Supplementary Material

The Dose and Duration-dependent Association between Melatonin Treatment and Overall Cognition in Alzheimer's Dementia: A Network Meta-Analysis of Randomized Placebo-Controlled Trials

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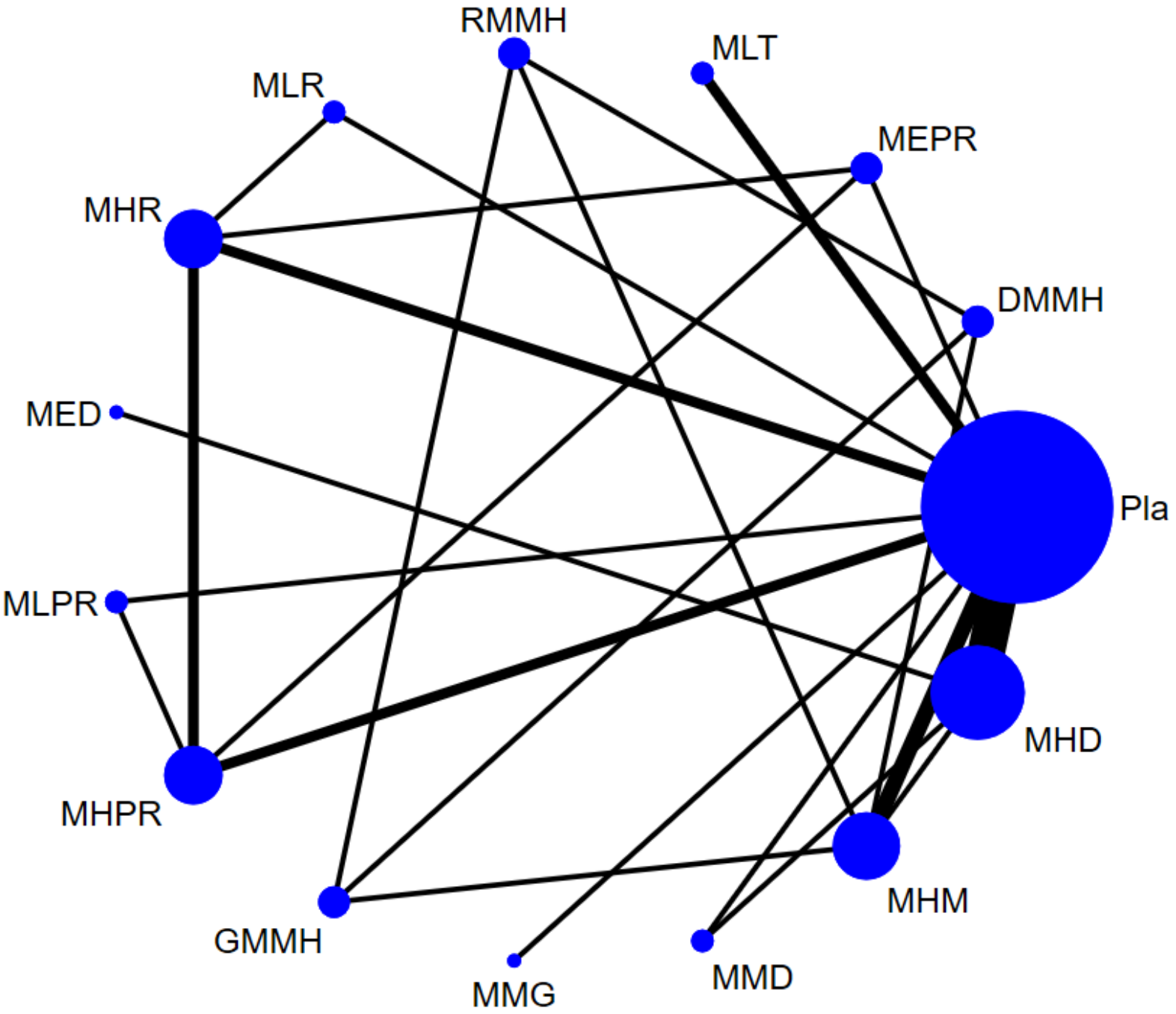
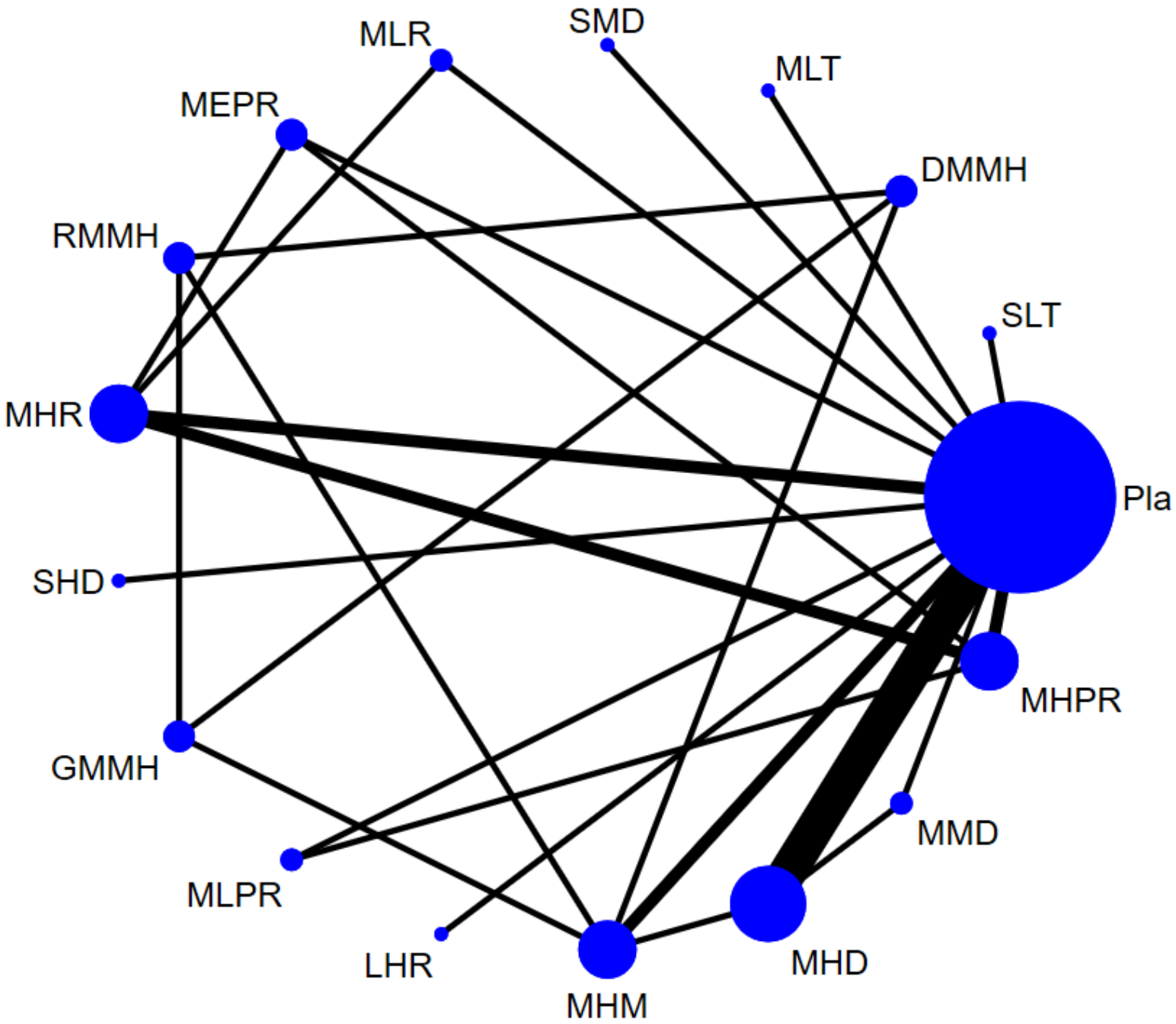
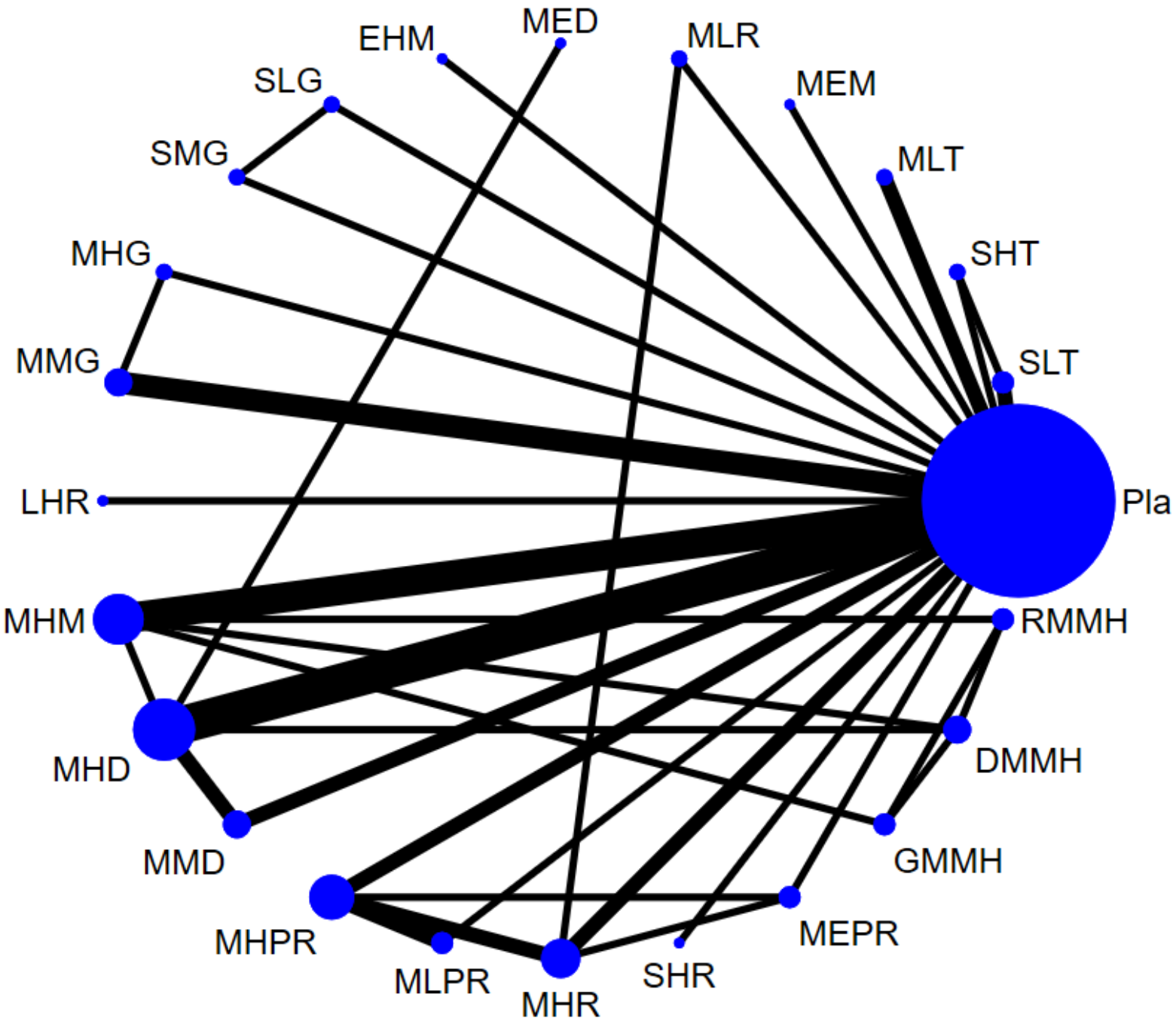


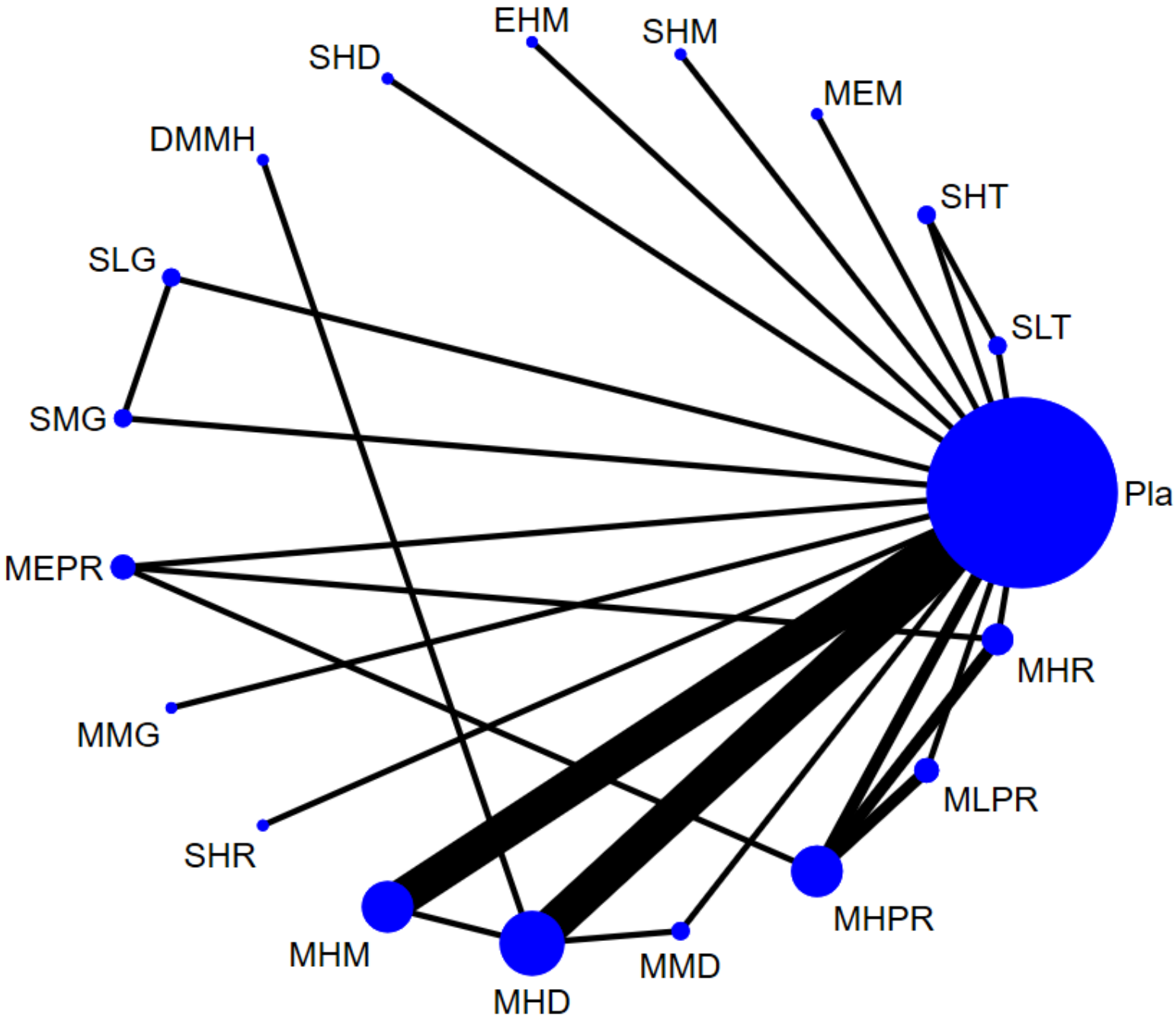
eFigure 1A network structure of NMA of cognition change: subgroup of medium-term treatment duration



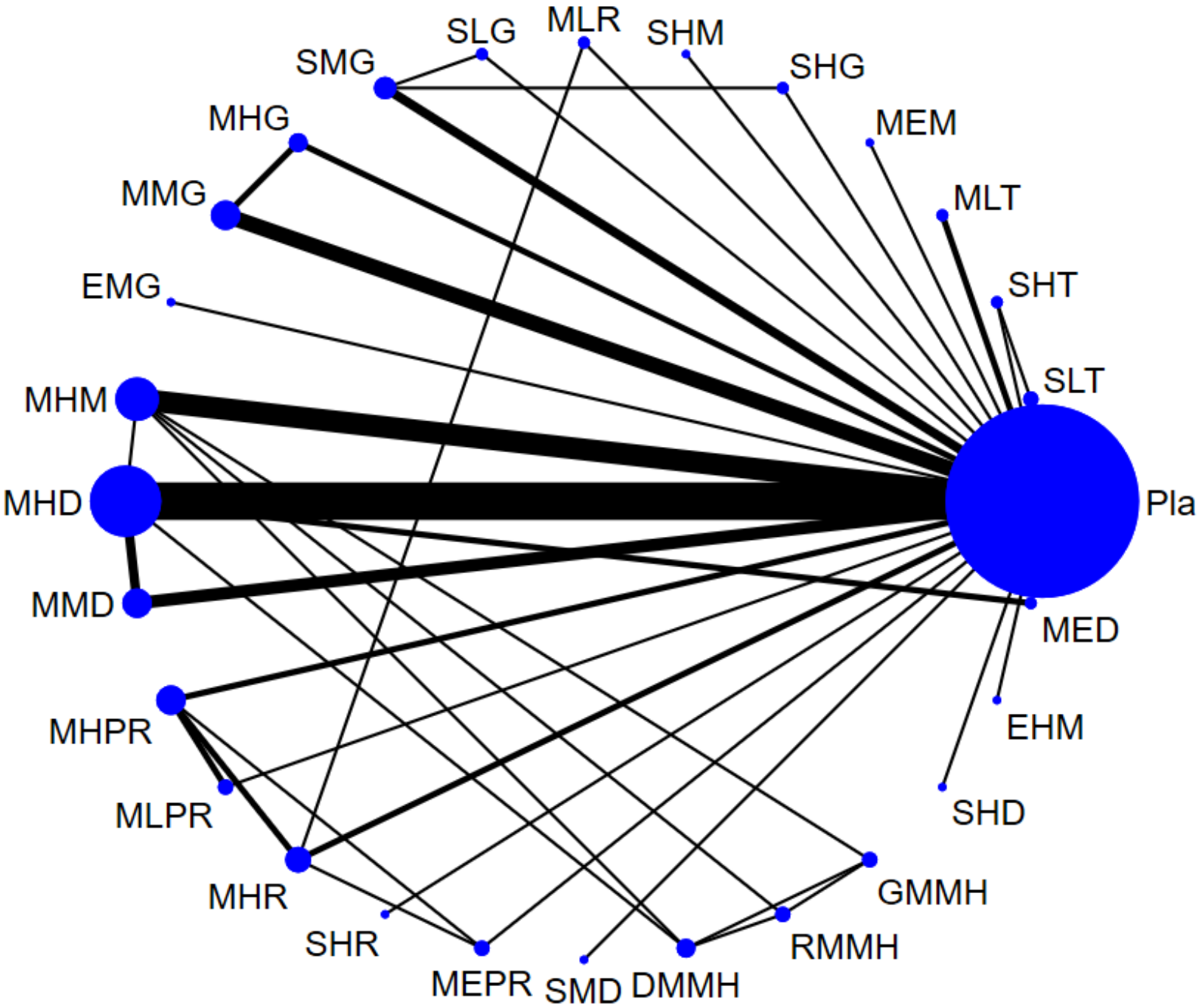
eFigure 1B network structure of NMA of cognition change: subgroup of exclude concomitant Mx



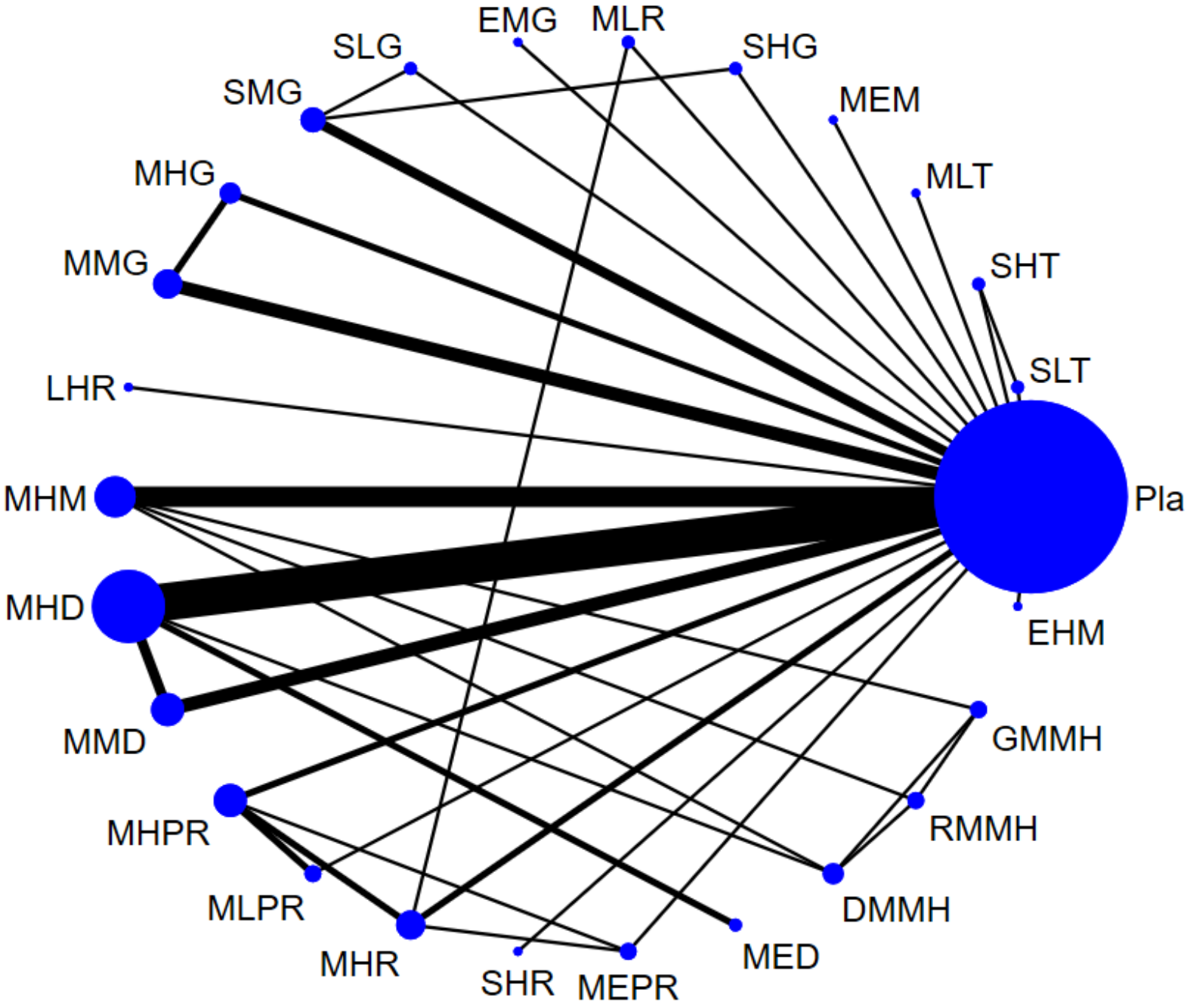
eFigure 1C network structure of NMA of quality of life change



