

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)

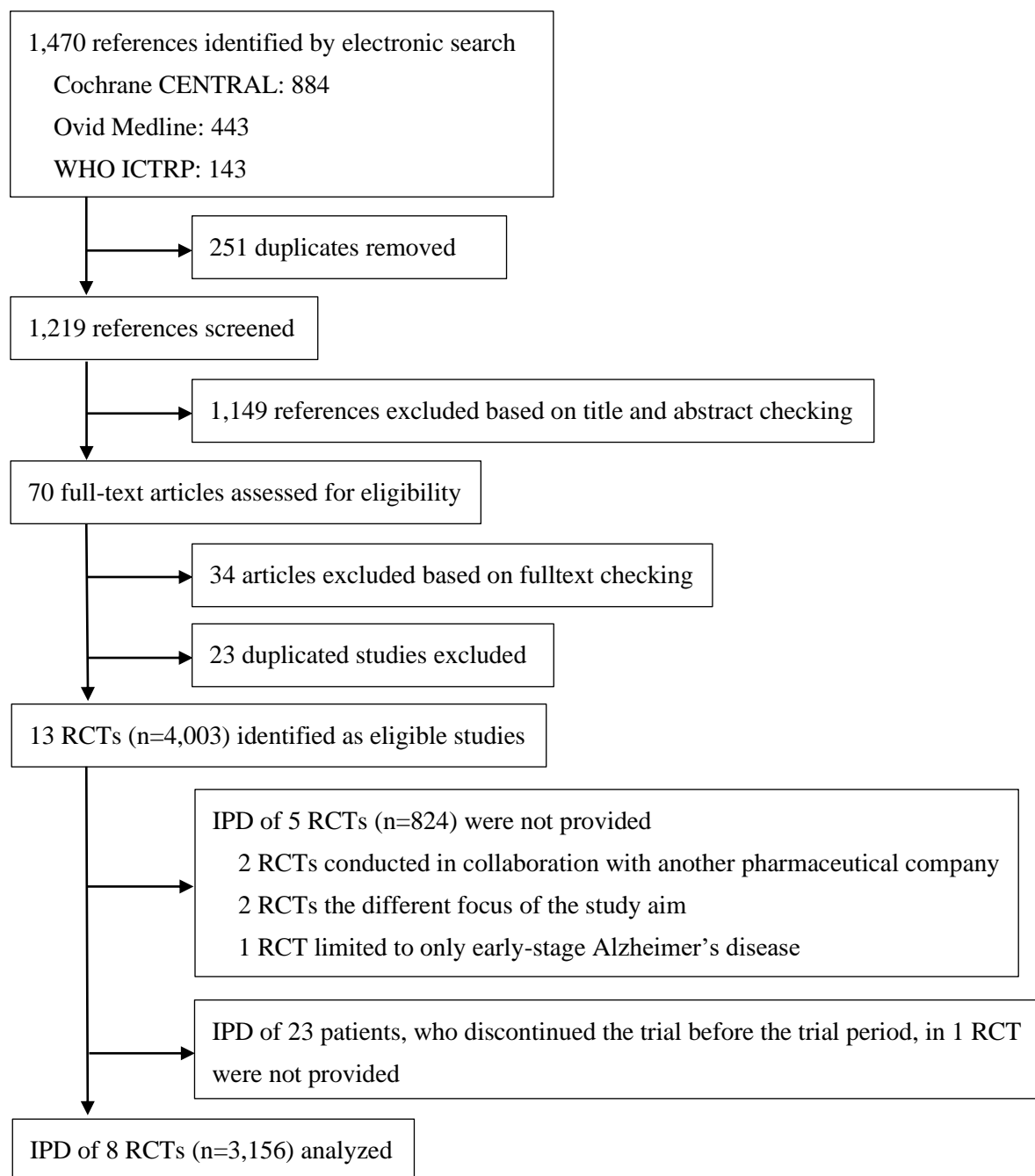
Source	Search strategy	Hits
Cochrane CENTRAL	(E2020 OR donepezil OR Aricept) AND (Alzheimer* OR dementia OR ((cognit* or memory* or mental*) and (declin* or impair* or los* or deteriorat*)) AND Placebo*	884
Medline (Ovid SP) Ovid Medline (R), In-Process & Other Non-Indexed Citations	1. donepezil.mp. 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.

