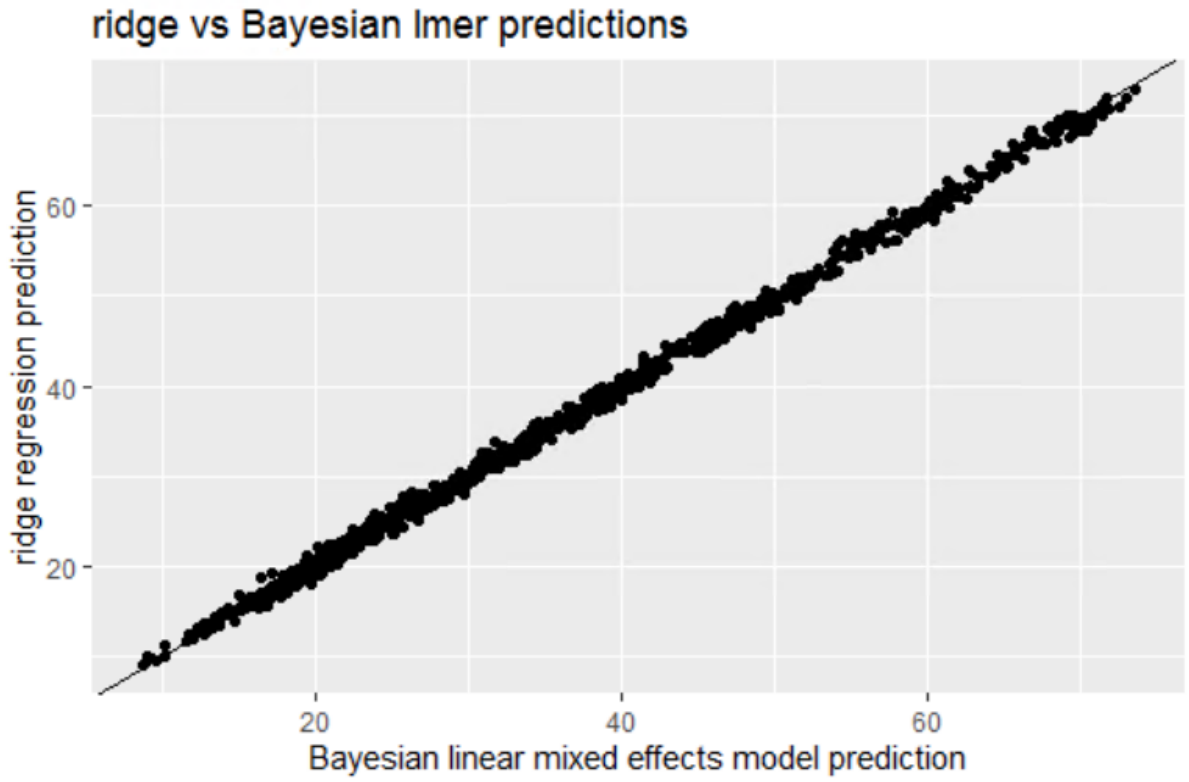
Supplementary Figure 3. Patient-specific treatment effect for Clinician's Interview-Based Impression of Change plus caregiver input (CIBIC-Plus) outcome



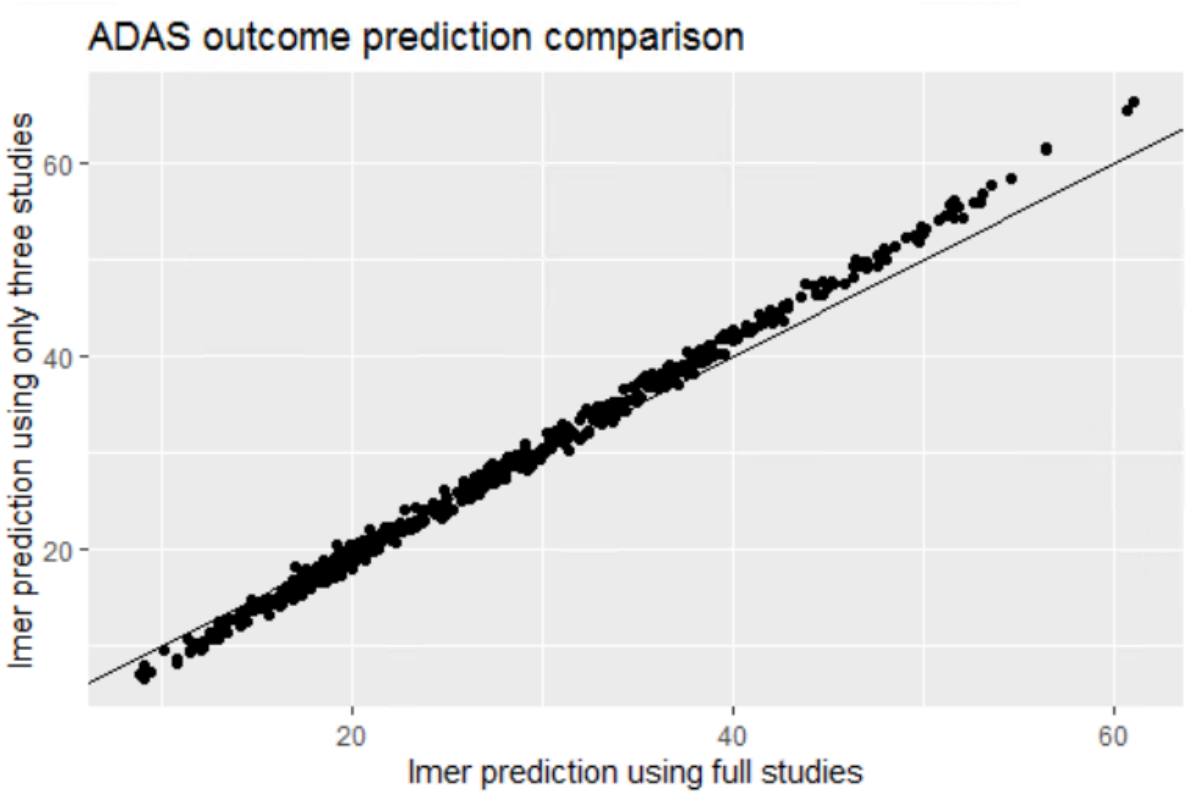
Supplementary Figure 4. Patient-specific treatment effect for all-cause dropout outcome in odds ratios



Supplementary Figure 5. Comparison between Bayesian linear mixed-effects model prediction and frequentist linear mixed-effects model prediction for placebo response in Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-cog) at 24 weeks



Supplementary Figure 6. Comparison between Bayesian linear mixed-effects model prediction and ridge regression model prediction for placebo response in Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-cog) at 24 weeks



Supplementary Figure 7. Comparison between linear mixed-effects model prediction using full dataset (eight studies) and linear mixed-effects model prediction using only three studies where Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-cog) was not transformed, for placebo response in ADAS-cog at 24 weeks

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