eFigure 1D network structure of NMA of changes of behavioral disturbance



eFigure 1E network structure of NMA of drop-out rate

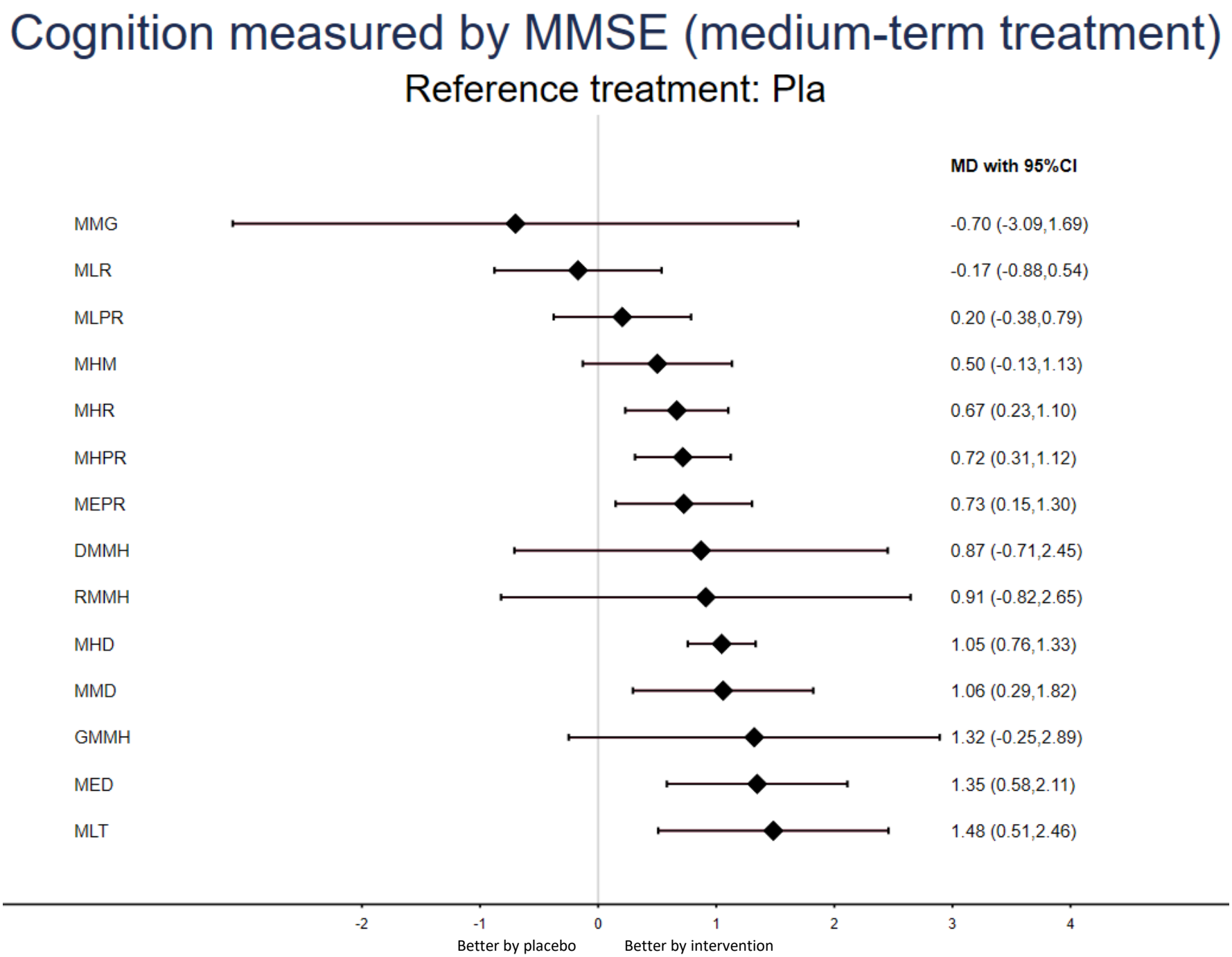


eFigure 1F network structure of NMA of rate of any adverse event reported

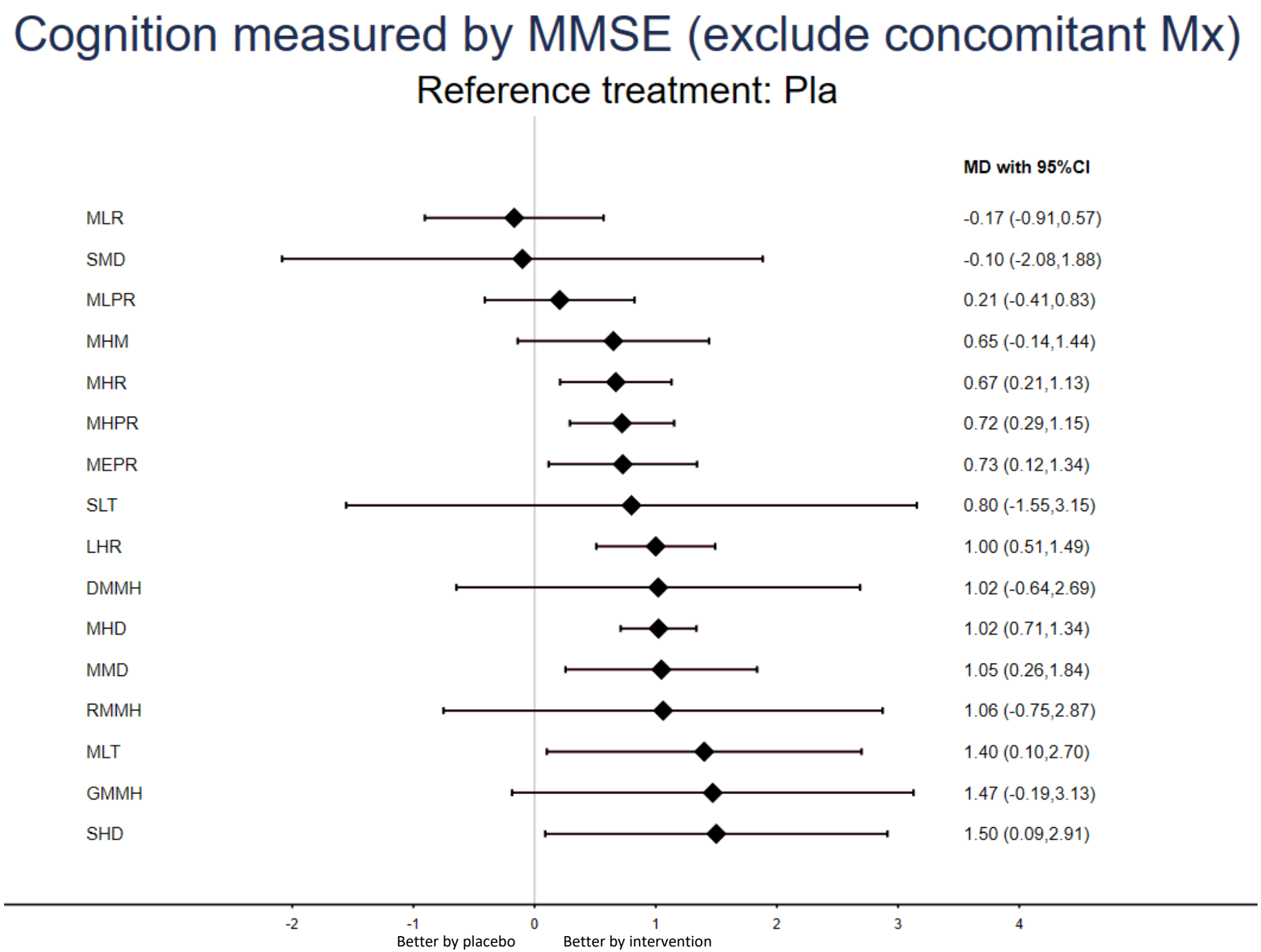
Figure legend of eFigure 1A-1F

The lines between nodes represent direct comparisons in various trials, and the size of each circle is proportional to the size of the population involved in each specific treatment. The thickness of the lines is proportional to the number of trials connected to the network.

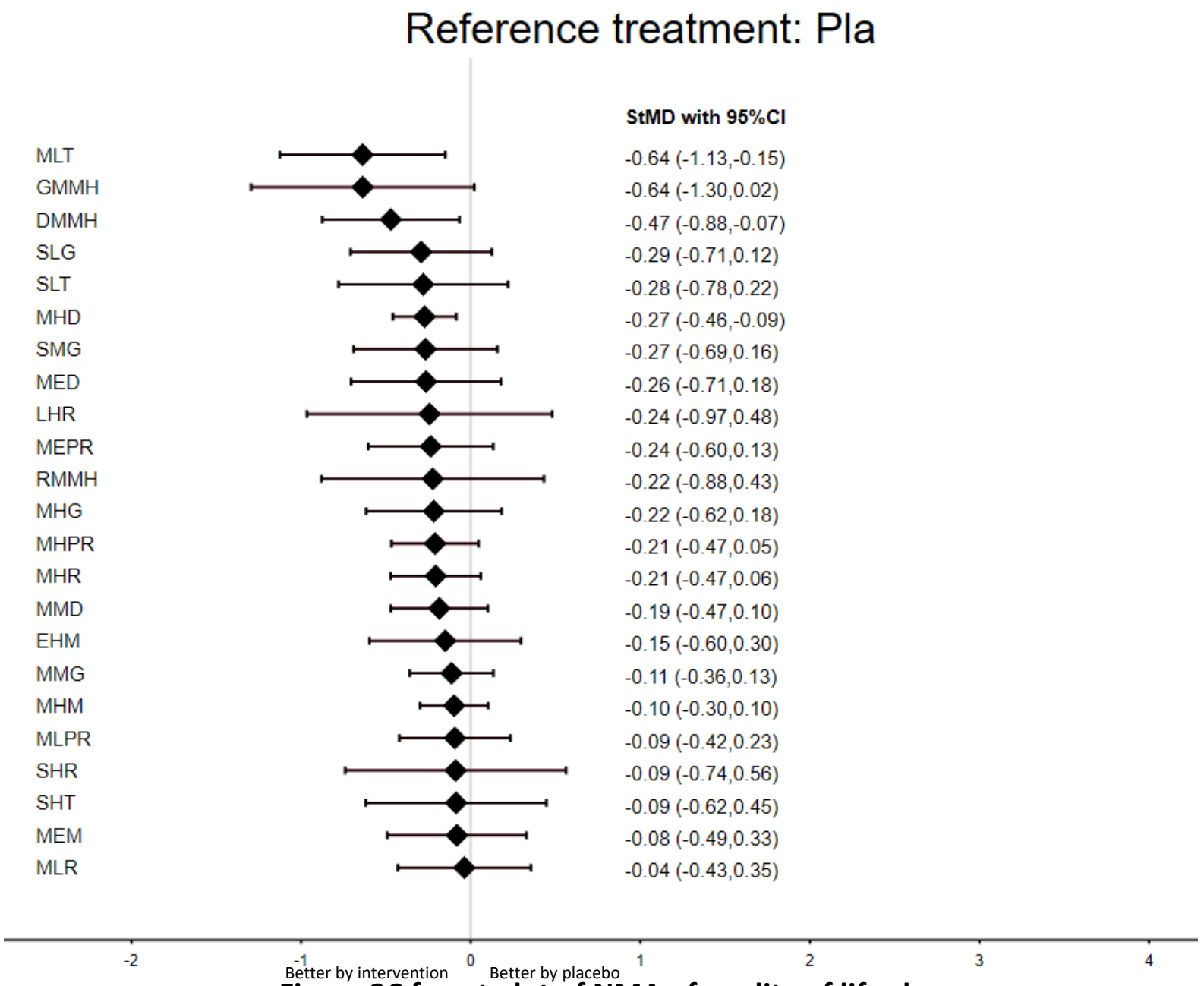
Abbreviation: CI: confidence interval; DMMH: medium-term high dose memantine plus high dose donepezil; EHM: extreme-long-term high dose memantine; EMG: extreme-long-term medium dose galantamine; ES: effect size; GMMH: medium-term high dose memantine plus low dose galantamine; LHR: long-term high dose rivastigmine; LLT: long-term low dose melatonin; MA: meta-analysis; MD: mean difference; MED: medium-term extreme high dose donepezil; MEM: medium-term extreme high dose memantine; MEPR: medium-term extreme high dose rivastigmine patch; MHD: medium-term high dose donepezil; MHG: medium-term high dose galantamine; MHM: medium-term high dose memantine; MHPR: medium-term high dose rivastigmine patch; MHR: medium-term high dose rivastigmine; MLPR: medium-term low dose rivastigmine patch; MLR: medium-term low dose rivastigmine; MLT: medium-term low dose melatonin; MMD: medium-term donepezil medium dose; MMG: medium-term medium dose galantamine; MMSE: mini-mental status examination; NMA: network meta-analysis; OR: odds ratio; Pla: Placebo; PRISMA: preferred reporting items for systematic reviews and meta-analyses; RCT: randomized controlled trial; RMMH: medium-term high dose memantine plus medium dose rivastigmine; SHD: short-term high dose donepezil; SHG: short-term high dose galantamine; SHM: short-term high dose memantine; SHR: short-term high dose rivastigmine; SHT: short-term high dose melatonin; SLG: short-term low dose galantamine; SLT: short-term low dose melatonin; SMD: short-term medium dose donepezil; SMG: short-term medium dose galantamine; SMT: short-term medium dose melatonin; StMD: standardized mean difference; SUCRA: surface under the cumulative ranking curve



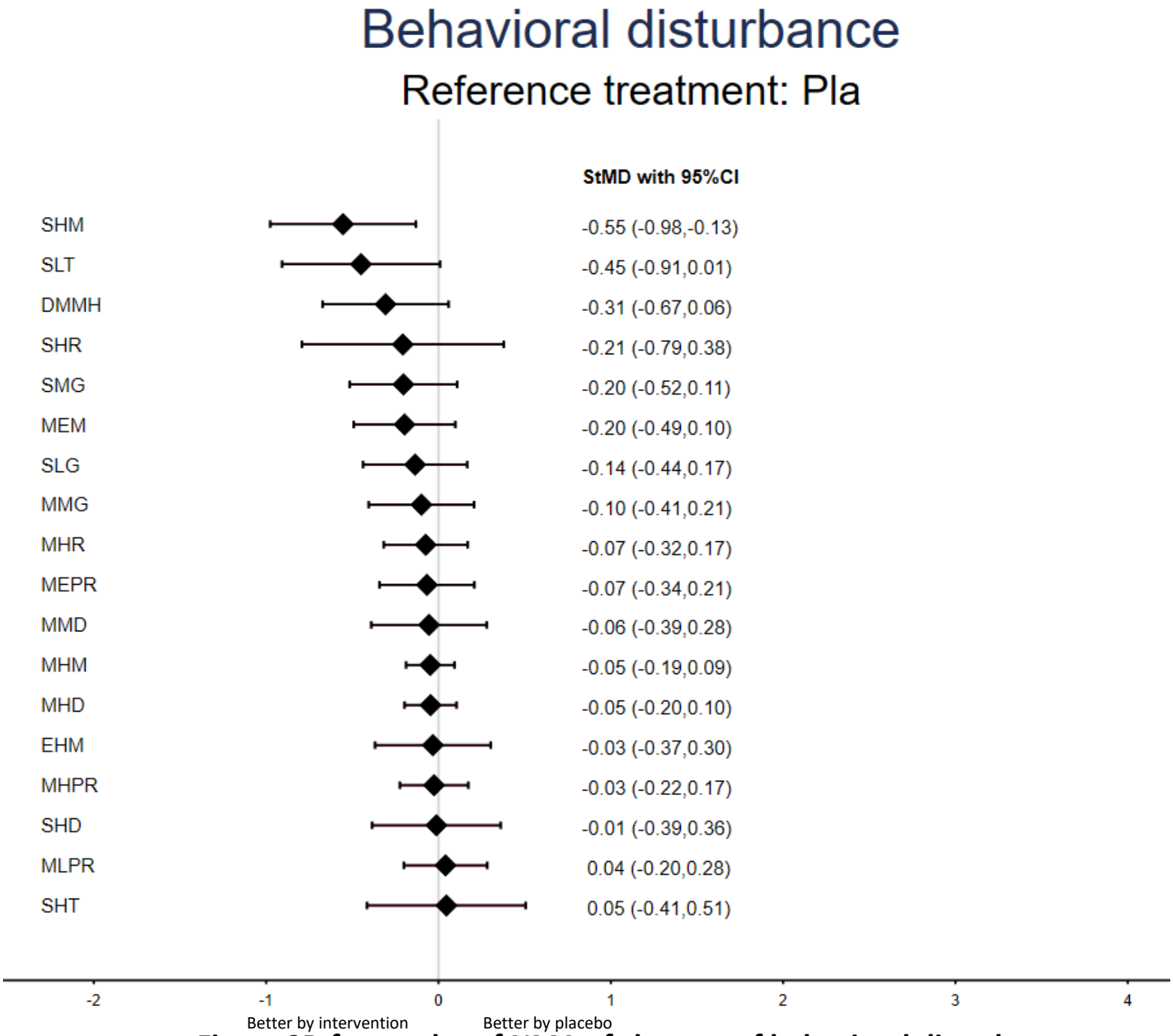
eFigure 2A forest plot of NMA of cognition change: subgroup of medium-term treatment duration



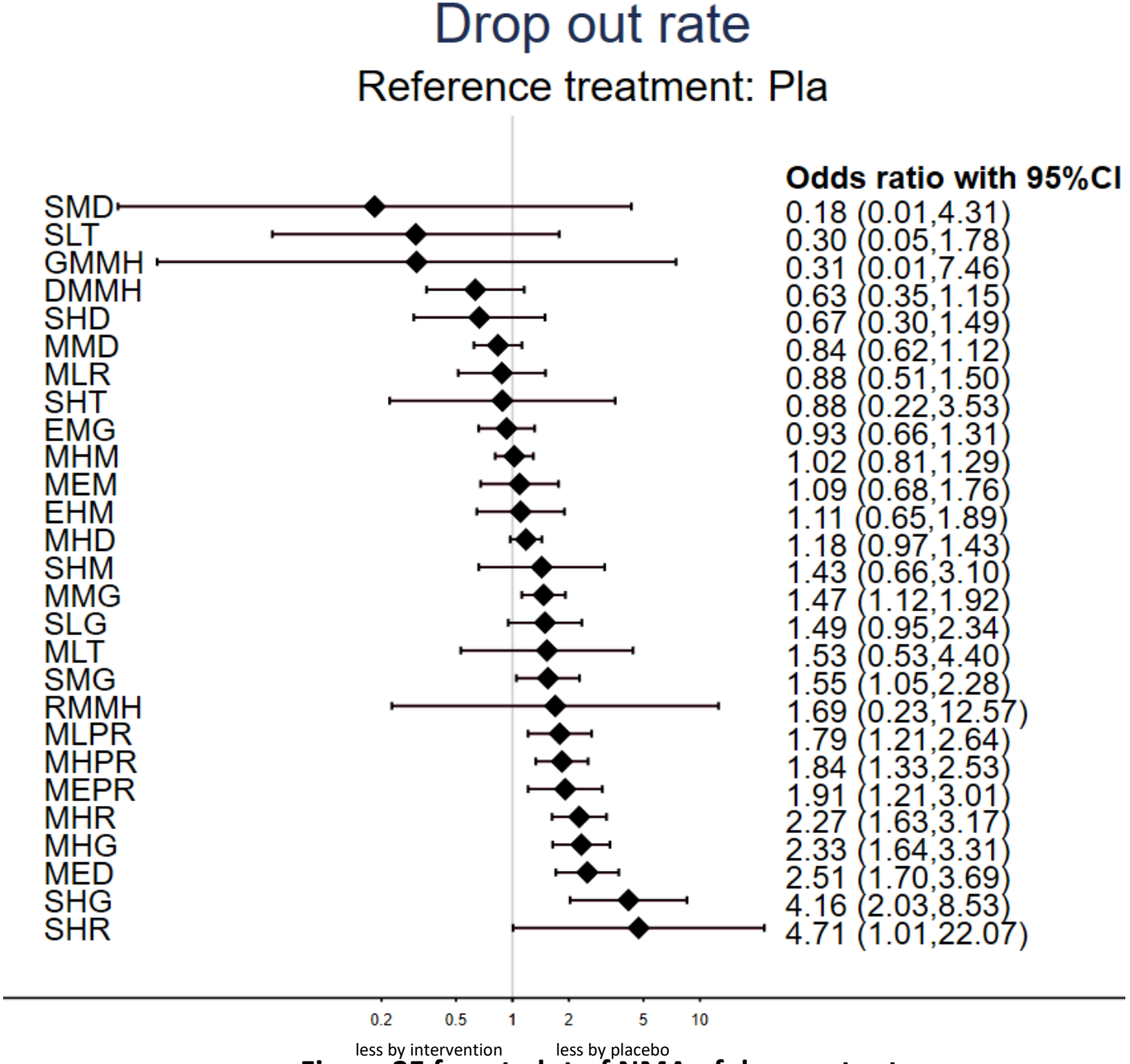
eFigure 2B forest plot of NMA of cognition change: subgroup of exclude concomitant Mx