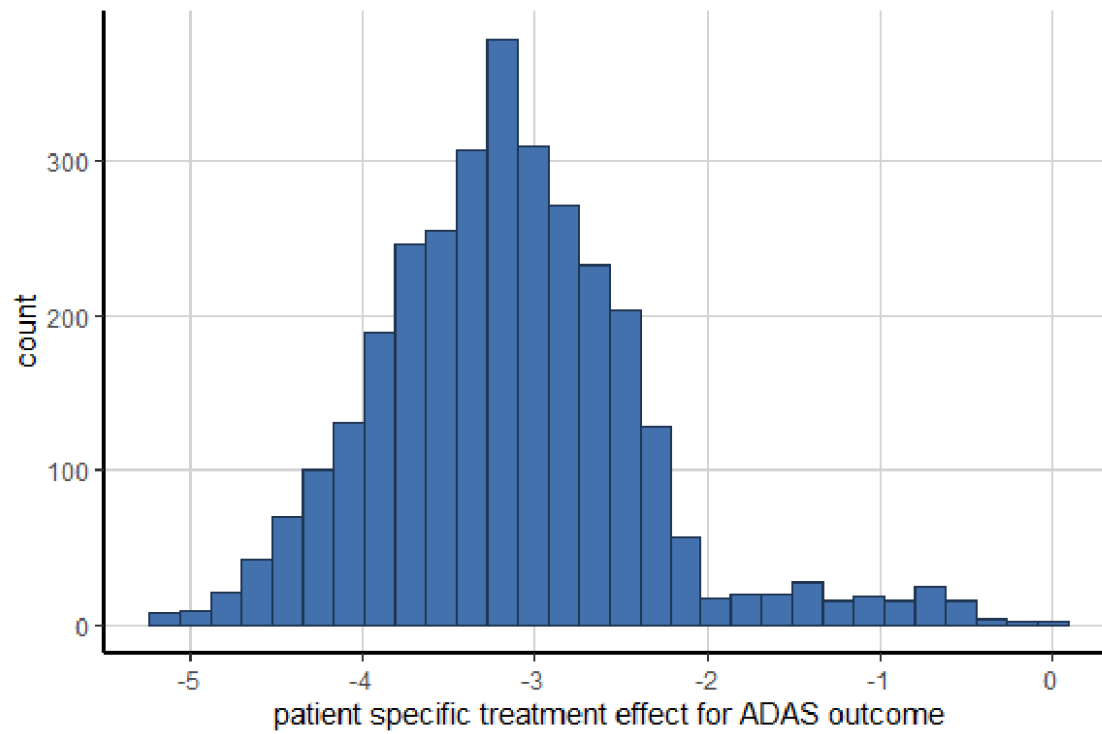
Supplementary Table 12. TRIPOD Checklist: Prediction Model Development and Validation

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.	3
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.	6, 7
	3b	D;V	Specify the objectives, including whether the study describes the development or validation of the model or both.	7
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.	8
	4b	D;V	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	8
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.	8
	5b	D;V	Describe eligibility criteria for participants.	8
	5c	D;V	Give details of treatments received, if relevant.	8
Outcome	6a	D;V	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	9, 10
	6b	D;V	Report any actions to blind assessment of the outcome to be predicted.	8
Predictors	7a	D;V	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.	11, 12
	7b	D;V	Report any actions to blind assessment of predictors for the outcome and other predictors.	8
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.	12, 13
Statistical analysis methods	10a	D	Describe how predictors were handled in the analyses.	13
	10b	D	Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.	13
	10c	V	For validation, describe how the predictions were calculated.	13
	10d	D;V	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	13
	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.	8, 13
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.	16-19
	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.	12, 16-19, 36
	13c	V	For validation, show a comparison with the development data of the distribution of important variables (demographics, predictors and outcome).	36
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).	17-20, 37
	15b	D	Explain how to the use the prediction model.	21, 40, 41
Model performance	16	D;V	Report performance measures (with CIs) for the prediction model.	17, 19, 20
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).	24, 25
Interpretation	19a	V	For validation, discuss the results with reference to performance in the development data, and any other validation data.	26
	19b	D;V	Give an overall interpretation of the results, considering objectives, limitations, results from similar studies, and other relevant evidence.	22-24
Implications	20	D;V	Discuss the potential clinical use of the model and implications for future research.	25, 26
Other information				
Supplementary information	21	D;V	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	21, 26, 29, 40, 41
Funding	22	D;V	Give the source of funding and the role of the funders for the present study.	28