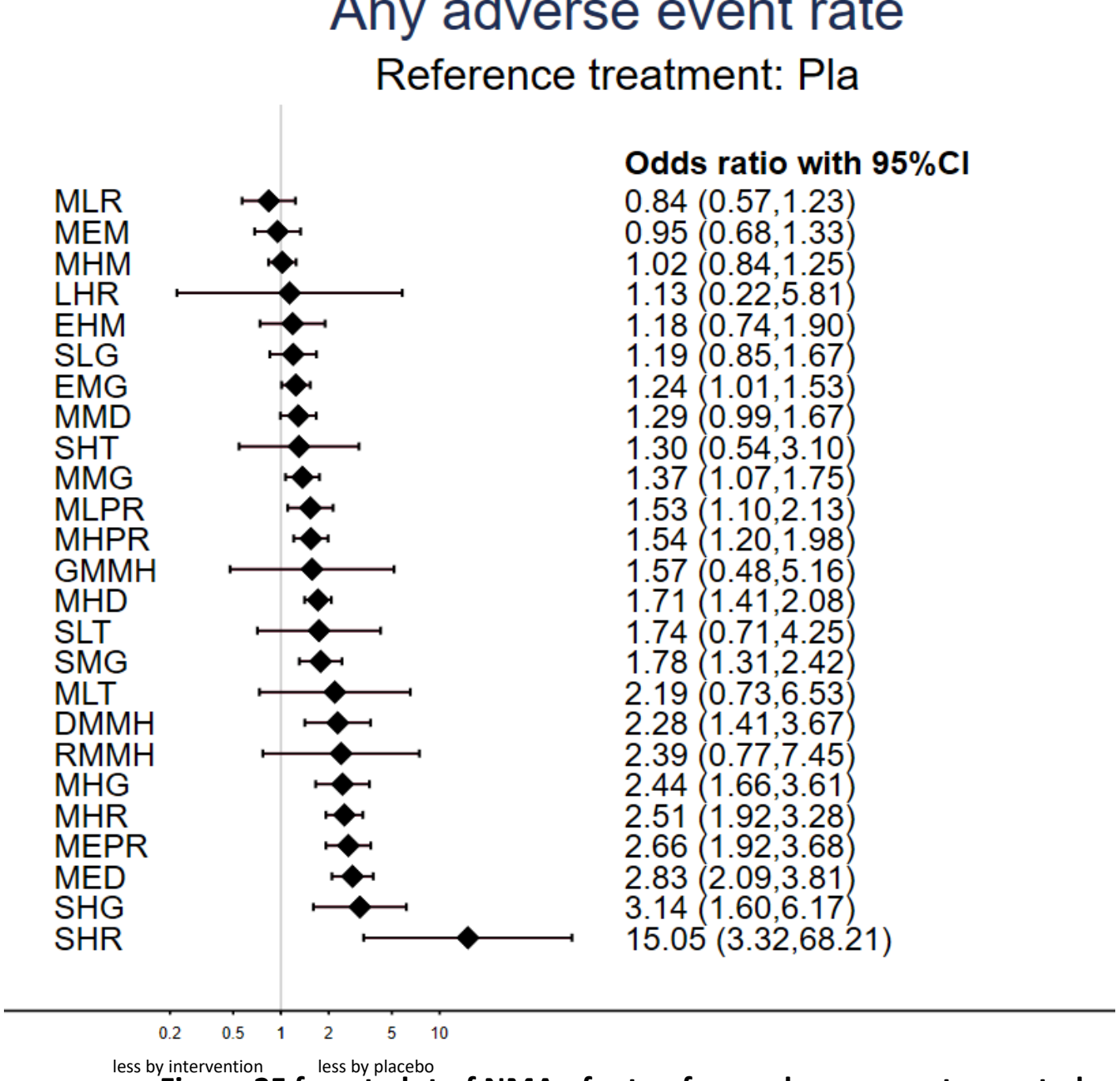
eFigure 2C forest plot of NMA of quality of life change



eFigure 2D forest plot of NMA of changes of behavioral disturbance



eFigure 2E forest plot of NMA of drop-out rate

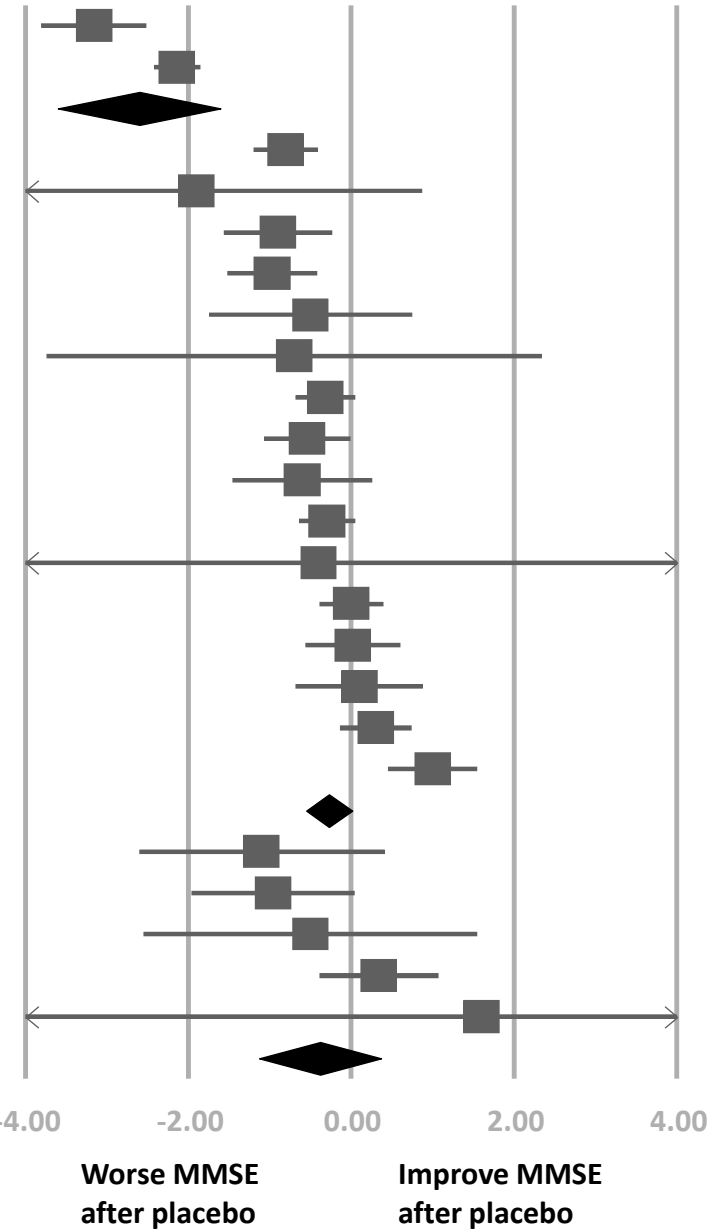


eFigure 2F forest plot of NMA of rate of any adverse event reported

Figure legend of eFigure 2A-2F

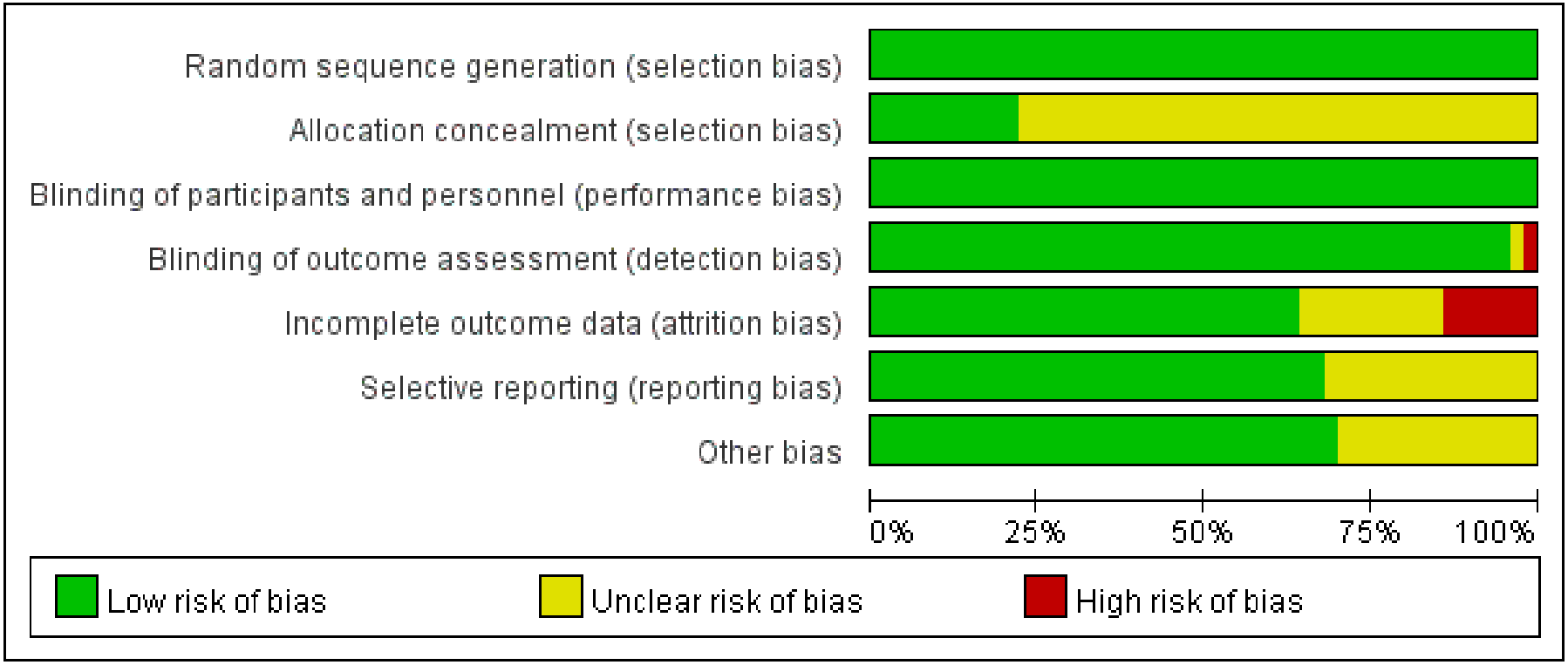
Abbreviation: CI: confidence interval; DMMH: medium-term high dose memantine plus high dose donepezil; EHM: extreme-long-term high dose memantine; EMG: extreme-long-term medium dose galantamine; ES: effect size; GMMH: medium-term high dose memantine plus low dose galantamine; LHR: long-term high dose rivastigmine; LLT: long-term low dose melatonin; MA: meta-analysis; MD: mean difference; MED: medium-term extreme high dose donepezil; MEM: medium-term extreme high dose memantine; MEPR: medium-term extreme high dose rivastigmine patch; MHD: medium-term high dose donepezil; MHG: medium-term high dose galantamine; MHM: medium-term high dose memantine; MHPR: medium-term high dose rivastigmine patch; MHR: medium-term high dose rivastigmine; MLPR: medium-term low dose rivastigmine patch; MLR: medium-term low dose rivastigmine; MLT: medium-term low dose melatonin; MMD: medium-term donepezil medium dose; MMG: medium-term medium dose galantamine; MMSE: mini-mental status examination; NMA: network meta-analysis; OR: odds ratio; Pla: Placebo; PRISMA: preferred reporting items for systematic reviews and meta-analyses; RCT: randomized controlled trial; RMMH: medium-term high dose memantine plus medium dose rivastigmine; SHD: short-term high dose donepezil; SHG: short-term high dose galantamine; SHM: short-term high dose memantine; SHR: short-term high dose rivastigmine; SHT: short-term high dose melatonin; SLG: short-term low dose galantamine; SLT: short-term low dose melatonin; SMD: short-term medium dose donepezil; SMG: short-term medium dose galantamine; SMT: short-term medium dose melatonin; StMD: standardized mean difference; SUCRA: surface under the cumulative ranking curve

Treatment duration	Study name	Difference in means	Lower limit	Upper limit	*p* value
Extreme long	Dysken, M.W. (2014)	-3.160	-3.807	-2.513	0.000
Extreme long	Hager, K. (2014)	-2.138	-2.423	-1.853	0.000
Extreme long		**-2.606**	**-3.604**	**-1.608**	**0.000**
Medium	Tariot, P.N. (2001)	-0.806	-1.204	-0.407	0.000
Medium	Wade, A.G. (2014)	-1.900	-4.674	0.874	0.179
Medium	Reisberg, B. (2003)	-0.900	-1.569	-0.231	0.008
Medium	Rogers, S.L. (1998)	-0.970	-1.519	-0.421	0.001
Medium	Gao, Q.W. (2009)	-0.500	-1.749	0.749	0.433
Medium	Likitjaroen, Y. (2012)	-0.700	-3.744	2.344	0.652
Medium	Feldman, H. (2001)	-0.316	-0.685	0.052	0.092
Medium	Rosler, M. (1999)	-0.540	-1.070	-0.010	0.046
Medium	Porsteinsson, A.P. (2008)	-0.600	-1.457	0.257	0.170
Medium	Nakamura, Y. (2011)	-0.300	-0.649	0.049	0.092
Medium	Wang, T. (2013)	-0.400	-4.987	4.187	0.864
Medium	Winblad, B. (2007)	0.000	-0.395	0.395	1.000
Medium	Black, S.E. (2007)	0.020	-0.568	0.608	0.947
Medium	Winblad, B. (2006)	0.100	-0.684	0.884	0.803
Medium	Seltzer, B. (2004)	0.303	-0.139	0.746	0.179
Medium	Jia, J. (2017)	1.000	0.451	1.549	0.000
Medium		**-0.274**	**-0.559**	**0.012**	**0.060**
Short	Vila-Castelar, C. (2019)	-1.100	-2.607	0.407	0.152
Short	Howard, R.J. (2007)	-0.960	-1.962	0.042	0.060
Short	Fox, C. (2012)	-0.500	-2.552	1.552	0.633
Short	Singer, C. (2003)	0.340	-0.394	1.074	0.364
Short	Asayama, K. (2003)	1.600	-5.564	8.764	0.662
Short		**-0.388**	**-1.138**	**0.363**	**0.311**

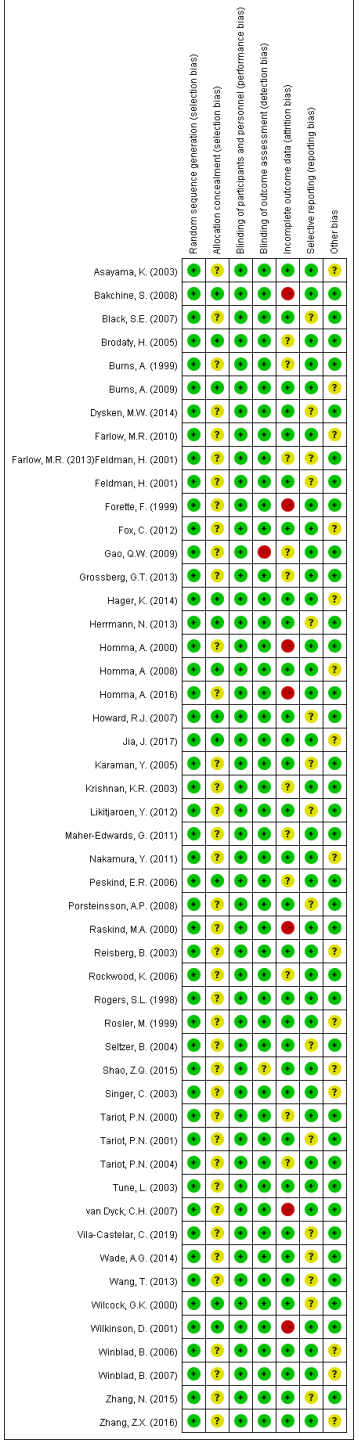


Interaction test *p* value < 0.001

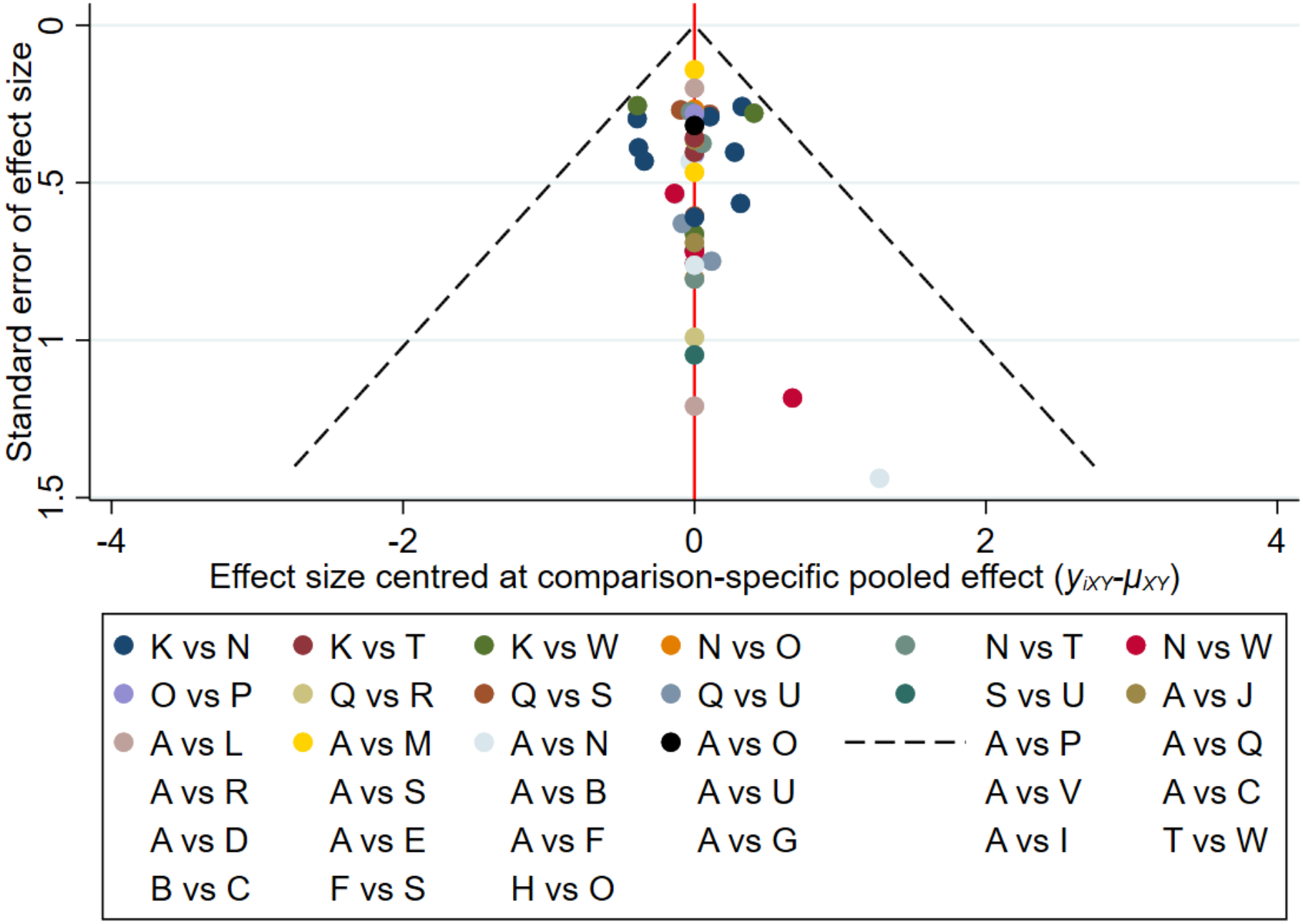
eFigure 3 transitivity assumption test of primary outcome



eFigure 4A overview of risk of bias



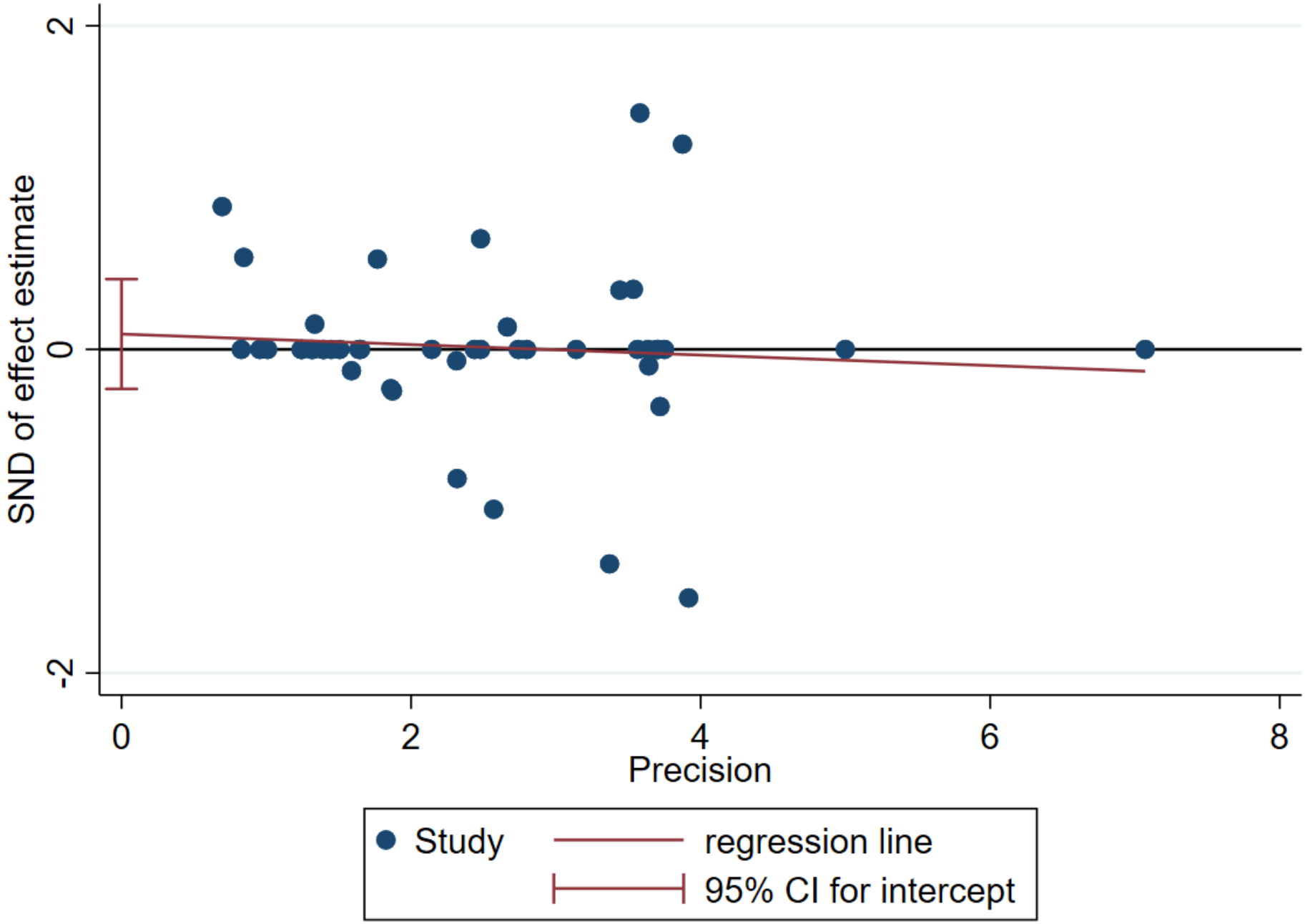
eFigure 4B detailed risk of bias in each study



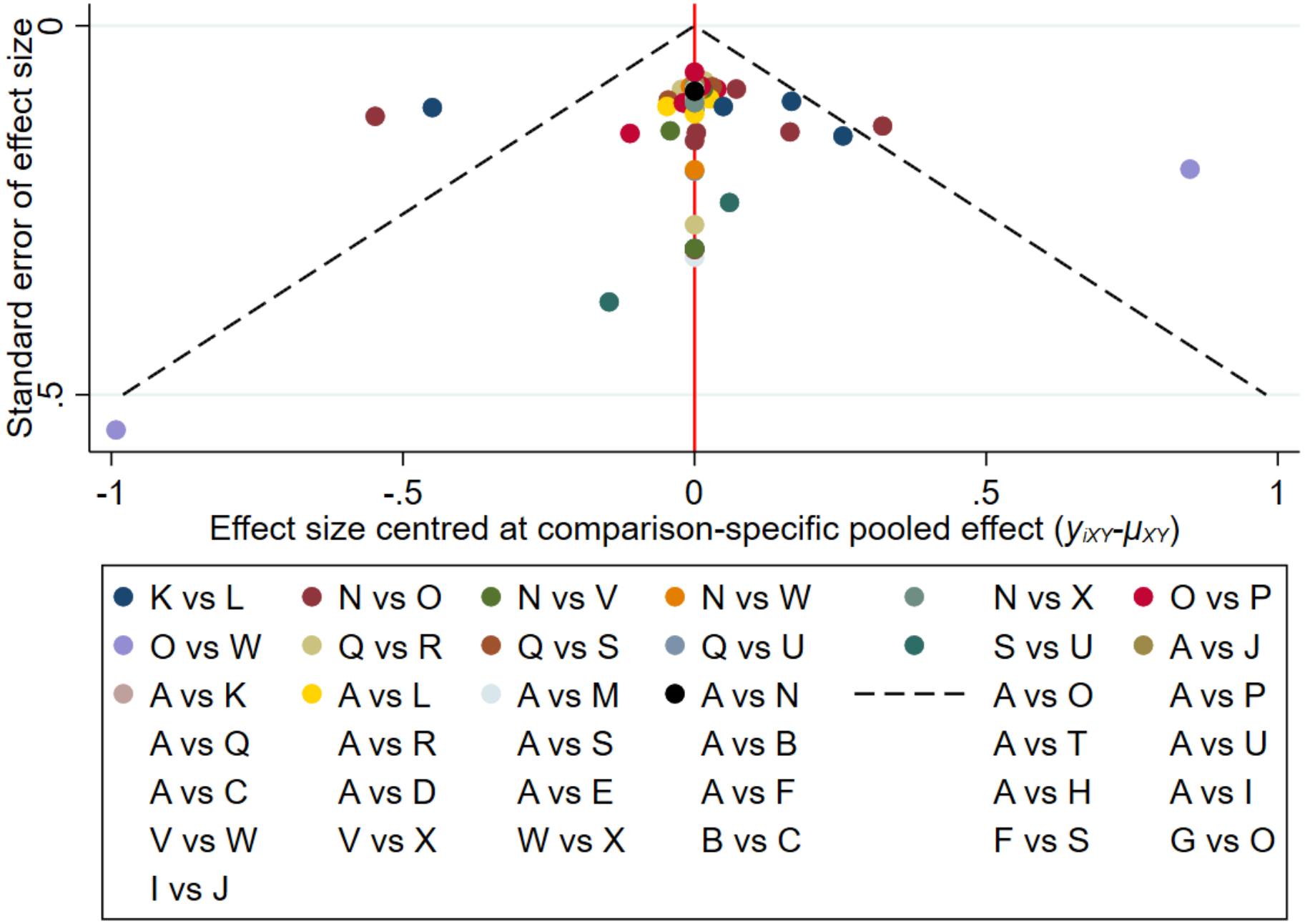
eFigure 5A Funnel plot of cognition change (measured in MMSE)