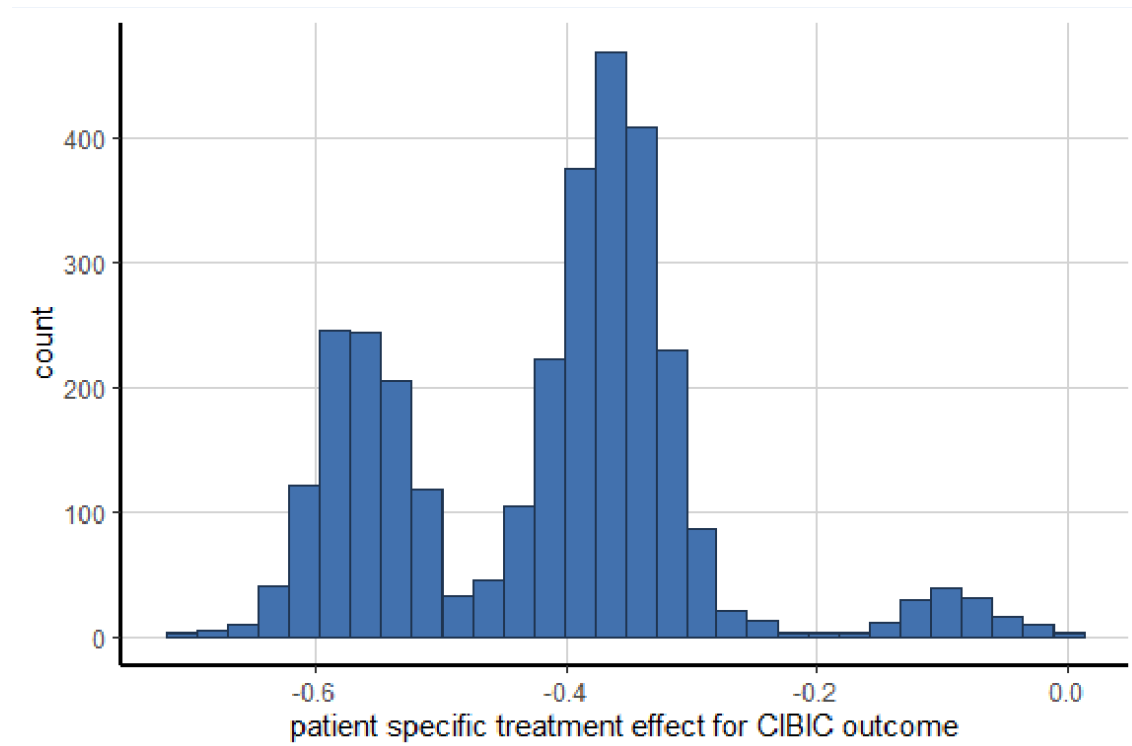
TRIPOD, Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis; NA, Not applicable.