Treatments used in eFigure 5A

A: Pla
B: SLT
C: SHT
D: MLT
E: SHM
F: MLR
G: EMG
H: MED
I: EHM
J: SHD
K: GMMH
L: MMG
M: LHR
N: MHM
O: MHD
P: MMD
Q: MHPR
R: MLPR
S: MHR
T: RMMH
U: MEPR
V: SMD
W: DMMH



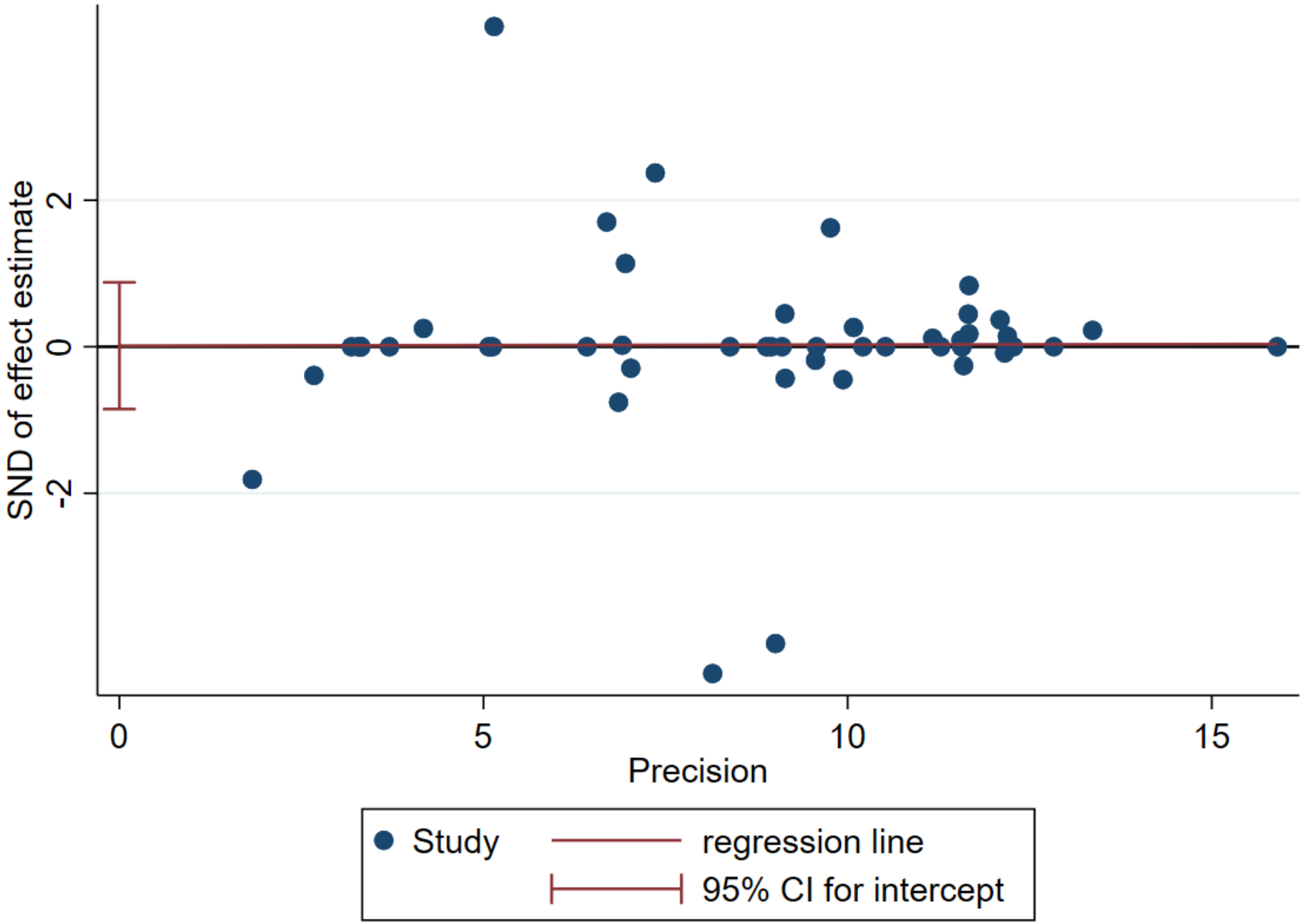
eFigure 5B Egger's regression of cognition change (measured in MMSE)



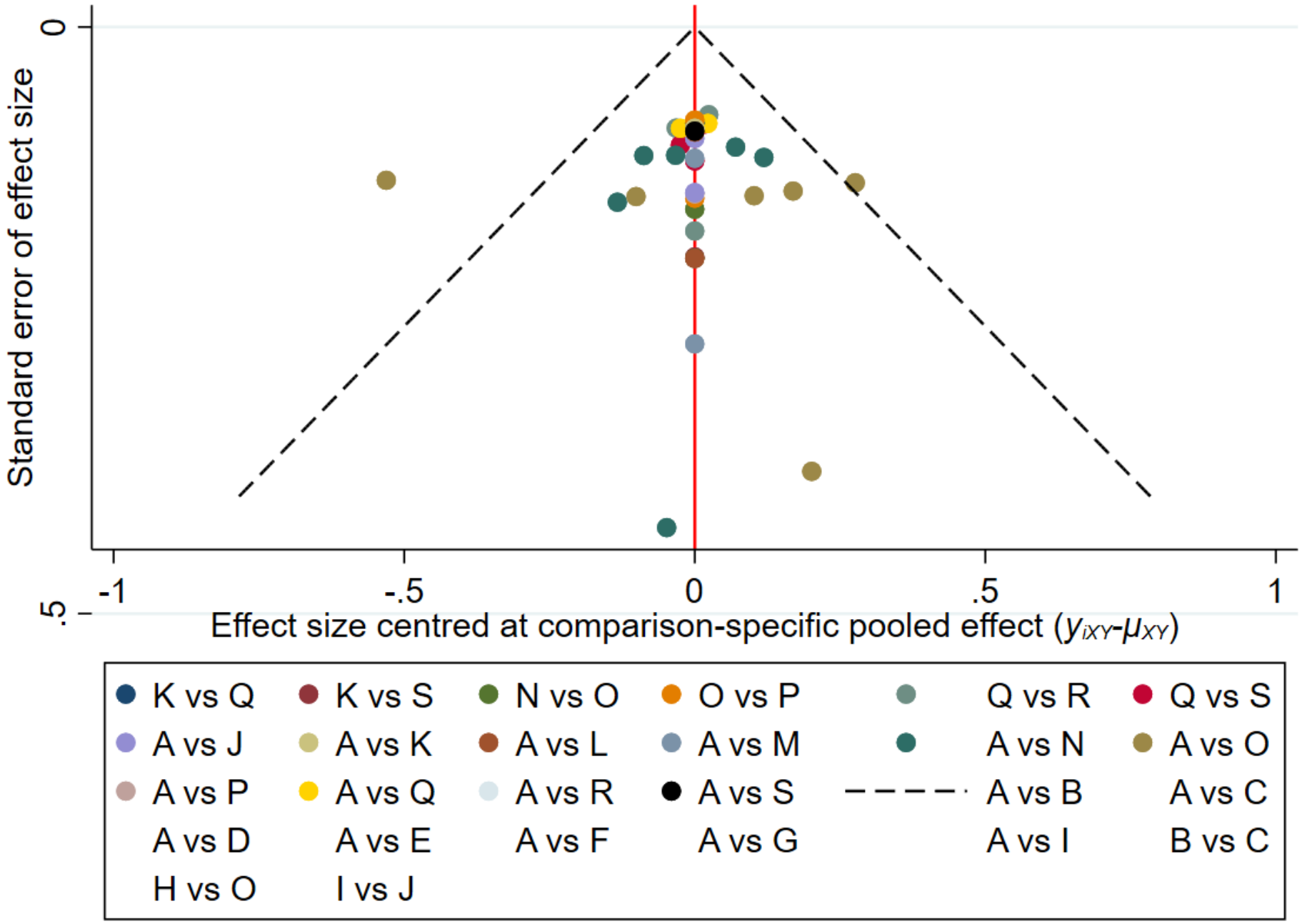
eFigure 5C Funnel plot of changes of quality of life

Treatments used in eFigure 5C

A: Pla
B: SLT
C: SHT
D: MLT
E: MEM
F: MLR
G: MED
H: EHM
I: SLG
J: SMG
K: MHG
L: MMG
M: LHR
N: MHM
O: MHD
P: MMD
Q: MHPR
R: MLPR
S: MHR
T: SHR
U: MEPR
V: GMMH
W: DMMH
X: RMMH



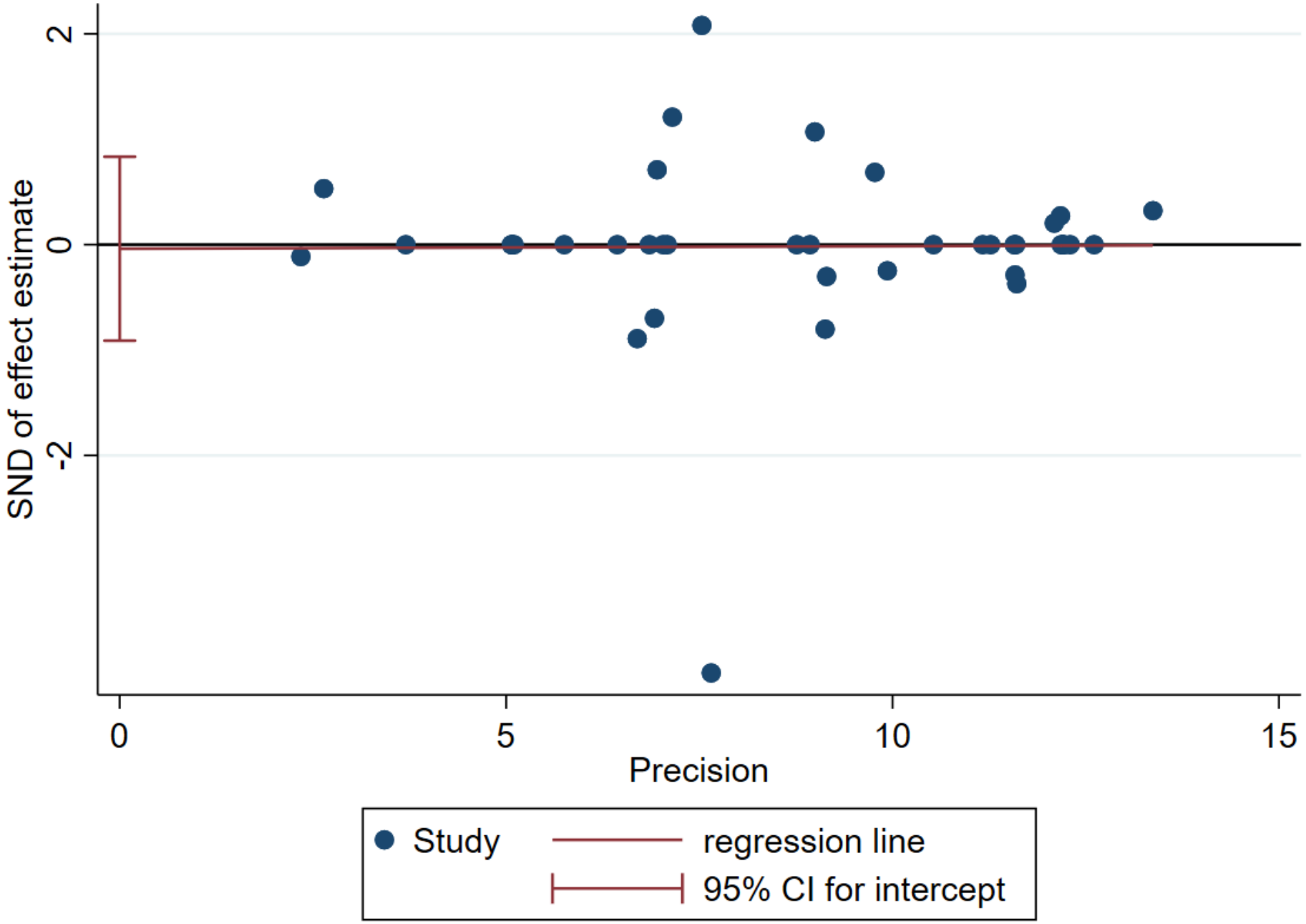
eFigure 5D Egger's regression of changes of quality of life



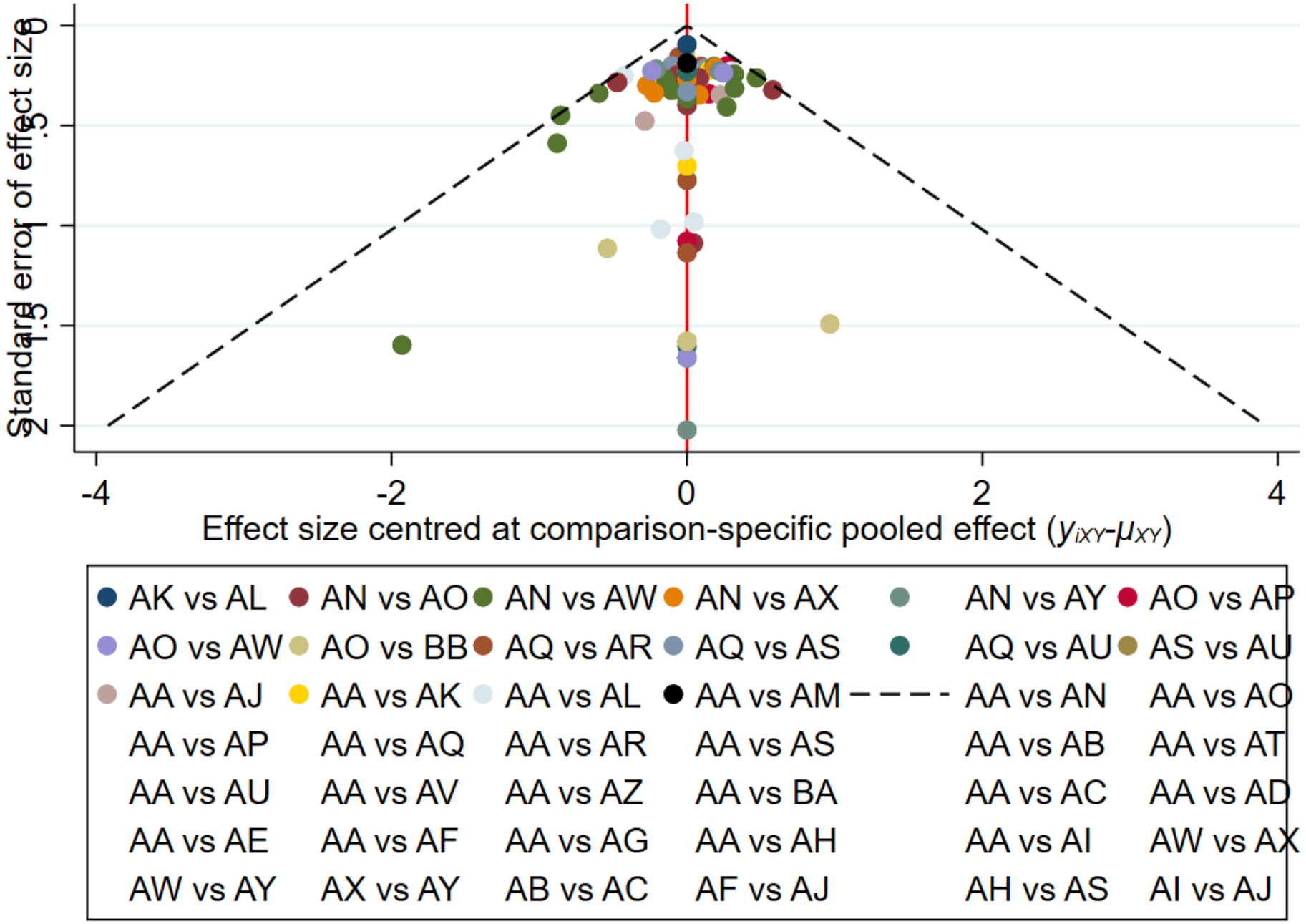
eFigure 5E Funnel plot of changes of behavioral disturbance

Treatments used in eFigure 5E

A: Pla
B: SLT
C: SHT
D: MEM
E: SHM
F: EHM
G: SHD
H: DMMH
I: SLG
J: SMG
K: MEPR
L: MMG
M: SHR
N: MHM
O: MHD
P: MMD
Q: MHPR
R: MLPR
S: MHR



eFigure 5F Egger's regression of changes of behavioral disturbance



eFigure 5G Funnel plot of drop-out rate

Treatments used eFigure 5G

AA: Pla
AB: SLT
AC: SHT
AD: MLT
AE: MEM
AF: SHG
AG: SHM
AH: MLR
AI: SLG
AJ: SMG
AK: MHG
AL: MMG
AM: EMG
AN: MHM
AO: MHD
AP: MMD
AQ: MHPR
AR: MLPR
AS: MHR
AT: SHR
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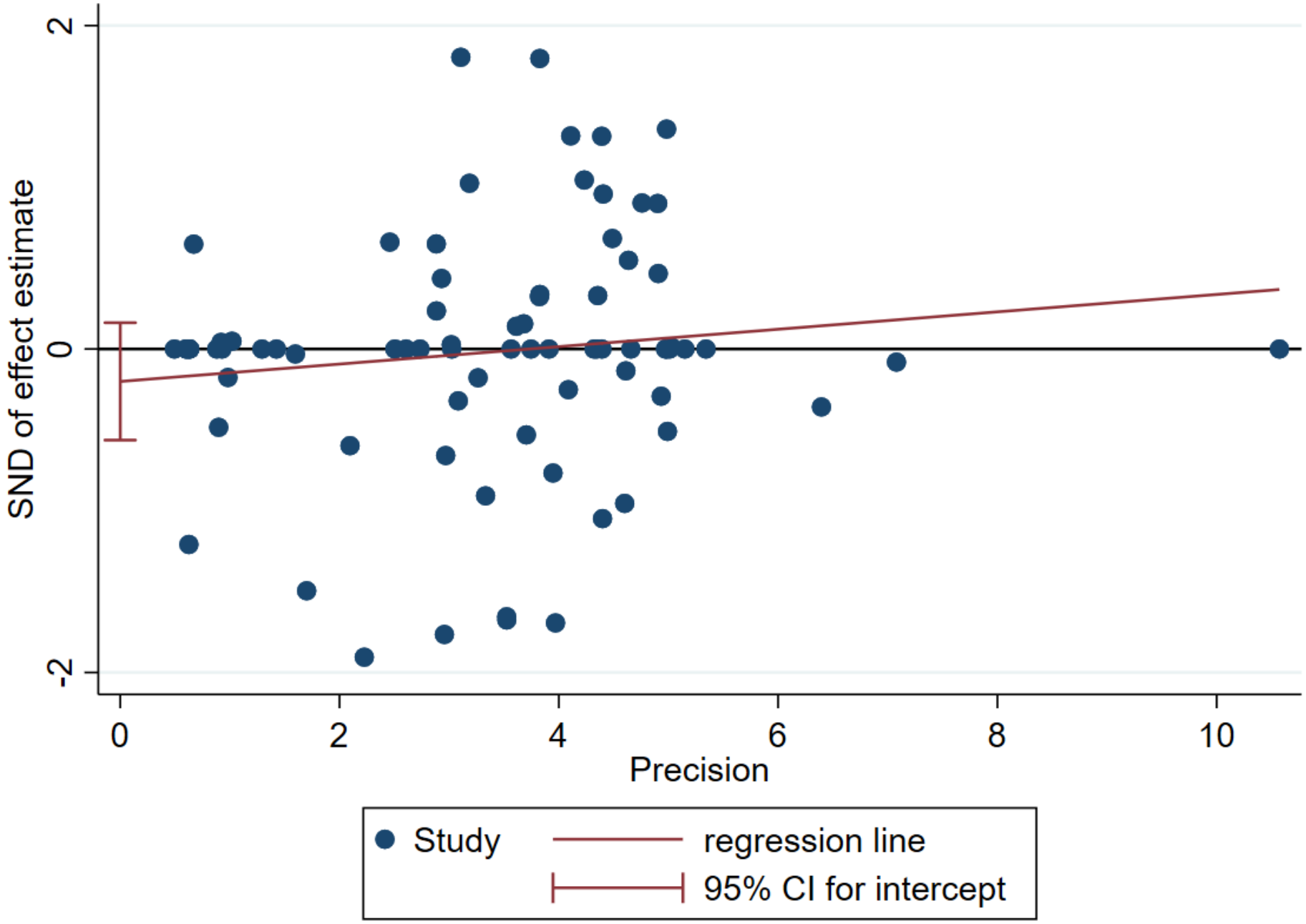
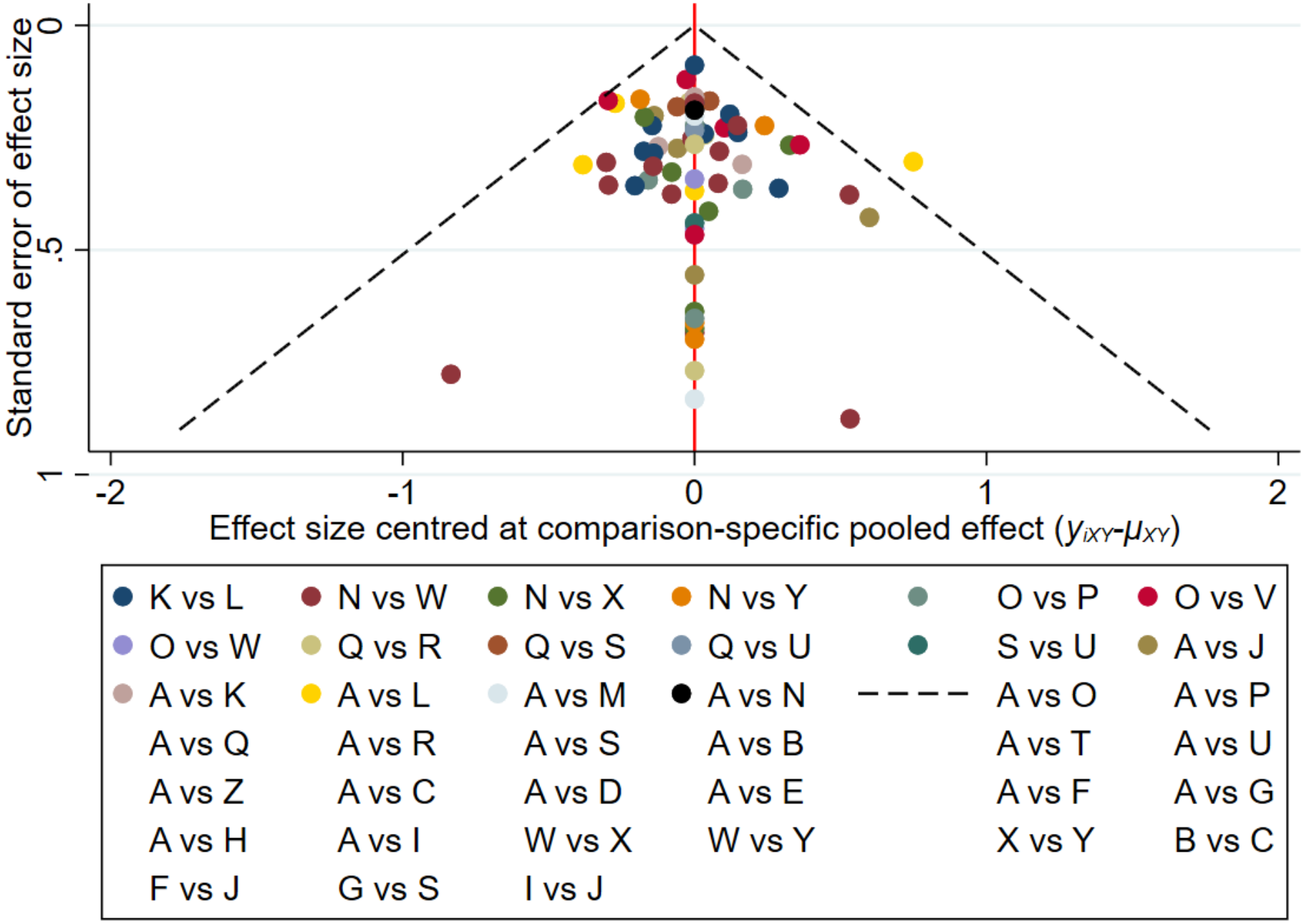
AV: SMD
AW: DMMH
AX: RMMH
AY: GMMH
AZ: SHD
BA: EHM
BB: MED