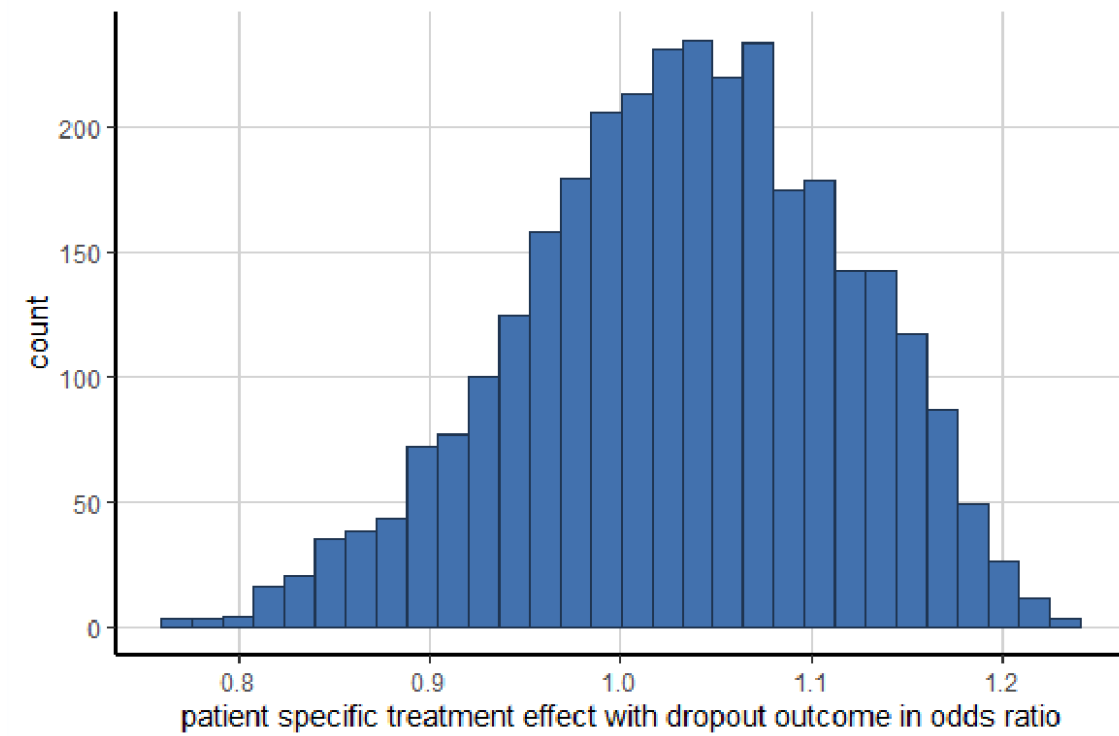
Supplementary Figure 1. PRISMA flow diagram for selection of studies
RCT, randomized controlled trial; IPD, individual participant data.



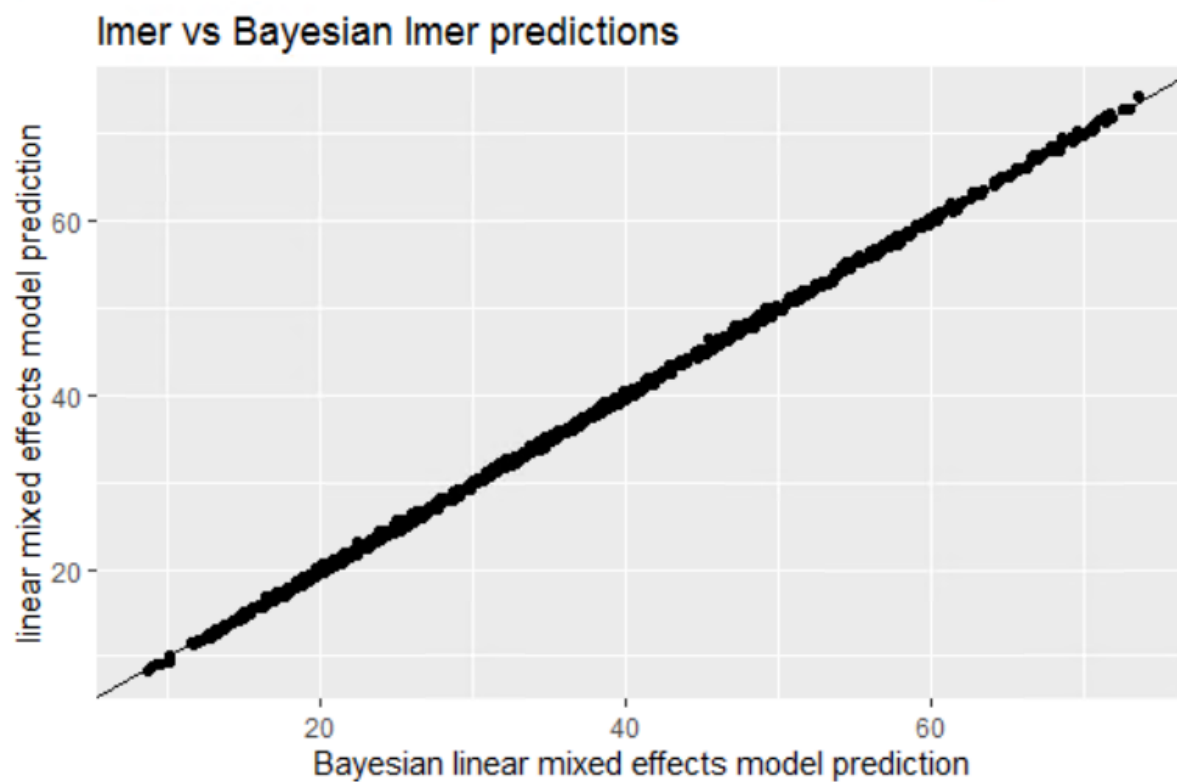
Supplementary Figure 2. Patient-specific treatment effect for Alzheimer’s Disease Assessment Scale-Cognitive Subscale (ADAS-cog) outcome



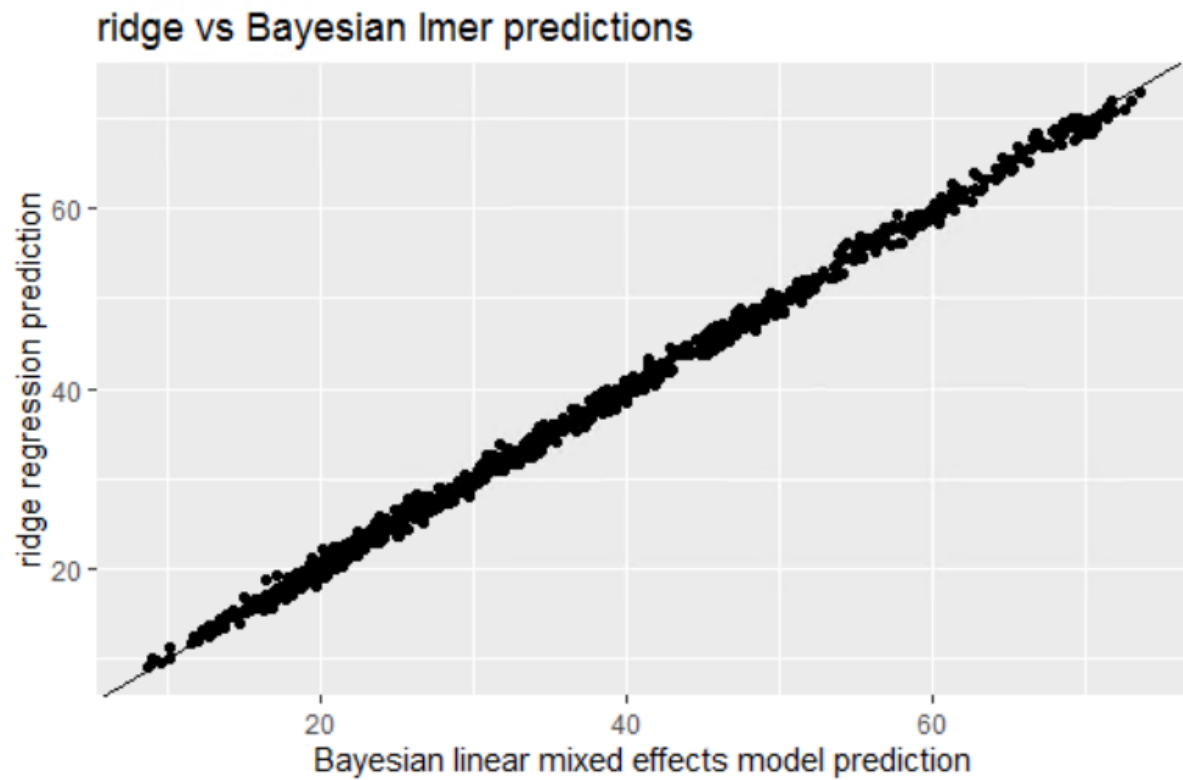
Supplementary Figure 3. Patient-specific treatment effect for Clinician's Interview-Based Impression of Change plus caregiver input (CIBIC-Plus) outcome