eFigure 5H Egger's regression of drop out rate



eFigure 5I Funnel plot of rate of any adverse event reported

Treatments used in eFigure 5I

A: Pla
B: SLT
C: SHT
D: MLT
E: MEM
F: SHG
G: MLR
H: EMG
I: SLG
J: SMG
K: MHG
L: MMG
M: LHR
N: MHM
O: MHD
P: MMD
Q: MHPR
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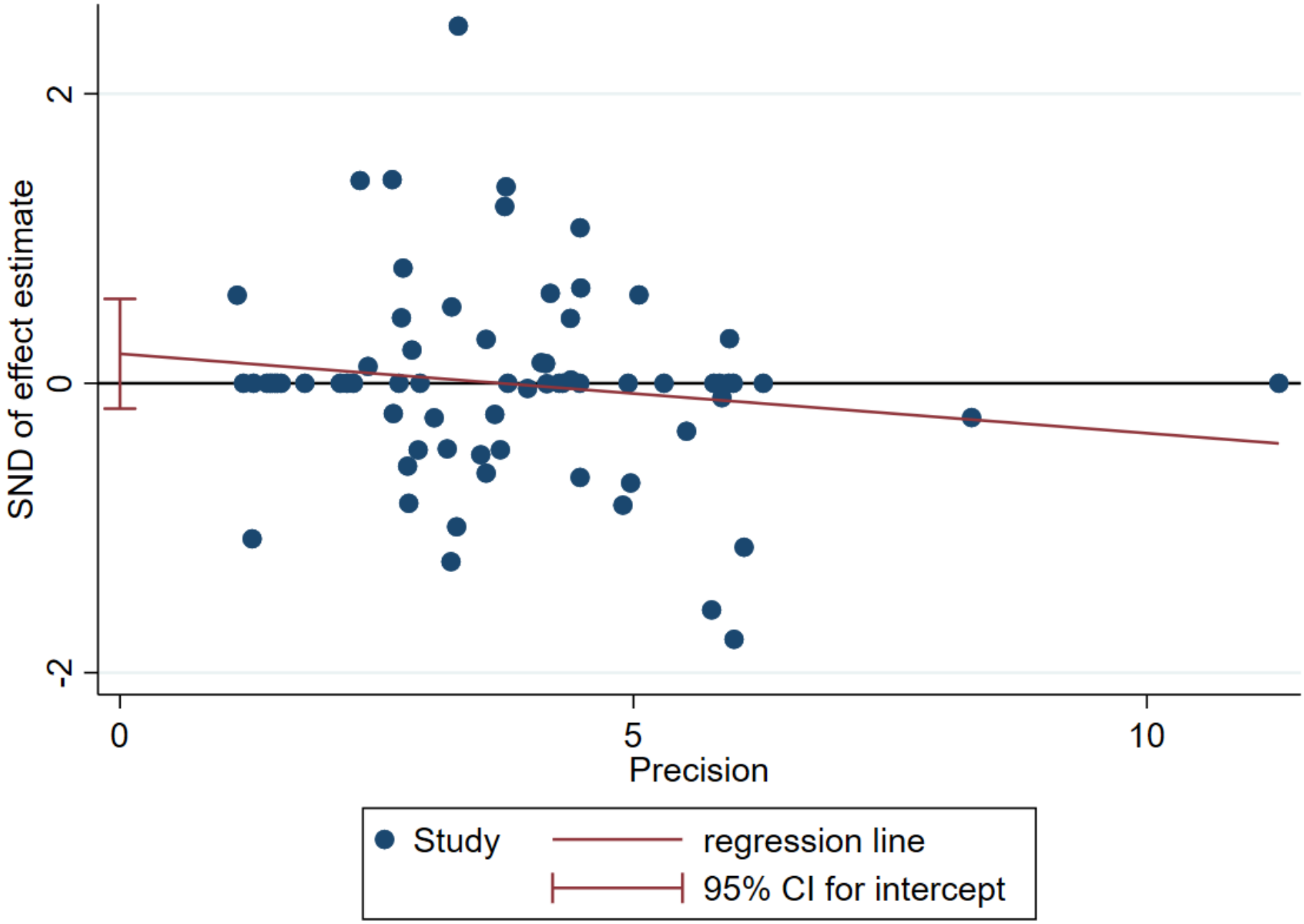
T: SHR
U: MEPR
V: MED
W: DMMH
X: RMMH
Y: GMMH
Z: EHM



eFigure 5J Egger's regression of rate of any adverse event reported

eTable 1: PRISMA 2020 checklist

Section and Topic	Item #	Checklist item	Page where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	6-7
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	6-7
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	8-9
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	8-9
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	8-9
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	8-9
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	8-9
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	9-10
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	9-10
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	9-10
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	9-10
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	9-10
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	10-11
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	10-11
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	10-11
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	11-12
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	11-12
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	12-13
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	12-13
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	14-15, Fig 1, eTab 2
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	14-15, eTab 4
Study characteristics	17	Cite each included study and present its characteristics.	14-15, eTab 5

Section and Topic	Item #	Checklist item	Page where item is reported
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	14-15, eFig 4
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	14-15, eTab 5
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	15-16, Fig 2
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	15-16, Fig 3
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	15-16, eTab 8-9
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	16-17
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	16-17, eFig 5
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	16-17, eTab 10
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	18-20
	23b	Discuss any limitations of the evidence included in the review.	20-21
	23c	Discuss any limitations of the review processes used.	20-21
	23d	Discuss implications of the results for practice, policy, and future research.	22
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	5
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	5
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	5
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	24
Competing interests	26	Declare any competing interests of review authors.	24
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	24

The current checklist followed the latest PRISMA 2020 guideline [1].

Reference

[1] Page, M.J.; McKenzie, J.E.; Bossuyt, P.M.; Boutron, I.; Hoffmann, T.C.; Mulrow, C.D.; Shamseer, L.; Tetzlaff, J.M.; Akl, E.A.; Brennan, S.E.; Chou, R.; Glanville, J.; Grimshaw, J.M.; Hrobjartsson, A.; Lalu, M.M.; Li, T.; Loder, E.W.; Mayo-Wilson, E.; McDonald, S.; McGuinness, L.A.; Stewart, L.A.; Thomas, J.; Tricco, A.C.; Welch, V.A.; Whiting, P.; Moher, D. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*, **2021**, *372*, n71.

eTable 2: the keyword used in each database and search result

Part of exogeneous melatonergic regimen

Database	Keyword	Limit	Date	Result
PubMed	(Disease, Alzheimer OR Alzheimer Sclerosis OR Sclerosis, Alzheimer OR Alzheimer Syndrome OR Syndrome, Alzheimer OR Alzheimer Dementia OR Dementia, Alzheimer OR Alzheimer-Type Dementia OR Alzheimer Type Dementia OR Dementia, Alzheimer-Type OR Primary Senile Degenerative Dementia OR Dementia, Senile OR Senile Dementia OR Dementia, Alzheimer Type OR Alzheimer Type Dementia OR Senile Dementia, Alzheimer Type OR Alzheimer Type Senile Dementia OR Dementia, Primary Senile Degenerative OR Alzheimer's Disease OR Disease, Alzheimer's OR Acute Confusional Senile Dementia OR Senile Dementia, Acute Confusional OR Dementia, Presenile OR Presenile Dementia OR Alzheimer Disease, Late Onset OR Late Onset Alzheimer Disease OR Alzheimer's Disease, Focal Onset OR Focal Onset Alzheimer's Disease OR Familial Alzheimer Disease OR Alzheimer Disease, Early Onset OR Early Onset Alzheimer Disease OR Presenile Alzheimer Dementia) AND (Mélatonine OR melatonin OR tasimelteon OR ramelteon OR agomelatine OR melatonin receptor agonist) AND (random OR randomized)	NA	2021/8/19	37
ClinicalKey	(Alzheimer disease OR dementia OR Alzheimer dementia) AND (Mélatonine OR Melatonin) AND (random OR randomized)	NA	2021/8/19	39
Cochrane CENTRAL	(Disease, Alzheimer OR Alzheimer Sclerosis OR Sclerosis, Alzheimer OR Alzheimer Syndrome OR Syndrome, Alzheimer OR Alzheimer Dementia OR Dementia, Alzheimer	NA	2021/8/19	24

	OR Alzheimer-Type Dementia OR Alzheimer Type Dementia OR Dementia, Alzheimer-Type OR Primary Senile Degenerative Dementia OR Dementia, Senile OR Senile Dementia OR Dementia, Alzheimer Type OR Alzheimer Type Dementia OR Senile Dementia, Alzheimer Type OR Alzheimer Type Senile Dementia OR Dementia, Primary Senile Degenerative OR Alzheimer's Disease OR Disease, Alzheimer's OR Acute Confusional Senile Dementia OR Senile Dementia, Acute Confusional OR Dementia, Presenile OR Presenile Dementia OR Alzheimer Disease, Late Onset OR Late Onset Alzheimer Disease OR Alzheimer's Disease, Focal Onset OR Focal Onset Alzheimer's Disease OR Familial Alzheimer Disease OR Alzheimer Disease, Early Onset OR Early Onset Alzheimer Disease OR Presenile Alzheimer Dementia) AND (Mélatonine OR melatonin OR tasimelteon OR ramelteon OR agomelatine OR melatonin receptor agonist) AND (random OR randomized)			
Embase	(Alzheimer disease OR dementia OR Alzheimer dementia) AND (Mélatonine OR Melatonin OR tasimelteon OR ramelteon OR agomelatine OR melatonin receptor agonist) AND (random OR randomized)	NA	2021/8/19	199
ProQuest	(Disease, Alzheimer OR Alzheimer Sclerosis OR Sclerosis, Alzheimer OR Alzheimer Syndrome OR Syndrome, Alzheimer OR Alzheimer Dementia OR Dementia, Alzheimer OR Alzheimer-Type Dementia OR Alzheimer Type Dementia OR Dementia, Alzheimer-Type OR Primary Senile Degenerative Dementia OR Dementia, Senile OR Senile Dementia OR Dementia, Alzheimer Type OR Alzheimer Type Dementia OR Senile Dementia, Alzheimer Type OR Alzheimer Type Senile Dementia OR Dementia, Primary Senile Degenerative OR Alzheimer's Disease OR Disease, Alzheimer's OR Acute	NA	2021/8/19	2143

	Confusional Senile Dementia OR Senile Dementia, Acute Confusional OR Dementia, Presenile OR Presenile Dementia OR Alzheimer Disease, Late Onset OR Late Onset Alzheimer Disease OR Alzheimer's Disease, Focal Onset OR Focal Onset Alzheimer's Disease OR Familial Alzheimer Disease OR Alzheimer Disease, Early Onset OR Early Onset Alzheimer Disease OR Presenile Alzheimer Dementia) AND (Mélatonine OR Melatonin) AND (random OR randomized)			
ScienceDirect	(Alzheimer disease OR dementia OR Alzheimer dementia) AND (Mélatonine OR Melatonin) AND (random OR randomized)	research article	2021/8/19	766
Web of Science	(Disease, Alzheimer OR Alzheimer Sclerosis OR Sclerosis, Alzheimer OR Alzheimer Syndrome OR Syndrome, Alzheimer OR Alzheimer Dementia OR Dementia, Alzheimer OR Alzheimer-Type Dementia OR Alzheimer Type Dementia OR Dementia, Alzheimer-Type OR Primary Senile Degenerative Dementia OR Dementia, Senile OR Senile Dementia OR Dementia, Alzheimer Type OR Alzheimer Type Dementia OR Senile Dementia, Alzheimer Type OR Alzheimer Type Senile Dementia OR Dementia, Primary Senile Degenerative OR Alzheimer's Disease OR Disease, Alzheimer's OR Acute Confusional Senile Dementia OR Senile Dementia, Acute Confusional OR Dementia, Presenile OR Presenile Dementia OR Alzheimer Disease, Late Onset OR Late Onset Alzheimer Disease OR Alzheimer's Disease, Focal Onset OR Focal Onset Alzheimer's Disease OR Familial Alzheimer Disease OR Alzheimer Disease, Early Onset OR Early Onset Alzheimer Disease OR Presenile Alzheimer Dementia) AND (Mélatonine OR melatonin OR tasimelteon OR ramelteon OR agomelatine OR melatonin receptor agonist) AND (random OR randomized)	NA	2021/8/19	83

ClinicalTrials.gov	(Alzheimer disease OR dementia OR Alzheimer dementia) AND (Mélatonine OR Melatonin OR tasimelteon OR ramelteon OR agomelatine OR melatonin receptor agonist) AND (random OR randomized)	NA	2021/8/19	5

Part of extra search for FDA approval agents

Database	Keyword	Limit	Date	Result
PubMed	(Disease, Alzheimer OR Alzheimer Sclerosis OR Sclerosis, Alzheimer OR Alzheimer Syndrome OR Syndrome, Alzheimer OR Alzheimer Dementia OR Dementia, Alzheimer OR Alzheimer-Type Dementia OR Alzheimer Type Dementia OR Dementia, Alzheimer-Type OR Primary Senile Degenerative Dementia OR Dementia, Senile OR Senile Dementia OR Dementia, Alzheimer Type OR Alzheimer Type Dementia OR Senile Dementia, Alzheimer Type OR Alzheimer Type Senile Dementia OR Dementia, Primary Senile Degenerative OR Alzheimer's Disease OR Disease, Alzheimer's OR Acute Confusional Senile Dementia OR Senile Dementia, Acute Confusional OR Dementia, Presenile OR Presenile Dementia OR Alzheimer Disease, Late Onset OR Late Onset Alzheimer Disease OR Alzheimer's Disease, Focal Onset OR Focal Onset Alzheimer's Disease OR Familial Alzheimer Disease OR Alzheimer Disease, Early Onset OR Early Onset Alzheimer Disease OR Presenile Alzheimer Dementia) AND (donepezil OR Aricept OR galantamine OR Razadyne OR rivastigmine OR Exelon OR memantine OR Namenda OR Namzaric) AND (random OR randomized OR randomised)	NA	2021/8/19	1146
ClinicalKey	(Disease, Alzheimer OR Alzheimer Sclerosis OR Sclerosis, Alzheimer OR Alzheimer Syndrome OR Syndrome, Alzheimer OR Alzheimer Dementia OR Dementia, Alzheimer	NA	2021/8/19	2

	OR Alzheimer-Type Dementia OR Alzheimer Type Dementia OR Dementia, Alzheimer-Type OR Primary Senile Degenerative Dementia OR Dementia, Senile OR Senile Dementia OR Dementia, Alzheimer Type OR Alzheimer Type Dementia OR Senile Dementia, Alzheimer Type OR Alzheimer Type Senile Dementia OR Dementia, Primary Senile Degenerative OR Alzheimer's Disease OR Disease, Alzheimer's OR Acute Confusional Senile Dementia OR Senile Dementia, Acute Confusional OR Dementia, Presenile OR Presenile Dementia OR Alzheimer Disease, Late Onset OR Late Onset Alzheimer Disease OR Alzheimer's Disease, Focal Onset OR Focal Onset Alzheimer's Disease OR Familial Alzheimer Disease OR Alzheimer Disease, Early Onset OR Early Onset Alzheimer Disease OR Presenile Alzheimer Dementia) AND (donepezil OR Aricept OR galantamine OR Razadyne OR rivastigmine OR Exelon OR memantine OR Namenda OR Namzaric) AND (random OR randomized OR randomised)			
Cochrane CENTRAL	(Disease, Alzheimer OR Alzheimer Sclerosis OR Sclerosis, Alzheimer OR Alzheimer Syndrome OR Syndrome, Alzheimer OR Alzheimer Dementia OR Dementia, Alzheimer OR Alzheimer-Type Dementia OR Alzheimer Type Dementia OR Dementia, Alzheimer-Type OR Primary Senile Degenerative Dementia OR Dementia, Senile OR Senile Dementia OR Dementia, Alzheimer Type OR Alzheimer Type Dementia OR Senile Dementia, Alzheimer Type OR Alzheimer Type Senile Dementia OR Dementia, Primary Senile Degenerative OR Alzheimer's Disease OR Disease, Alzheimer's OR Acute Confusional Senile Dementia OR Senile Dementia, Acute Confusional OR Dementia, Presenile OR Presenile Dementia OR Alzheimer Disease, Late Onset OR Late Onset Alzheimer Disease OR Alzheimer's Disease, Focal Onset OR Focal Onset Alzheimer's	NA	2021/8/19	1383

	Disease OR Familial Alzheimer Disease OR Alzheimer Disease, Early Onset OR Early Onset Alzheimer Disease OR Presenile Alzheimer Dementia) AND (donepezil OR Aricept OR galantamine OR Razadyne OR rivastigmine OR Exelon OR memantine OR Namenda OR Namzaric) AND (random OR randomized OR randomised)			
Embase	(Alzheimer disease OR dementia OR Alzheimer dementia) AND (donepezil OR Aricept OR galantamine OR Razadyne OR rivastigmine OR Exelon OR memantine OR Namenda OR Namzaric) AND (random OR randomized OR randomised)	NA	2021/8/19	2672
ProQuest	(Disease, Alzheimer OR Alzheimer Sclerosis OR Sclerosis, Alzheimer OR Alzheimer Syndrome OR Syndrome, Alzheimer OR Alzheimer Dementia OR Dementia, Alzheimer OR Alzheimer-Type Dementia OR Alzheimer Type Dementia OR Dementia, Alzheimer-Type OR Primary Senile Degenerative Dementia OR Dementia, Senile OR Senile Dementia OR Dementia, Alzheimer Type OR Alzheimer Type Dementia OR Senile Dementia, Alzheimer Type OR Alzheimer Type Senile Dementia OR Dementia, Primary Senile Degenerative OR Alzheimer's Disease OR Disease, Alzheimer's OR Acute Confusional Senile Dementia OR Senile Dementia, Acute Confusional OR Dementia, Presenile OR Presenile Dementia OR Alzheimer Disease, Late Onset OR Late Onset Alzheimer Disease OR Alzheimer's Disease, Focal Onset OR Focal Onset Alzheimer's Disease OR Familial Alzheimer Disease OR Alzheimer Disease, Early Onset OR Early Onset Alzheimer Disease OR Presenile Alzheimer Dementia) AND (donepezil OR Aricept OR galantamine OR Razadyne OR rivastigmine OR Exelon OR memantine OR Namenda OR Namzaric) AND (random OR randomized OR randomised)	NA	2021/8/19	2971
ScienceDirect	(Alzheimer) AND (donepezil OR galantamine OR rivastigmine OR memantine) AND	research	2021/8/19	2290

	(random)	article		
Web of Science	(Alzheimer) AND (donepezil OR galantamine OR rivastigmine OR memantine) AND (random)	NA	2021/8/19	51
ClinicalTrials.gov	(Alzheimer disease OR dementia OR Alzheimer dementia) AND (donepezil OR Aricept OR galantamine OR Razadyne OR rivastigmine OR Exelon OR memantine OR Namenda OR Namzaric) AND (random OR randomized OR randomised)	NA	2021/8/19	105

Abbreviation: NA: not apply

eTable 3: subgroup of different dosage of individual regimen

Regimen	Subgroup	Range
Galantamine	low dose	less or equal to 16mg/day
	medium dose	more than 16 mg/day but less or equal to 24 mg/day
	high dose	more than 24 mg/day
Rivastigmine capsule	low dose	less or equal to 4 mg/day
	medium dose	more than 4 mg/day but less or equal to 6 mg/day
	high dose	more than 6 mg/day but less or equal to 12 mg/day
Rivastigmine patch	low dose	less or equal to 4.6 mg/day
	high dose	more than 4.6 mg/day but less or equal to 13.3 mg/day
	extreme high dose	more than 13.3 mg/day
Memantine	high dose	less or equal to 20 mg/day
	extreme high dose	more than 20 mg/day
Donepezil	medium dose	less or equal to 5 mg/day
	high dose	more than 5 mg/day but less or equal to 10 mg/day
	extreme high dose	more than 10 mg/day
Melatonin	low dose	less or equal to 3 mg/day
	medium dose	more than 5 mg/day but less than 10 mg/day
	high dose	at least 10 mg/day

Subgrouping according to Dou KX, et al (2018)[1]

Reference:

[1] Dou, K.X.; Tan, M.S.; Tan, C.C.; Cao, X.P.; Hou, X.H.; Guo, Q.H.; Tan, L.; Mok, V.; Yu, J.T. Comparative safety and effectiveness of cholinesterase inhibitors and memantine for Alzheimer's disease: a network meta-analysis of 41 randomized controlled trials. *Alzheimers Res Ther*, **2018**, *10*(1), 126.

eTable 4: Excluded studies and reason

Reason (numbers)	Numbers	References
References		
All patients had received donepezil at baseline and selected patients with poor response to donepezil	1	[1]
Applied wide range dosage of rivastigmine but not a specific dosage (range 2-12 mg/day in this study)	2	[2, 3]
Comparison of different titration method but not different medication	1	[4]
Duplicate sample source	4	[5-8]
Exclude patients with definite dementia	6	[9-14]
Investigate additional citalopram to memantine but not to compare medication of interest	1	[15]
Investigate to withdraw medication but not prescription of medication	3	[16-18]
Lack of adequate control	1	[19]
Meta-analysis	10	[20-31]
Mixed different and wide-range dosage of memantine into one group	1	[32]
Network meta-analysis	3	[33-35]
Not randomized controlled trials	4	[36-39]
Not randomized to the different galantamine dose group	1	[40]
Not related to medication of interest	18	[41-58]
Not related to target outcome	5	[59-63]
Only provide baseline demographic data of cognition but not provide the post-treatment cognition level	1	[64]
Review article	5	[65-70]
Selected patients with poor response to rivastigmine patch	1	[71]

The control also consume active treatment Nimotop, which was no medication of interest	1	[72]

References:

[1] Johannsen, P.; Salmon, E.; Hampel, H.; Xu, Y.; Richardson, S.; Qvitzau, S.; Schindler, R.; Group, A.S. Assessing therapeutic efficacy in a progressive disease: a study of donepezil in Alzheimer's disease. *CNS Drugs*, **2006**, *20*(4), 311-325.