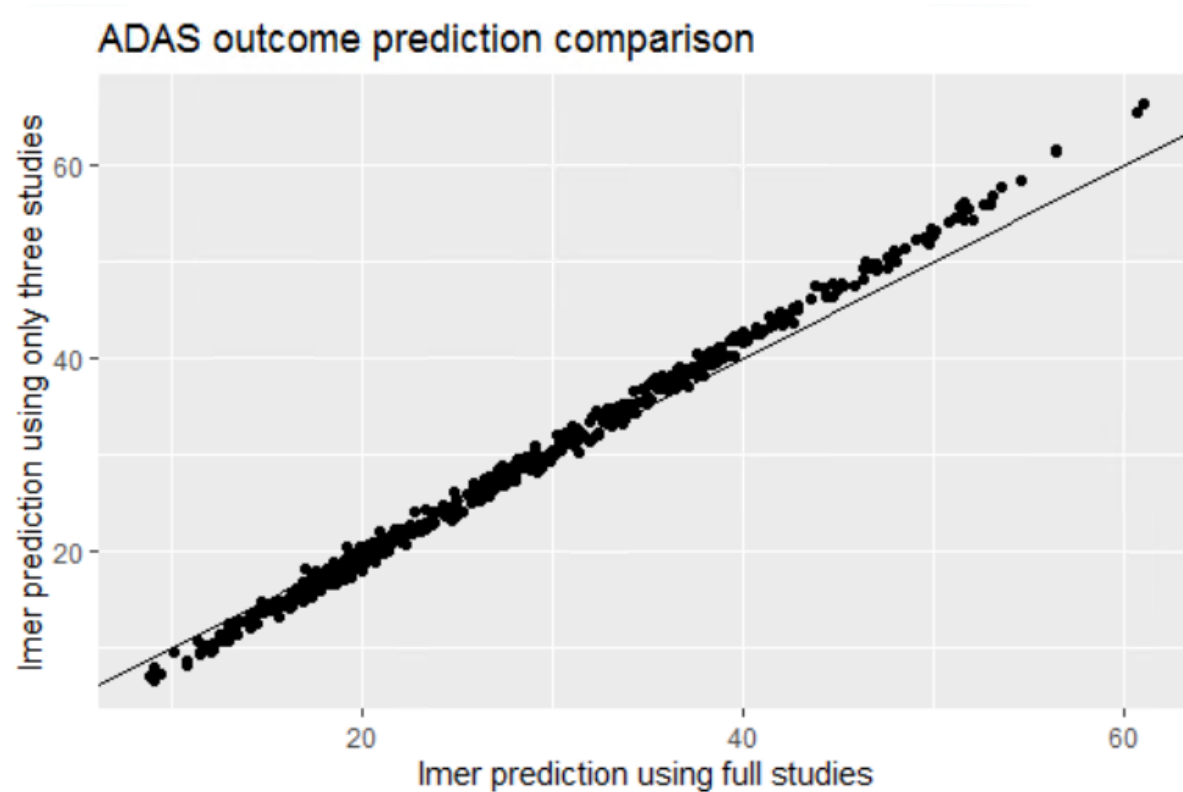
Supplementary Figure 4. Patient-specific treatment effect for all-cause dropout outcome in odds ratios



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

REFERENCES

- [1] Homma A, Takeda M, Imai Y, Uda F, Hasegawa K, Kameyama M, Nishimura T (2000) Clinical efficacy and safety of donepezil on cognitive and global function in patients with Alzheimer's disease: a 24-week, multicenter, double-blind, placebo-controlled study in Japan. *Dement Geriatr Cogn Disord* **11**, 299-313.
- [2] Rogers SL, Farlow MR, Doody RS, Mohs R, Friedhoff LT (1998) A 24-week, double-blind, placebo-controlled trial of donepezil in patients with Alzheimer's disease. *Neurology* **50**, 291-298.
- [3] Burns A, Rossor M, Hecker J, Gauthier S, Petit H, Möller HJ, Rogers SL, Friedhoff LT (1999) The effects of donepezil in Alzheimer's disease - results from a multinational trial. *Dement Geriatr Cogn Disord* **10**, 237-244.
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- [6] Tariot PN, Cummings JL, I R Katz JM, Perdomo CA, Schwam EM, Whalen E (2001) A randomized, double-blind, placebo-controlled study of the efficacy and safety of donepezil in patients with Alzheimer's disease in the nursing home setting. *J Am Geriatr Soc* **49**, 1590-1599.

- [7] Mohs RC, Doody RS, Morris JC, Ieni JR, Rogers SL, Perdomo CA, Pratt RD (2001) A 1-year, placebo-controlled preservation of function survival study of donepezil in AD patients. *Neurology* **57**, 481-488.
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