[2] Feldman, H.H.; Lane, R.; Study, G. Rivastigmine: a placebo controlled trial of twice daily and three times daily regimens in patients with Alzheimer's disease. *J Neurol Neurosurg Psychiatry*, **2007**, *78*(10), 1056-1063.

[3] Bullock, R.; Touchon, J.; Bergman, H.; Gambina, G.; He, Y.; Rapatz, G.; Nagel, J.; Lane, R. Rivastigmine and donepezil treatment in moderate to moderately-severe Alzheimer's disease over a 2-year period. *Curr Med Res Opin*, **2005**, *21*(8), 1317-1327.

[4] Hong, Y.J.; Han, H.J.; Youn, Y.C.; Park, K.W.; Yang, D.W.; Kim, S.; Kim, H.J.; Kim, J.E.; Lee, J.H.; study, O. Safety and tolerability of donepezil 23 mg with or without intermediate dose titration in patients with Alzheimer's disease taking donepezil 10 mg: a multicenter, randomized, open-label, parallel-design, three-arm, prospective trial. *Alzheimers Res Ther*, **2019**, *11*(1), 37.

[5] Grossberg, G.T.; Alva, G.; Hendrix, S.; Ellison, N.; Kane, M.C.; Edwards, J. Memantine ER Maintains Patient Response in Moderate to Severe Alzheimer's Disease: Post Hoc Analyses From a Randomized, Controlled, Clinical Trial of Patients Treated With Cholinesterase Inhibitors. *Alzheimer Dis Assoc Disord*, **2018**, *32*(3), 173-178.

[6] Winblad, B.; Grossberg, G.; Frolich, L.; Farlow, M.; Zechner, S.; Nagel, J.; Lane, R. IDEAL: a 6-month, double-blind, placebo-controlled study of the first skin patch for Alzheimer disease. *Neurology*, **2007**, *69*(4 Suppl 1), S14-22.

[7] Reisberg, B.; Doody, R.; Stoffler, A.; Schmitt, F.; Ferris, S.; Mobius, H.J. A 24-week open-label extension study of memantine in moderate to severe Alzheimer disease. *Arch Neurol*, **2006**, *63*(1), 49-54.

[8] Rogers, S.L.; Doody, R.S.; Mohs, R.C.; Friedhoff, L.T. Donepezil improves cognition and global function in Alzheimer disease: a 15-week, double-blind, placebo-controlled study. Donepezil Study Group. *Arch Intern Med*, **1998**, *158*(9), 1021-1031.

[9] Montero-Odasso, M.; Speechley, M.; Chertkow, H.; Sarquis-Adamson, Y.; Wells, J.; Borrie, M.; Vanderhaeghe, L.; Zou, G.Y.; Fraser, S.; Bherer,

L.; Muir-Hunter, S.W. Donepezil for gait and falls in mild cognitive impairment: a randomized controlled trial. *Eur J Neurol*, **2019**, *26*(4), 651-659.
[10] Fan, Y.; Yuan, L.; Ji, M.; Yang, J.; Gao, D. The effect of melatonin on early postoperative cognitive decline in elderly patients undergoing hip arthroplasty: A randomized controlled trial. *J Clin Anesth*, **2017**, *39*, 77-81.
[11] Rondanelli, M.; Opizzi, A.; Faliva, M.; Mozzoni, M.; Antoniello, N.; Cazzola, R.; Savare, R.; Cerutti, R.; Grossi, E.; Cestaro, B. Effects of a diet integration with an oily emulsion of DHA-phospholipids containing melatonin and tryptophan in elderly patients suffering from mild cognitive impairment. *Nutr Neurosci*, **2012**, *15*(2), 46-54.
[12] Garzon, C.; Guerrero, J.M.; Aramburu, O.; Guzman, T. Effect of melatonin administration on sleep, behavioral disorders and hypnotic drug discontinuation in the elderly: a randomized, double-blind, placebo-controlled study. *Aging Clin Exp Res*, **2009**, *21*(1), 38-42.
[13] Petersen, R.C.; Thomas, R.G.; Grundman, M.; Bennett, D.; Doody, R.; Ferris, S.; Galasko, D.; Jin, S.; Kaye, J.; Levey, A.; Pfeiffer, E.; Sano, M.; van Dyck, C.H.; Thal, L.J.; Alzheimer's Disease Cooperative Study, G. Vitamin E and donepezil for the treatment of mild cognitive impairment. *N Engl J Med*, **2005**, *352*(23), 2379-2388.
[14] Hamdieh, M.; Abbasinazari, M.; Badri, T.; Saberi-Isfeedvajani, M.; Arzani, G. The impact of melatonin on the alleviation of cognitive impairment during electroconvulsive therapy: A double-blind controlled trial. *Neurology, Psychiatry and Brain Research*, **2017**, *24*, 30-34.
[15] Zhou, T.; Wang, J.; Xin, C.; Kong, L.; Wang, C. Effect of memantine combined with citalopram on cognition of BPSD and moderate Alzheimer's disease: A clinical trial. *Exp Ther Med*, **2019**, *17*(3), 1625-1630.
[16] Soler, A.; Amer, G.; Leiva, A.; Ripoll, J.; Llorente, M.A.; Leiva, A.; Taltavull, J.M.; Molina, R.; Llobera, J. Continuation versus discontinuation of treatment for severe dementia: randomized, pragmatic, open-label, clinical trial to evaluate the efficacy of continuing drug treatment in patients with severe dementia (STOP-DEM). *BMC Geriatr*, **2019**, *19*(1), 101.
[17] Hong, Y.J.; Choi, S.H.; Jeong, J.H.; Park, K.W.; Na, H.R. Effectiveness of Anti-Dementia Drugs in Extremely Severe Alzheimer's Disease: A 12-Week, Multicenter, Randomized, Single-Blind Study. *J Alzheimers Dis*, **2018**, *63*(3), 1035-1044.
[18] Howard, R.; McShane, R.; Lindesay, J.; Ritchie, C.; Baldwin, A.; Barber, R.; Burns, A.; Dening, T.; Findlay, D.; Holmes, C.; Hughes, A.; Jacoby, R.; Jones, R.; Jones, R.; McKeith, I.; Macharouthu, A.; O'Brien, J.; Passmore, P.; Sheehan, B.; Juszczak, E.; Katona, C.; Hills, R.; Knapp, M.; Ballard, C.; Brown, R.; Banerjee, S.; Onions, C.; Griffin, M.; Adams, J.; Gray, R.; Johnson, T.; Bentham, P.; Phillips, P. Donepezil and memantine for

moderate-to-severe Alzheimer's disease. *N Engl J Med*, **2012**, *366*(10), 893-903.
[19] Connelly, P.J.; Prentice, N.P.; Cousland, G.; Bonham, J. A randomised double-blind placebo-controlled trial of folic acid supplementation of cholinesterase inhibitors in Alzheimer's disease. *Int J Geriatr Psychiatry*, **2008**, *23*(2), 155-160.
[20] Glinz, D.; Gloy, V.L.; Monsch, A.U.; Kressig, R.W.; Patel, C.; McCord, K.A.; Ademi, Z.; Tomonaga, Y.; Schwenkglenks, M.; Bucher, H.C.; Raatz, H. Acetylcholinesterase inhibitors combined with memantine for moderate to severe Alzheimer's disease: a meta-analysis. *Swiss Med Wkly*, **2019**, *149*, w20093.
[21] Li, D.D.; Zhang, Y.H.; Zhang, W.; Zhao, P. Meta-Analysis of Randomized Controlled Trials on the Efficacy and Safety of Donepezil, Galantamine, Rivastigmine, and Memantine for the Treatment of Alzheimer's Disease. *Front Neurosci*, **2019**, *13*, 472.
[22] McShane, R.; Westby, M.J.; Roberts, E.; Minakaran, N.; Schneider, L.; Farrimond, L.E.; Maayan, N.; Ware, J.; Debarros, J. Memantine for dementia. *Cochrane Database Syst Rev*, **2019**, *3*, CD003154.
[23] Birks, J.S.; Harvey, R.J. Donepezil for dementia due to Alzheimer's disease. *Cochrane Database Syst Rev*, **2018**, *6*, CD001190.
[24] Kishi, T.; Matsunaga, S.; Iwata, N. The effects of memantine on behavioral disturbances in patients with Alzheimer's disease: a meta-analysis. *Neuropsychiatr Dis Treat*, **2017**, *13*, 1909-1928.
[25] McCleery, J.; Cohen, D.A.; Sharpley, A.L. Pharmacotherapies for sleep disturbances in dementia. *Cochrane Database Syst Rev*, **2016**, *11*, CD009178.
[26] Wang, Y.Y.; Zheng, W.; Ng, C.H.; Ungvari, G.S.; Wei, W.; Xiang, Y.T. Meta-analysis of randomized, double-blind, placebo-controlled trials of melatonin in Alzheimer's disease. *Int J Geriatr Psychiatry*, **2017**, *32*(1), 50-57.
[27] Zhang, W.; Chen, X.Y.; Su, S.W.; Jia, Q.Z.; Ding, T.; Zhu, Z.N.; Zhang, T. Exogenous melatonin for sleep disorders in neurodegenerative diseases: a meta-analysis of randomized clinical trials. *Neurol Sci*, **2016**, *37*(1), 57-65.
[28] Xu, J.; Wang, L.L.; Dammer, E.B.; Li, C.B.; Xu, G.; Chen, S.D.; Wang, G. Melatonin for sleep disorders and cognition in dementia: a meta-analysis of randomized controlled trials. *Am J Alzheimers Dis Other Demen*, **2015**, *30*(5), 439-447.
[29] McCleery, J.; Cohen, D.A.; Sharpley, A.L. Pharmacotherapies for sleep disturbances in Alzheimer's disease. *Cochrane Database Syst Rev*, **2014**, (3), CD009178.

[30] Sumsuzzman, D.M.; Choi, J.; Jin, Y.; Hong, Y. Neurocognitive effects of melatonin treatment in healthy adults and individuals with Alzheimer's disease and insomnia: A systematic review and meta-analysis of randomized controlled trials. *Neurosci Biobehav Rev*, **2021**, *127*, 459-473.
[31] McCleery, J.; Sharpley, A.L. Pharmacotherapies for sleep disturbances in dementia. *Cochrane Database Syst Rev*, **2020**, *11*, CD009178.
[32] Nakamura, Y.; Kitamura, S.; Homma, A.; Shiosakai, K.; Matsui, D. Efficacy and safety of memantine in patients with moderate-to-severe Alzheimer's disease: results of a pooled analysis of two randomized, double-blind, placebo-controlled trials in Japan. *Expert Opin Pharmacother*, **2014**, *15*(7), 913-925.
[33] Cui, C.C.; Sun, Y.; Wang, X.Y.; Zhang, Y.; Xing, Y. The effect of anti-dementia drugs on Alzheimer disease-induced cognitive impairment: A network meta-analysis. *Medicine (Baltimore)*, **2019**, *98*(27), e16091.
[34] Thancharoen, O.; Limwattananon, C.; Waleekhachonloet, O.; Rattanachotphanit, T.; Limwattananon, P.; Limpawattana, P. Ginkgo biloba Extract (EGb761), Cholinesterase Inhibitors, and Memantine for the Treatment of Mild-to-Moderate Alzheimer's Disease: A Network Meta-Analysis. *Drugs Aging*, **2019**, *36*(5), 435-452.
[35] Dou, K.X.; Tan, M.S.; Tan, C.C.; Cao, X.P.; Hou, X.H.; Guo, Q.H.; Tan, L.; Mok, V.; Yu, J.T. Comparative safety and effectiveness of cholinesterase inhibitors and memantine for Alzheimer's disease: a network meta-analysis of 41 randomized controlled trials. *Alzheimers Res Ther*, **2018**, *10*(1), 126.
[36] Manni, R.; Cremascoli, R.; Perretti, C.; De Icco, R.; Picascia, M.; Ghezzi, C.; Cerri, S.; Sinforiani, E.; Terzaghi, M. Evening melatonin timing secretion in real life conditions in patients with Alzheimer disease of mild to moderate severity. *Sleep Med*, **2019**, *63*, 122-126.
[37] Huisa, B.N.; Thomas, R.G.; Jin, S.; Oltersdorf, T.; Taylor, C.; Feldman, H.H. Memantine and Acetylcholinesterase Inhibitor Use in Alzheimer's Disease Clinical Trials: Potential for Confounding by Indication. *J Alzheimers Dis*, **2019**, *67*(2), 707-713.
[38] Devore, E.E.; Harrison, S.L.; Stone, K.L.; Holton, K.F.; Barrett-Connor, E.; Ancoli-Israel, S.; Yaffe, K.; Ensrud, K.; Cawthon, P.M.; Redline, S.; Orwoll, E.; Schernhammer, E.S.; Osteoporotic Fractures in Men Study Research, G. Association of urinary melatonin levels and aging-related outcomes in older men. *Sleep Med*, **2016**, *23*, 73-80.
[39] Santoro, A.; Siviero, P.; Minicuci, N.; Bellavista, E.; Mishto, M.; Olivieri, F.; Marchegiani, F.; Chiamenti, A.M.; Benussi, L.; Ghidoni, R.;

Nacmias, B.; Bagnoli, S.; Ginestroni, A.; Scarpino, O.; Feraco, E.; Gianni, W.; Cruciani, G.; Paganelli, R.; Di Iorio, A.; Scognamiglio, M.; Grimaldi, L.M.; Gabelli, C.; Sorbi, S.; Binetti, G.; Crepaldi, G.; Franceschi, C. Effects of donepezil, galantamine and rivastigmine in 938 Italian patients with Alzheimer's disease: a prospective, observational study. *CNS Drugs*, **2010**, *24*(2), 163-176.

[40] Rockwood, K.; Mintzer, J.; Truyen, L.; Wessel, T.; Wilkinson, D. Effects of a flexible galantamine dose in Alzheimer's disease: a randomised, controlled trial. *J Neurol Neurosurg Psychiatry*, **2001**, *71*(5), 589-595.

[41] Fullerton, T.; Binneman, B.; David, W.; Delnomdedieu, M.; Kupiec, J.; Lockwood, P.; Mancuso, J.; Miceli, J.; Bell, J. A Phase 2 clinical trial of PF-05212377 (SAM-760) in subjects with mild to moderate Alzheimer's disease with existing neuropsychiatric symptoms on a stable daily dose of donepezil. *Alzheimers Res Ther*, **2018**, *10*(1), 38.

[42] Gault, L.M.; Lenz, R.A.; Ritchie, C.W.; Meier, A.; Othman, A.A.; Tang, Q.; Berry, S.; Pritchett, Y.; Robieson, W.Z. ABT-126 monotherapy in mild-to-moderate Alzheimer's dementia: randomized double-blind, placebo and active controlled adaptive trial and open-label extension. *Alzheimers Res Ther*, **2016**, *8*(1), 44.

[43] Gault, L.M.; Ritchie, C.W.; Robieson, W.Z.; Pritchett, Y.; Othman, A.A.; Lenz, R.A. A phase 2 randomized, controlled trial of the alpha7 agonist ABT-126 in mild-to-moderate Alzheimer's dementia. *Alzheimers Dement (N Y)*, **2015**, *1*(1), 81-90.

[44] Haig, G.M.; Pritchett, Y.; Meier, A.; Othman, A.A.; Hall, C.; Gault, L.M.; Lenz, R.A. A randomized study of H3 antagonist ABT-288 in mild-to-moderate Alzheimer's dementia. *J Alzheimers Dis*, **2014**, *42*(3), 959-971.

[45] Sano, M.; Bell, K.L.; Galasko, D.; Galvin, J.E.; Thomas, R.G.; van Dyck, C.H.; Aisen, P.S. A randomized, double-blind, placebo-controlled trial of simvastatin to treat Alzheimer disease. *Neurology*, **2011**, *77*(6), 556-563.

[46] Maher-Edwards, G.; Zvartau-Hind, M.; Hunter, A.J.; Gold, M.; Hopton, G.; Jacobs, G.; Davy, M.; Williams, P. Double-blind, controlled phase II study of a 5-HT6 receptor antagonist, SB-742457, in Alzheimer's disease. *Curr Alzheimer Res*, **2010**, *7*(5), 374-385.

[47] Doody, R.S.; Gavrilova, S.I.; Sano, M.; Thomas, R.G.; Aisen, P.S.; Bachurin, S.O.; Seely, L.; Hung, D.; dimebon, i. Effect of dimebon on cognition, activities of daily living, behaviour, and global function in patients with mild-to-moderate Alzheimer's disease: a randomised, double-blind, placebo-controlled study. *Lancet*, **2008**, *372*(9634), 207-215.

[48] Mintzer, J.E.; Tune, L.E.; Breder, C.D.; Swanink, R.; Marcus, R.N.; McQuade, R.D.; Forbes, A. Aripiprazole for the treatment of psychoses in

institutionalized patients with Alzheimer dementia: a multicenter, randomized, double-blind, placebo-controlled assessment of three fixed doses. *Am J Geriatr Psychiatry*, **2007**, *15*(11), 918-931.
[49] Zhang, Z.; Wang, X.; Chen, Q.; Shu, L.; Wang, J.; Shan, G. [Clinical efficacy and safety of huperzine Alpha in treatment of mild to moderate Alzheimer disease, a placebo-controlled, double-blind, randomized trial]. *Zhonghua Yi Xue Za Zhi*, **2002**, *82*(14), 941-944.
[50] Adair, J.C.; Knoefel, J.E.; Morgan, N. Controlled trial of N-acetylcysteine for patients with probable Alzheimer's disease. *Neurology*, **2001**, *57*(8), 1515-1517.
[51] Frolich, L.; Atri, A.; Ballard, C.; Tariot, P.N.; Molinuevo, J.L.; Boneva, N.; Geist, M.A.; Raket, L.L.; Cummings, J.L. Open-Label, Multicenter, Phase III Extension Study of Idalopirdine as Adjunctive to Donepezil for the Treatment of Mild-Moderate Alzheimer's Disease. *J Alzheimers Dis*, **2019**, *67*(1), 303-313.
[52] Atri, A.; Frolich, L.; Ballard, C.; Tariot, P.N.; Molinuevo, J.L.; Boneva, N.; Windfeld, K.; Raket, L.L.; Cummings, J.L. Effect of Idalopirdine as Adjunct to Cholinesterase Inhibitors on Change in Cognition in Patients With Alzheimer Disease: Three Randomized Clinical Trials. *JAMA*, **2018**, *319*(2), 130-142.
[53] Bloniecki, V.; Aarsland, D.; Blennow, K.; Cummings, J.; Falahati, F.; Winblad, B.; Freund-Levi, Y. Effects of Risperidone and Galantamine Treatment on Alzheimer's Disease Biomarker Levels in Cerebrospinal Fluid. *J Alzheimers Dis*, **2017**, *57*(2), 387-393.
[54] Frolich, L.; Ashwood, T.; Nilsson, J.; Eckerwall, G.; Sirocco, I. Effects of AZD3480 on cognition in patients with mild-to-moderate Alzheimer's disease: a phase IIb dose-finding study. *J Alzheimers Dis*, **2011**, *24*(2), 363-374.
[55] Thal, L.J.; Grundman, M.; Berg, J.; Ernstrom, K.; Margolin, R.; Pfeiffer, E.; Weiner, M.F.; Zamrini, E.; Thomas, R.G. Idebenone treatment fails to slow cognitive decline in Alzheimer's disease. *Neurology*, **2003**, *61*(11), 1498-1502.
[56] Simons, M.; Schwarzler, F.; Lutjohann, D.; von Bergmann, K.; Beyreuther, K.; Dichgans, J.; Wormstall, H.; Hartmann, T.; Schulz, J.B. Treatment with simvastatin in normocholesterolemic patients with Alzheimer's disease: A 26-week randomized, placebo-controlled, double-blind trial. *Ann Neurol*, **2002**, *52*(3), 346-350.
[57] Wang, P.N.; Liao, S.Q.; Liu, R.S.; Liu, C.Y.; Chao, H.T.; Lu, S.R.; Yu, H.Y.; Wang, S.J.; Liu, H.C. Effects of estrogen on cognition, mood, and cerebral blood flow in AD: a controlled study. *Neurology*, **2000**, *54*(11), 2061-2066.

[58] Mulnard, R.A.; Cotman, C.W.; Kawas, C.; van Dyck, C.H.; Sano, M.; Doody, R.; Koss, E.; Pfeiffer, E.; Jin, S.; Gamst, A.; Grundman, M.; Thomas, R.; Thal, L.J. Estrogen replacement therapy for treatment of mild to moderate Alzheimer disease: a randomized controlled trial. Alzheimer's Disease Cooperative Study. *JAMA*, **2000**, *283*(8), 1007-1015.
[59] Jaiswal, S.J.; McCarthy, T.J.; Wineinger, N.E.; Kang, D.Y.; Song, J.; Garcia, S.; van Niekerk, C.J.; Lu, C.Y.; Loeks, M.; Owens, R.L. Melatonin and Sleep in Preventing Hospitalized Delirium: A Randomized Clinical Trial. *Am J Med*, **2018**, *131*(9), 1110-1117 e1114.
[60] Gehrman, P.R.; Connor, D.J.; Martin, J.L.; Shochat, T.; Corey-Bloom, J.; Ancoli-Israel, S. Melatonin fails to improve sleep or agitation in double-blind randomized placebo-controlled trial of institutionalized patients with Alzheimer disease. *Am J Geriatr Psychiatry*, **2009**, *17*(2), 166-169.
[61] Dowling, G.A.; Burr, R.L.; Van Someren, E.J.; Hubbard, E.M.; Luxenberg, J.S.; Mastick, J.; Cooper, B.A. Melatonin and bright-light treatment for rest-activity disruption in institutionalized patients with Alzheimer's disease. *J Am Geriatr Soc*, **2008**, *56*(2), 239-246.
[62] Serfaty, M.; Kennell-Webb, S.; Warner, J.; Blizard, R.; Raven, P. Double blind randomised placebo controlled trial of low dose melatonin for sleep disorders in dementia. *Int J Geriatr Psychiatry*, **2002**, *17*(12), 1120-1127.
[63] Haffmans, P.M.; Sival, R.C.; Lucius, S.A.; Cats, Q.; van Gelder, L. Bright light therapy and melatonin in motor restless behaviour in dementia: a placebo-controlled study. *Int J Geriatr Psychiatry*, **2001**, *16*(1), 106-110.
[64] Xu, L.; Yu, H.; Sun, H.; Hu, B.; Geng, Y. Dietary Melatonin Therapy Alleviates the Lamina Cribrosa Damages in Patients with Mild Cognitive Impairments: A Double-Blinded, Randomized Controlled Study. *Med Sci Monit*, **2020**, *26*, e923232.
[65] Watanabe, M.; Nakamura, Y.; Yoshiyama, Y.; Kagimura, T.; Kawaguchi, H.; Matsuzawa, H.; Tachibana, Y.; Nishimura, K.; Kubota, N.; Kobayashi, M.; Saito, T.; Tamura, K.; Sato, T.; Takahashi, M.; Japanese Society of Scaling Keys of Evaluation Techniques for, C.N.S.D.H.s.g.; Homma, A. Analyses of natural courses of Japanese patients with Alzheimer's disease using placebo data from placebo-controlled, randomized clinical trials: Japanese Study on the Estimation of Clinical course of Alzheimer's disease. *Alzheimers Dement (N Y)*, **2019**, *5*, 398-408.
[66] Koola, M.M.; Nikiforuk, A.; Pillai, A.; Parsaik, A.K. Galantamine-memantine combination superior to donepezil-memantine combination in Alzheimer's disease: critical dissection with an emphasis on kynurenic acid and mismatch negativity. *J Geriatr Care Res*, **2018**, *5*(2), 57-67.
[67] Urrestarazu, E.; Iriarte, J. Clinical management of sleep disturbances in Alzheimer's disease: current and emerging strategies. *Nat Sci Sleep*,

2016, *8*, 21-33.
[68] Cardinali, D.P.; Vigo, D.E.; Olivar, N.; Vidal, M.F.; Brusco, L.I. Melatonin Therapy in Patients with Alzheimer's Disease. *Antioxidants (Basel)*, **2014**, *3*(2), 245-277.
[69] Cardinali, D.P.; Furio, A.M.; Brusco, L.I. Clinical aspects of melatonin intervention in Alzheimer's disease progression. *Curr Neuropharmacol*, **2010**, *8*(3), 218-227.
[70] Glass, O.M.; Hermida, A.P.; Hershenberg, R.; Schwartz, A.C. Considerations and Current Trends in the Management of the Geriatric Patient on a Consultation-Liaison Service. *Curr Psychiatry Rep*, **2020**, *22*(5), 21.
[71] Cummings, J.; Froelich, L.; Black, S.E.; Bakchine, S.; Bellelli, G.; Molinuevo, J.L.; Kressig, R.W.; Downs, P.; Caputo, A.; Strohmaier, C. Randomized, double-blind, parallel-group, 48-week study for efficacy and safety of a higher-dose rivastigmine patch (15 vs. 10 cm(2)) in Alzheimer's disease. *Dement Geriatr Cogn Disord*, **2012**, *33*(5), 341-353.
[72] Ma, Y.; Ji, J.; Li, G.; Yang, S.; Pan, S. Effects of donepezil on cognitive functions and the expression level of beta-amyloid in peripheral blood of patients with Alzheimer's disease. *Exp Ther Med*, **2018**, *15*(2), 1875-1878.

eTable 5: Characteristics of the included studies

Study name	Diagnostic criteria	Baseline dementia severity	Comparison	Subjects	Mean age	Female proportion	Treatment duration	Duration subgroup	Country
Vila-Castelar, C. (2019)[1]	NINCDS-ADRDA	mild to moderate probable AD, MMSE around 15-26	Donepezil medium dose Placebo	12 11	79.3±7.4 81.7±3.8	66.7 63.6	6 weeks	Short	USA
Jia, J. (2017)[2]	DSM-IV and NINCDS-ADRDA	moderate to severe probable AD, MMSE around 1-12	Donepezil high dose Placebo	157 156	71.6±8.6 70.0±9.6	67.5 62.2	24 weeks	Medium	China
Homma, A. (2016)[3]	DSM-IV	moderate to severe probable AD, MMSE around 1-12	Donepezil high dose Donepezil extreme high dose	161 179	76.2±8.8 75.7±8.8	69.6 69.3	24 weeks	Medium	Japan
Zhang, Z.X. (2016)[4]	NINCDS-ADRDA	moderate probable AD, MMSE around 10-20	Rivastigmine patch high dose Rivastigmine high dose	248 253	70.4±8.0 69.8±8.2	56.5 54.9	24 weeks	Medium	China
Shao, Z.Q. (2015)[5]	DSM-IV	mild to moderate probable AD, MMSE around 10-24	Memantine high dose Memantine high dose + donepezil high dose Memantine high dose + rivastigmine medium dose Memantine high dose + Galantamine low dose	22 22 22 22	73.0±7.1 73.4±6.0 73.1±7.1 73.4±7.8	50.0 54.5 50.0 50.0	24 weeks	Medium	China
Zhang, N. (2015)[6]	NINCDS-ADRDA	mild to moderate probable AD, MMSE around 10-24	Memantine high dose Donepezil high dose	80 87	69.8±8.1 70.1±8.0	61.3 59.8	24 weeks	Medium	China
Dysken, M.W. (2014)[7]	NINCDS-ADRDA	mild to moderate probable AD, MMSE around 12-26	Memantine high dose Placebo	155 152	78.8±7.2 79.4±7.0	3.9 2.0	208 weeks	Extreme long	USA
Hager, K. (2014)[8]	NINCDS-ADRDA	mild to moderate probable AD, MMSE around 10-26	Galantamine medium dose Placebo	1024 1021	73.0±8.9 73.0±8.7	65.5 64.1	104 weeks	Extreme long	Multiple countries
Wade, A.G. (2014)[9]	NA	mild to moderate AD and Mini-Mental State Examination (MMSE) score at least 15	Melatonin low dose Placebo	39 34	73.5±8.6 77.3±6.6	41.0 58.8	24 weeks	Medium	Multiple countries
Farlow, M.R. (2013)[10]	NINCDS-ADRDA	moderate to severe probable AD, MMSE around 3 to 12	Rivastigmine patch high dose Rivastigmine patch low dose	356 360	77.6±8.7 76.5±9.4	63.8 65.0	24 weeks	Medium	USA
Grossberg, G.T. (2013)[11]	DSM-IV and NINCDS-ADRDA	moderate to severe probable AD, MMSE around 3-14	Memantine extreme high dose Placebo	341 335	76.2±8.4 76.8±7.8	71.6 72.5	24 weeks	Medium	Multiple countries

Herrmann, N. (2013)[12]	NINCDS-ADRDA	moderate to severe probable AD, MMSE around 8-18	Memantine high dose Placebo	182 187	74.7±7.9 75.1±6.9	57.7 58.8	24 weeks	Medium	Canada
Wang, T. (2013)[13]	DSM-IV and NINCDS-ADRDA	moderate to severe probable AD, MMSE around 4-20	Memantine high dose Placebo	11 11	65.7±12.5 64.7±11.5	63.6 63.6	24 weeks	Medium	China
Fox, C. (2012)[14]	NINCDS-ADRDA	moderate to severe probable AD, MMSE around 1-19	Memantine high dose Placebo	72 77	84.9±6.7 84.4±6.6	72.2 75.3	12 weeks	Short	UK
Likitjaroen, Y. (2012)[15]	NINCDS-ADRDA	mild to moderate probable AD, MMSE around 22.5 ± 2.7	Galantamine medium dose Placebo	14 11	73.5±7.2 76.4±7.9	57.1 63.6	24 weeks	Medium	Germany
Maher-Edwards, G. (2011)[16]	NINCDS-ADRDA	mild to moderate probable AD, MMSE around 12-24	Donepezil high dose Placebo	67 61	71.1±8.4 71.6±6.7	63.0 70.0	24 weeks	Medium	Multiple countries
Nakamura, Y. (2011)[17]	NINCDS-ADRDA	moderate probable AD, MMSE around 10-20	Rivastigmine patch low dose Rivastigmine patch high dose Placebo	282 287 286	74.3±7.5 75.1±6.9 74.5±7.4	68.8 67.9 68.2	24 weeks	Medium	Japan
Farlow, M.R. (2010)[18]	DSM-IV and NINCDS-ADRDA	moderate to severe probable AD, MMSE around 0-20	Donepezil extreme high dose Donepezil high dose	963 471	73.9±8.5 73.8±8.6	63.0 62.4	24 weeks	Medium	Multiple countries
Burns, A. (2009)[19]	DSM-IV and NINCDS-ADRDA	moderate to severe probable AD, MMSE around 5-12	Galantamine medium dose Placebo	207 200	83.7±5.7 83.5±5.8	80.7 81.0	24 weeks	Medium	Multiple countries
Gao, Q.W. (2009)[20]	NINCDS-ADRDA	mild probable AD, MMSE around 17-24	Melatonin low dose Placebo	15 16	77.1±3.2 76.9±2.8	0.0 0.0	24 weeks	Medium	China
Bakchine, S. (2008)[21]	DSM-IV and NINCDS-ADRDA	mild to moderate probable AD, MMSE around 11-23	Memantine high dose Placebo	318 152	74.0±7.4 73.3±6.9	64.8 59.9	24 weeks	Medium	Multiple countries
Homma, A. (2008)[22]	DSM-IV	moderate to severe probable AD, MMSE around 1-12	Donepezil medium dose Donepezil high dose Placebo	96 92 102	78.0±8.9 76.9±7.9 79.7±7.5	79.2 79.3 82.4	24 weeks	Medium	Japan
Porsteinsson, A.P. (2008)[23]	NINCDS-ADRDA	mild to moderate probable AD, MMSE around 10-22	Memantine high dose Placebo	217 216	74.9±7.64 76.0±8.43	53.9 50.5	24 weeks	Medium	USA
Black, S.E. (2007)[24]	DSM-IV and NINCDS-ADRDA	moderate to severe probable AD, MMSE around 1-12	Donepezil high dose Placebo	176 167	78.0±8.0 78.0±8.2	72.7 67.7	24 weeks	Medium	Multiple countries
Howard, R.J. (2007)[25]	NINCDS-ADRDA	moderate to severe probable AD	Donepezil high dose Placebo	128 131	84.9±7.3 84.4±8.2	82.0 87.0	12 weeks	Short	UK

van Dyck, C.H. (2007)[26]	NINCDS-ADRDA	moderate to severe probable AD, MMSE around 5 to 14	Memantine high dose Placebo	178 172	78.1±8.2 78.3±7.6	72.5 70.3	24 weeks	Medium	USA
Winblad, B. (2007)[27]	NINCDS-ADRDA	moderate probable AD, MMSE around 10-20	Rivastigmine patch high dose Rivastigmine patch extreme high dose Rivastigmine high dose Placebo	291 303 294 302	73.6±7.9 74.2±7.7 72.8±8.2 73.9±7.3	68.0 66.0 65.6 66.6	24 weeks	Medium	Multiple countries
Peskind, E.R. (2006)[28]	NINCDS-ADRDA	mild to moderate probable AD, MMSE around 10-22	Memantine high dose Placebo	201 202	78.0±7.3 77.0±8.2	60.2 57.4	24 weeks	Medium	USA
Rockwood, K. (2006)[29]	NINCDS-ADRDA	mild to moderate probable AD, MMSE around 10-25	Galantamine medium dose Placebo	64 66	77.0 78.0	64.1 62.1	16 weeks	Short	Canada
Winblad, B. (2006)[30]	DSM-IV and NINCDS-ADRDA	severe probable AD, MMSE around 1-10	Donepezil high dose Placebo	128 120	84.5±6.0 85.3±5.9	78.9 74.2	24 weeks	Medium	Sweden
Brodaty, H. (2005)[31]	NINCDS-ADRDA	mild to moderate probable AD, MMSE around 10-24	Galantamine medium dose (data of general form) Placebo	326 320	76.5±7.8 76.3±8.0	63.8 64.1	26 weeks	Medium	Multiple countries
Karaman, Y. (2005)[32]	NINCDS-ADRDA	moderate probable AD, MMSE around 14 over a period of at least 6 months	Rivastigmine high dose Placebo	24 20	74.1±4.3 73.4±4.0	54.2 55.0	52 weeks	Long	Turkey
Seltzer, B. (2004)[33]	DSM-IV and NINCDS-ADRDA	mild probable AD, MMSE around 21-26	Donepezil high dose Placebo	96 57	73.3±9.6 75.1±8.8	50.0 59.6	24 weeks	Medium	USA
Tariot, P.N. (2004)[34]	NINCDS-ADRDA	moderate to severe probable AD, MMSE around 5-14	Memantine high dose + donepezil high dose Donepezil high dose + placebo	202 201	75.5±8.5 75.5±8.7	63.4 66.7	24 weeks	Medium	USA
Asayama, K. (2003)[35]	DSM-IV and NINCDS-ADRDA	not specified	Melatonin low dose Placebo	11 9	78.9±7.3 79.4±5.3	90.9 77.8	4 weeks	Short	Japan
Krishnan, K.R. (2003)[36]	DSM-IV and NINCDS-ADRDA	mild to moderate probable AD, MMSE around 10-26	Donepezil high dose Placebo	34 33	74.4±7.0 72.4±10.1	73.5 69.7	24 weeks	Medium	USA
Reisberg, B. (2003)[37]	DSM-IV and NINCDS-ADRDA	moderate to severe probable AD, MMSE around 3-14	Memantine high dose Placebo	97 84	75.5±8.2 75.8±7.3	72.2 65.5	28 weeks	Medium	USA

Singer, C. (2003)[38]	NINCDS-ADRDA	probable AD	Melatonin low dose Melatonin high dose Placebo	54 51 52	78.4±8.2 76.5±10.1 77.0±8.5	56.1	8 weeks	Short	Multiple countries
Tune, L. (2003)[39]	NINCDS-ADRDA	mild to moderate probable AD, MMSE around 10-26	Donepezil high dose Placebo	14 14	73.7 72.2	78.6 71.4	24 weeks	Medium	USA
Feldman, H. (2001)[40]	NINCDS-ADRDA	moderate to severe probable AD, screening standardized MMSE around 5 to 17	Donepezil high dose Placebo	144 146	73.3 74.0	61.1 61.0	24 weeks	Medium	Multiple countries
Tariot, P.N. (2001)[41]	NINCDS-ADRDA	mild to severe probable AD, MMSE around 5-26	Donepezil high dose Placebo	103 105	85.4 85.9	83.0 82.0	24 weeks	Medium	USA
Wilkinson, D. (2001)[42]	DSM-III-R and NINCDS-ADRDA	mild to moderate probable AD, MMSE around 13-24	Galantamine medium dose Galantamine high dose Placebo	144 54 87	72.8±8.4 75.4±7.3 74.2±8.4	57.2 57.0 59.0	12 weeks	Short	UK
Homma, A. (2000)[43]	DSM-IV	mild to moderate probable AD, MMSE around 10-26	Donepezil medium dose Placebo	116 112	70.1±7.6 69.4±8.8	68.1 66.1	24 weeks	Medium	Japan
Raskind, M.A. (2000)[44]	NINCDS-ADRDA	mild to moderate probable AD, MMSE around 11-24 over a period of at least 6 months	Galantamine medium dose Galantamine high dose Placebo	212 211 213	75.9±7.3 75.0±8.7 75.3±8.8	65.6 58.8 61.5	24 weeks	Medium	USA
Tariot, P.N. (2000)[45]	NINCDS-ADRDA	mild to moderate probable AD, MMSE around 10-22 over a period of at least 6 months	Galantamine low dose Galantamine medium dose Placebo	419 273 286	76.2±8.0 77.7±6.6 77.1±8.5	63.0 67.0 62.2	21 weeks	Short	USA
Wilcock, G.K. (2000)[46]	NINCDS-ADRDA	mild to moderate probable AD, MMSE around 11-24	Galantamine medium dose Galantamine high dose Placebo	220 218 215	71.9±8.3 72.1±8.6 72.7±7.6	63.2 63.3 61.4	24 weeks	Medium	Multiple countries
Burns, A. (1999)[47]	DSM-III-R and NINCDS-ADRDA	mild to moderate probable AD, MMSE around 10-26	Donepezil medium dose Donepezil high dose Placebo	271 273 274	72.0±8.2 72.0±8.3 71.0±8.3	60.5 56.8 55.1	30 weeks	Medium	Multiple countries
Forette, F. (1999)[48]	NINCDS-ADRDA	mild to moderate probable AD, MMSE around 12-26	Rivastigmine high dose Placebo	51 19	70.7±8.4 72.5±4.8	NA	18 weeks	Short	Multiple countries
Rosler, M. (1999)[49]	DSM-IV and NINCDS-ADRDA	mild to moderate probable AD, MMSE around 10-26	Rivastigmine low dose Rivastigmine high dose Placebo	209 164 208	72	59	26 weeks	Medium	Multiple countries

Rogers, S.L. (1998)[50]	DSM-III-R and NINCDS-ADRDA	mild to moderate probable AD, MMSE around 10-26	Donepezil high dose	157	74.6±7.5	61.8		
			Donepezil medium dose	154	72.9±7.4	63.0	24 weeks	Medium USA
			Placebo	162	72.6±7.6	61.1		

Abbreviation: AD: Alzheimer's dementia; DSM-5: Diagnostic and Statistical Manual of Mental Disorders, 5th edition; DSM-III: Diagnostic and Statistical Manual of Mental Disorders, 3rd edition; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, 4th edition; MMSE: Mini-Mental State Examination; NA: not available; NINCDS-ADRDA: National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association

References:

[1] Vila-Castelar, C.; Ly, J.J.; Kaplan, L.; Van Dyk, K.; Berger, J.T.; Macina, L.O.; Stewart, J.L.; Foldi, N.S. Attention Measures of Accuracy, Variability, and Fatigue Detect Early Response to Donepezil in Alzheimer's Disease: A Randomized, Double-blind, Placebo-Controlled Pilot Trial. *Arch Clin Neuropsychol*, **2019**, *34*(3), 277-289.

[2] Jia, J.; Wei, C.; Jia, L.; Tang, Y.; Liang, J.; Zhou, A.; Li, F.; Shi, L.; Doody, R.S. Efficacy and Safety of Donepezil in Chinese Patients with Severe Alzheimer's Disease: A Randomized Controlled Trial. *J Alzheimers Dis*, **2017**, *56*(4), 1495-1504.

[3] Homma, A.; Atarashi, H.; Kubota, N.; Nakai, K.; Takase, T. Efficacy and Safety of Sustained Release Donepezil High Dose versus Immediate Release Donepezil Standard Dose in Japanese Patients with Severe Alzheimer's Disease: A Randomized, Double-Blind Trial. *J Alzheimers Dis*, **2016**, *52*(1), 345-357.

[4] Zhang, Z.X.; Hong, Z.; Wang, Y.P.; He, L.; Wang, N.; Zhao, Z.X.; Zhao, G.; Shang, L.; Weisskopf, M.; Callegari, F.; Strohmaier, C. Rivastigmine Patch in Chinese Patients with Probable Alzheimer's disease: A 24-week, Randomized, Double-Blind Parallel-Group Study Comparing Rivastigmine Patch (9.5 mg/24 h) with Capsule (6 mg Twice Daily). *CNS Neurosci Ther*, **2016**, *22*(6), 488-496.

[5] Shao, Z.Q. Comparison of the efficacy of four cholinesterase inhibitors in combination with memantine for the treatment of Alzheimer's disease. *Int J Clin Exp Med*, **2015**, *8*(2), 2944-2948.

[6] Zhang, N.; Wei, C.; Du, H.; Shi, F.D.; Cheng, Y. The Effect of Memantine on Cognitive Function and Behavioral and Psychological Symptoms

in Mild-to-Moderate Alzheimer's Disease Patients. *Dement Geriatr Cogn Disord*, **2015**, *40*(1-2), 85-93.
[7] Dysken, M.W.; Sano, M.; Asthana, S.; Vertrees, J.E.; Pallaki, M.; Llorente, M.; Love, S.; Schellenberg, G.D.; McCarten, J.R.; Malphurs, J.; Prieto, S.; Chen, P.; Loreck, D.J.; Trapp, G.; Bakshi, R.S.; Mintzer, J.E.; Heidebrink, J.L.; Vidal-Cardona, A.; Arroyo, L.M.; Cruz, A.R.; Zachariah, S.; Kowall, N.W.; Chopra, M.P.; Craft, S.; Thielke, S.; Turvey, C.L.; Woodman, C.; Monnell, K.A.; Gordon, K.; Tomaska, J.; Segal, Y.; Peduzzi, P.N.; Guarino, P.D. Effect of vitamin E and memantine on functional decline in Alzheimer disease: the TEAM-AD VA cooperative randomized trial. *JAMA*, **2014**, *311*(1), 33-44.
[8] Hager, K.; Baseman, A.S.; Nye, J.S.; Brashear, H.R.; Han, J.; Sano, M.; Davis, B.; Richards, H.M. Effects of galantamine in a 2-year, randomized, placebo-controlled study in Alzheimer's disease. *Neuropsychiatr Dis Treat*, **2014**, *10*, 391-401.
[9] Wade, A.G.; Farmer, M.; Harari, G.; Fund, N.; Laudon, M.; Nir, T.; Frydman-Marom, A.; Zisapel, N. Add-on prolonged-release melatonin for cognitive function and sleep in mild to moderate Alzheimer's disease: a 6-month, randomized, placebo-controlled, multicenter trial. *Clin Interv Aging*, **2014**, *9*, 947-961.
[10] Farlow, M.R.; Grossberg, G.T.; Sadowsky, C.H.; Meng, X.; Somogyi, M. A 24-week, randomized, controlled trial of rivastigmine patch 13.3 mg/24 h versus 4.6 mg/24 h in severe Alzheimer's dementia. *CNS Neurosci Ther*, **2013**, *19*(10), 745-752.
[11] Grossberg, G.T.; Manes, F.; Allegri, R.F.; Gutierrez-Robledo, L.M.; Gloger, S.; Xie, L.; Jia, X.D.; Pejovic, V.; Miller, M.L.; Perhach, J.L.; Graham, S.M. The safety, tolerability, and efficacy of once-daily memantine (28 mg): a multinational, randomized, double-blind, placebo-controlled trial in patients with moderate-to-severe Alzheimer's disease taking cholinesterase inhibitors. *CNS Drugs*, **2013**, *27*(6), 469-478.
[12] Herrmann, N.; Gauthier, S.; Boneva, N.; Lemming, O.M.; Investigators. A randomized, double-blind, placebo-controlled trial of memantine in a behaviorally enriched sample of patients with moderate-to-severe Alzheimer's disease. *Int Psychogeriatr*, **2013**, *25*(6), 919-927.
[13] Wang, T.; Huang, Q.; Reiman, E.M.; Chen, K.; Li, X.; Li, G.; Lin, Z.; Li, C.; Xiao, S. Effects of memantine on clinical ratings, fluorodeoxyglucose positron emission tomography measurements, and cerebrospinal fluid assays in patients with moderate to severe Alzheimer dementia: a 24-week, randomized, clinical trial. *J Clin Psychopharmacol*, **2013**, *33*(5), 636-642.
[14] Fox, C.; Crugel, M.; Maidment, I.; Auestad, B.H.; Coulton, S.; Treloar, A.; Ballard, C.; Boustani, M.; Katona, C.; Livingston, G. Efficacy of memantine for agitation in Alzheimer's dementia: a randomised double-blind placebo controlled trial. *PLoS One*, **2012**, *7*(5), e35185.

[15] Likitjaroen, Y.; Meindl, T.; Friese, U.; Wagner, M.; Buerger, K.; Hampel, H.; Teipel, S.J. Longitudinal changes of fractional anisotropy in Alzheimer's disease patients treated with galantamine: a 12-month randomized, placebo-controlled, double-blinded study. *Eur Arch Psychiatry Clin Neurosci*, **2012**, *262*(4), 341-350.
[16] Maher-Edwards, G.; Dixon, R.; Hunter, J.; Gold, M.; Hopton, G.; Jacobs, G.; Hunter, J.; Williams, P. SB-742457 and donepezil in Alzheimer disease: a randomized, placebo-controlled study. *Int J Geriatr Psychiatry*, **2011**, *26*(5), 536-544.
[17] Nakamura, Y.; Imai, Y.; Shigeta, M.; Graf, A.; Shirahase, T.; Kim, H.; Fujii, A.; Mori, J.; Homma, A. A 24-week, randomized, double-blind, placebo-controlled study to evaluate the efficacy, safety and tolerability of the rivastigmine patch in Japanese patients with Alzheimer's disease. *Dement Geriatr Cogn Dis Extra*, **2011**, *1*(1), 163-179.
[18] Farlow, M.R.; Salloway, S.; Tariot, P.N.; Yardley, J.; Moline, M.L.; Wang, Q.; Brand-Schieber, E.; Zou, H.; Hsu, T.; Satlin, A. Effectiveness and tolerability of high-dose (23 mg/d) versus standard-dose (10 mg/d) donepezil in moderate to severe Alzheimer's disease: A 24-week, randomized, double-blind study. *Clin Ther*, **2010**, *32*(7), 1234-1251.
[19] Burns, A.; Bernabei, R.; Bullock, R.; Cruz Jentoft, A.J.; Frolich, L.; Hock, C.; Raivio, M.; Triau, E.; Vandewoude, M.; Wimo, A.; Came, E.; Van Baelen, B.; Hammond, G.L.; van Oene, J.C.; Schwalen, S. Safety and efficacy of galantamine (Reminyl) in severe Alzheimer's disease (the SERAD study): a randomised, placebo-controlled, double-blind trial. *Lancet Neurol*, **2009**, *8*(1), 39-47.
[20] Gao, Q.W.; Lio, Y.; Luo, G.Q.; Xiang, W.; Peng, K.R. Effect of melatonin on mild Alzheimer’s disease in elderly male patients. *Parct Geriatr*, **2009**, *23*(1), 56-58.
[21] Bakchine, S.; Loft, H. Memantine treatment in patients with mild to moderate Alzheimer's disease: results of a randomised, double-blind, placebo-controlled 6-month study. *J Alzheimers Dis*, **2008**, *13*(1), 97-107.
[22] Homma, A.; Imai, Y.; Tago, H.; Asada, T.; Shigeta, M.; Iwamoto, T.; Takita, M.; Arimoto, I.; Koma, H.; Ohbayashi, T. Donepezil treatment of patients with severe Alzheimer's disease in a Japanese population: results from a 24-week, double-blind, placebo-controlled, randomized trial. *Dement Geriatr Cogn Disord*, **2008**, *25*(5), 399-407.
[23] Porsteinsson, A.P.; Grossberg, G.T.; Mintzer, J.; Olin, J.T.; Memantine, M.E.M.M.D.S.G. Memantine treatment in patients with mild to moderate Alzheimer's disease already receiving a cholinesterase inhibitor: a randomized, double-blind, placebo-controlled trial. *Curr Alzheimer*

Res, **2008**, *5*(1), 83-89.
[24] Black, S.E.; Doody, R.; Li, H.; McRae, T.; Jambor, K.M.; Xu, Y.; Sun, Y.; Perdomo, C.A.; Richardson, S. Donepezil preserves cognition and global function in patients with severe Alzheimer disease. *Neurology*, **2007**, *69*(5), 459-469.
[25] Howard, R.J.; Juszczak, E.; Ballard, C.G.; Bentham, P.; Brown, R.G.; Bullock, R.; Burns, A.S.; Holmes, C.; Jacoby, R.; Johnson, T.; Knapp, M.; Lindesay, J.; O'Brien, J.T.; Wilcock, G.; Katona, C.; Jones, R.W.; DeCesare, J.; Rodger, M.; Group, C.-A.T. Donepezil for the treatment of agitation in Alzheimer's disease. *N Engl J Med*, **2007**, *357*(14), 1382-1392.
[26] van Dyck, C.H.; Tariot, P.N.; Meyers, B.; Malca Resnick, E.; Memantine, M.E.M.M.D.S.G. A 24-week randomized, controlled trial of memantine in patients with moderate-to-severe Alzheimer disease. *Alzheimer Dis Assoc Disord*, **2007**, *21*(2), 136-143.
[27] Winblad, B.; Cummings, J.; Andreasen, N.; Grossberg, G.; Onofrj, M.; Sadowsky, C.; Zechner, S.; Nagel, J.; Lane, R. A six-month double-blind, randomized, placebo-controlled study of a transdermal patch in Alzheimer's disease--rivastigmine patch versus capsule. *Int J Geriatr Psychiatry*, **2007**, *22*(5), 456-467.
[28] Peskind, E.R.; Potkin, S.G.; Pomara, N.; Ott, B.R.; Graham, S.M.; Olin, J.T.; McDonald, S. Memantine treatment in mild to moderate Alzheimer disease: a 24-week randomized, controlled trial. *Am J Geriatr Psychiatry*, **2006**, *14*(8), 704-715.
[29] Rockwood, K.; Fay, S.; Song, X.; MacKnight, C.; Gorman, M.; Video-Imaging Synthesis of Treating Alzheimer's Disease, I. Attainment of treatment goals by people with Alzheimer's disease receiving galantamine: a randomized controlled trial. *CMAJ*, **2006**, *174*(8), 1099-1105.
[30] Winblad, B.; Kilander, L.; Eriksson, S.; Minthon, L.; Batsman, S.; Wetterholm, A.L.; Jansson-Blixt, C.; Haglund, A.; Severe Alzheimer's Disease Study, G. Donepezil in patients with severe Alzheimer's disease: double-blind, parallel-group, placebo-controlled study. *Lancet*, **2006**, *367*(9516), 1057-1065.
[31] Brodaty, H.; Corey-Bloom, J.; Potocnik, F.C.; Truyen, L.; Gold, M.; Damaraju, C.R. Galantamine prolonged-release formulation in the treatment of mild to moderate Alzheimer's disease. *Dement Geriatr Cogn Disord*, **2005**, *20*(2-3), 120-132.
[32] Karaman, Y.; Erdogan, F.; Koseoglu, E.; Turan, T.; Ersoy, A.O. A 12-month study of the efficacy of rivastigmine in patients with advanced moderate Alzheimer's disease. *Dement Geriatr Cogn Disord*, **2005**, *19*(1), 51-56.
[33] Seltzer, B.; Zolnouni, P.; Nunez, M.; Goldman, R.; Kumar, D.; Ieni, J.; Richardson, S.; Donepezil "402" Study, G. Efficacy of donepezil in early-

stage Alzheimer disease: a randomized placebo-controlled trial. *Arch Neurol*, **2004**, *61*(12), 1852-1856.
[34] Tariot, P.N.; Farlow, M.R.; Grossberg, G.T.; Graham, S.M.; McDonald, S.; Gergel, I.; Memantine Study, G. Memantine treatment in patients with moderate to severe Alzheimer disease already receiving donepezil: a randomized controlled trial. *JAMA*, **2004**, *291*(3), 317-324.
[35] Asayama, K.; Yamadera, H.; Ito, T.; Suzuki, H.; Kudo, Y.; Endo, S. Double blind study of melatonin effects on the sleep-wake rhythm, cognitive and non-cognitive functions in Alzheimer type dementia. *J Nippon Med Sch*, **2003**, *70*(4), 334-341.
[36] Krishnan, K.R.; Charles, H.C.; Doraiswamy, P.M.; Mintzer, J.; Weisler, R.; Yu, X.; Perdomo, C.; Ieni, J.R.; Rogers, S. Randomized, placebo-controlled trial of the effects of donepezil on neuronal markers and hippocampal volumes in Alzheimer's disease. *Am J Psychiatry*, **2003**, *160*(11), 2003-2011.
[37] Reisberg, B.; Doody, R.; Stoffler, A.; Schmitt, F.; Ferris, S.; Mobius, H.J.; Memantine Study, G. Memantine in moderate-to-severe Alzheimer's disease. *N Engl J Med*, **2003**, *348*(14), 1333-1341.
[38] Singer, C.; Tractenberg, R.E.; Kaye, J.; Schafer, K.; Gamst, A.; Grundman, M.; Thomas, R.; Thal, L.J.; Alzheimer's Disease Cooperative, S. A multicenter, placebo-controlled trial of melatonin for sleep disturbance in Alzheimer's disease. *Sleep*, **2003**, *26*(7), 893-901.
[39] Tune, L.; Tiseo, P.J.; Ieni, J.; Perdomo, C.; Pratt, R.D.; Votaw, J.R.; Jewart, R.D.; Hoffman, J.M. Donepezil HCl (E2020) maintains functional brain activity in patients with Alzheimer disease: results of a 24-week, double-blind, placebo-controlled study. *Am J Geriatr Psychiatry*, **2003**, *11*(2), 169-177.
[40] Feldman, H.; Gauthier, S.; Hecker, J.; Vellas, B.; Subbiah, P.; Whalen, E.; Donepezil, M.S.I.G. A 24-week, randomized, double-blind study of donepezil in moderate to severe Alzheimer's disease. *Neurology*, **2001**, *57*(4), 613-620.
[41] Tariot, P.N.; Cummings, J.L.; Katz, I.R.; Mintzer, J.; Perdomo, C.A.; Schwam, E.M.; Whalen, E. 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*, **2001**, *49*(12), 1590-1599.
[42] Wilkinson, D.; Murray, J. Galantamine: a randomized, double-blind, dose comparison in patients with Alzheimer's disease. *Int J Geriatr Psychiatry*, **2001**, *16*(9), 852-857.
[43] Homma, A.; Takeda, M.; Imai, Y.; Udaka, F.; Hasegawa, K.; Kameyama, M.; Nishimura, T. 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. E2020 Study Group. *Dement Geriatr Cogn Disord*, **2000**, *11*(6), 299-313.
[44] Raskind, M.A.; Peskind, E.R.; Wessel, T.; Yuan, W. Galantamine in AD: A 6-month randomized, placebo-controlled trial with a 6-month extension. The Galantamine USA-1 Study Group. *Neurology*, **2000**, *54*(12), 2261-2268.
[45] Tariot, P.N.; Solomon, P.R.; Morris, J.C.; Kershaw, P.; Lilienfeld, S.; Ding, C. A 5-month, randomized, placebo-controlled trial of galantamine in AD. The Galantamine USA-10 Study Group. *Neurology*, **2000**, *54*(12), 2269-2276.
[46] Wilcock, G.K.; Lilienfeld, S.; Gaens, E. Efficacy and safety of galantamine in patients with mild to moderate Alzheimer's disease: multicentre randomised controlled trial. Galantamine International-1 Study Group. *BMJ*, **2000**, *321*(7274), 1445-1449.
[47] Burns, A.; Rossor, M.; Hecker, J.; Gauthier, S.; Petit, H.; Moller, H.J.; Rogers, S.L.; Friedhoff, L.T. The effects of donepezil in Alzheimer's disease - results from a multinational trial. *Dement Geriatr Cogn Disord*, **1999**, *10*(3), 237-244.
[48] Forette, F.; Anand, R.; Gharabawi, G. A phase II study in patients with Alzheimer's disease to assess the preliminary efficacy and maximum tolerated dose of rivastigmine (Exelon). *Eur J Neurol*, **1999**, *6*(4), 423-429.
[49] Rosler, M.; Anand, R.; Cicin-Sain, A.; Gauthier, S.; Agid, Y.; Dal-Bianco, P.; Stahelin, H.B.; Hartman, R.; Gharabawi, M. Efficacy and safety of rivastigmine in patients with Alzheimer's disease: international randomised controlled trial. *BMJ*, **1999**, *318*(7184), 633-638.
[50] Rogers, S.L.; Farlow, M.R.; Doody, R.S.; Mohs, R.; Friedhoff, L.T. A 24-week, double-blind, placebo-controlled trial of donepezil in patients with Alzheimer's disease. Donepezil Study Group. *Neurology*, **1998**, *50*(1), 136-145.

eTable 6A: SUCRA of the improvement of cognition (measured by MMSE)

Treatment	SUCRA
MLT	83.4
MED	81.1
SHD	80.7
GMMH	74.0
SHM	73.0
MHD	72.0
MMD	70.4
LHR	68.9
RMMH	59.3
DMMH	58.2
EMG	54.7
MHPR	53.6
MEPR	52.8
MHR	50.0
MHM	41.6
SLT	28.2
EHM	28.2
MLPR	27.8
SMD	27.4

Pla	19.5
MMG	17.5
MLR	15.5
SHT	12.2

Sorted by efficacy rankings, with superior treatments (those producing the greatest improvement in cognition) listed first

eTable 6B: SUCRA of the improvement of cognition (measured by MMSE): subgroup of medium-term treatment duration

Treatment	SUCRA
MLT	84.2
MED	82.0
GMMH	73.9
MHD	71.2
MMD	69.1
RMMH	57.8
DMMH	56.4
MEPR	52.3
MHPR	51.3
MHR	48.1
MHM	38.9
MLPR	24.6
Pla	15.2
MMG	13.4
MLR	11.6

Sorted by efficacy rankings, with superior treatments (those producing the greatest improvement in cognition) listed first

eTable 6C: SUCRA of the improvement of cognition (measured by MMSE): subgroup of exclude concomitant medication

Treatment	SUCRA
SHD	77.9
GMMH	76.9
MLT	74.6
MHD	66.1
MMD	66.0
LHR	64.6
DMMH	60.2
RMMH	60.1
SLT	50.6
MEPR	49.2
MHPR	48.4
MHR	44.2
MHM	42.6
SMD	23.2
MLPR	21.5
Pla	13.4
MLR	10.4

Sorted by efficacy rankings, with superior treatments (those producing the greatest improvement in cognition) listed first

eTable 6D: SUCRA of the improvement of quality of life

Treatment	SUCRA
MLT	11.0
GMMH	13.9
DMMH	20.8
MHD	39.4
SLG	39.5
SLT	42.9
MED	43.0
SMG	43.4
MEPR	46.4
LHR	47.3
MHPR	48.8
RMMH	48.9
MHG	49.5
MHR	49.8
MMD	52.7
EHM	57.6
SHR	61.3
SHT	64.7
MMG	64.9

MLPR	65.6
MHM	66.5
MEM	67.2
MLR	71.9
Pla	83.1

Sorted by efficacy rankings, with superior treatments (those producing the greatest improvement in quality of life) listed first

eTable 6E: SUCRA of the improvement of behavioral disturbance

Treatment	SUCRA
SHM	6.5
SLT	13.2
DMMH	23.8
MEM	34.6
SMG	35.4
SHR	41.3
SLG	45.8
MMG	51.1
MHR	56.1
MEPR	56.5
MMD	57.2
MHM	59.7
MHD	60.2
EHM	61.5
MHPR	63.7
SHD	64.8
SHT	70.5
Pla	72.5
MLPR	75.6

Sorted by efficacy rankings, with superior treatments (those producing the greatest improvement in behavioral disturbance) listed first

eTable 6F: SUCRA of the acceptability in aspect of drop-out rate

Treatment	SUCRA
SLT	88.4
SMD	85.5
DMMH	84.3
SHD	80.9
GMMH	77.8
MMD	77.2
MLR	71.3
EMG	70.4
Pla	66.6
MHM	65.3
SHT	62.9
MEM	61.4
EHM	58.7
MHD	54.3
SHM	44.1
MLT	42.4
MMG	41.2
SLG	41.1
RMMH	40.4

SMG	38.7
MLPR	30.6
MHPR	28.2
MEPR	26.2
MHG	16.9
MHR	16.8
MED	14.2
SHR	9.0
SHG	5.2

Sorted by tolerability rankings, with superior treatments (those producing the lowest drop-out rate) listed first

eTable 6G: SUCRA of the rate of any adverse event reported

Treatment	SUCRA
MLR	92.2
MEM	87.0
Pla	85.8
MHM	83.8
EHM	72.4
SLG	71.4
EMG	68.9
MMD	66.2
SHT	63.4
LHR	63.4
MMG	61.2
GMMH	53.3
MLPR	53.2
MHPR	51.7
SLT	47.4
MHD	44.3
SMG	42.4
MLT	34.8
RMMH	31.7

DMMH	27.9
MHG	23.5
MHR	22.0
MEPR	19.6
MED	16.7
SHG	15.0
SHR	0.8

Sorted by tolerability rankings, with superior treatments (those producing the lowest rate of any adverse event reported) listed first

Abbreviation: CI: confidence interval; DMMH: medium-term high dose memantine plus high dose donepezil; EHM: extreme-long-term high dose memantine; EMG: extreme-long-term medium dose galantamine; ES: effect size; GMMH: medium-term high dose memantine plus low dose galantamine; LHR: long-term high dose rivastigmine; LLT: long-term low dose melatonin; MA: meta-analysis; MD: mean difference; MED: medium-term extreme high dose donepezil; MEM: medium-term extreme high dose memantine; MEPR: medium-term extreme high dose rivastigmine patch; MHD: medium-term high dose donepezil; MHG: medium-term high dose galantamine; MHM: medium-term high dose memantine; MHPR: medium-term high dose rivastigmine patch; MHR: medium-term high dose rivastigmine; MLPR: medium-term low dose rivastigmine patch; MLR: medium-term low dose rivastigmine; MLT: medium-term low dose melatonin; MMD: medium-term donepezil medium dose; MMG: medium-term medium dose galantamine; MMSE: mini-mental status examination; NMA: network meta-analysis; OR: odds ratio; Pla: Placebo; PRISMA: preferred reporting items for systematic reviews and meta-analyses; RCT: randomized controlled trial; RMMH: medium-term high dose memantine plus medium dose rivastigmine; SHD: short-term high dose donepezil; SHG: short-term high dose galantamine; SHM: short-term high dose memantine; SHR: short-term high dose rivastigmine; SHT: short-term high dose melatonin; SLG: short-term low dose galantamine; SLT: short-term low dose melatonin; SMD: short-term medium dose donepezil; SMG: short-term medium dose galantamine; SMT: short-term medium dose melatonin; StMD: standardized mean difference; SUCRA: surface under the cumulative ranking curve

eTable 7A: League table of the improvement of cognition (measured by MMSE) : subgroup of medium-term treatment duration

MLT												***1.48 (0.54,2.43)**		
0.14 (-1.10,1.38)	MED		0.30 (-0.32,0.92)											
0.16 (-1.69,2.01)	0.02 (-1.72,1.77)	GMMH			0.41 (-1.07,1.89)	0.45 (-0.85,1.75)				0.82 (-0.58,2.22)				
0.44 (-0.58,1.45)	0.30 (-0.41,1.01)	0.28 (-1.32,1.87)	MHD	0.15 (-0.65,0.95)						-0.37 (-1.94,1.20)		***1.08 (0.83,1.34)**		
0.43 (-0.81,1.66)	0.29 (-0.75,1.33)	0.26 (-1.48,2.01)	-0.01 (-0.78,0.75)	MMD								***1.21 (0.42,2.00)**		
0.57 (-1.42,2.56)	0.43 (-1.45,2.32)	0.41 (-1.11,1.93)	0.13 (-1.62,1.89)	0.15 (-1.75,2.04)	RMMH	0.04 (-1.45,1.53)				0.41 (-1.17,1.99)				
0.61 (-1.24,2.47)	0.47 (-1.28,2.22)	0.45 (-0.89,1.79)	0.17 (-1.43,1.77)	0.19 (-1.57,1.94)	0.04 (-1.49,1.57)	DMMH				0.37 (-1.04,1.78)				
0.76 (-0.37,1.89)	0.62 (-0.34,1.58)	0.60 (-1.08,2.27)	0.32 (-0.33,0.97)	0.33 (-0.63,1.29)	0.19 (-1.64,2.01)	0.15 (-1.54,1.83)	MEPR	-0.20 (-0.74,0.34)	0.10 (-0.43,0.63)			***0.90 (0.35,1.45)**		
0.77 (-0.29,1.82)	0.63 (-0.24,1.50)	0.60 (-1.02,2.23)	0.33 (-0.17,0.83)	0.34 (-0.53,1.21)	0.19 (-1.59,1.97)	0.15 (-1.48,1.78)	0.01 (-0.56,0.58)	MHPR	0.21 (-0.18,0.59)		0.30 (-0.23,0.83)	0.69 (-0.09,1.48)		
0.82 (-0.25,1.89)	0.68 (-0.20,1.56)	0.66 (-0.97,2.29)	0.38 (-0.14,0.91)	0.39 (-0.49,1.27)	0.25 (-1.54,2.03)	0.21 (-1.43,1.84)	0.06 (-0.51,0.63)	0.05 (-0.36,0.46)	MHR			***0.83 (0.39,1.26)**		***0.94 (0.24,1.64)**
0.98 (-0.18,2.14)	0.84 (-0.14,1.83)	0.82 (-0.62,2.26)	0.54 (-0.13,1.22)	0.56 (-0.43,1.54)	0.41 (-1.20,2.02)	0.37 (-1.08,1.82)	0.22 (-0.63,1.08)	0.22 (-0.53,0.96)	0.16 (-0.60,0.93)	MHM		0.33 (-0.31,0.97)		
***1.28 (0.14,2.41)**	***1.14 (0.18,2.10)**	1.12 (-0.56,2.79)	***0.84 (0.19,1.49)**	0.85 (-0.11,1.81)	0.71 (-1.12,2.54)	0.67 (-1.02,2.35)	0.52 (-0.24,1.29)	0.51 (-0.07,1.10)	0.46 (-0.20,1.12)	0.30 (-0.56,1.15)	MLPR	0.00 (-0.52,0.52)		
***1.48 (0.51,2.46)**	***1.35 (0.58,2.11)**	1.32 (-0.25,2.89)	***1.05 (0.76,1.33)**	***1.06 (0.29,1.82)**	0.91 (-0.82,2.65)	0.87 (-0.71,2.45)	***0.73 (0.15,1.30)**	***0.72 (0.31,1.12)**	***0.67 (0.23,1.10)**	0.50 (-0.13,1.13)	0.20 (-0.38,0.79)	Pla	0.70 (-1.67,3.07)	0.06 (-0.66,0.78)
2.18 (-0.40,4.77)	2.05 (-0.47,4.56)	2.02 (-0.84,4.88)	1.75 (-0.66,4.16)	1.76 (-0.75,4.27)	1.61 (-1.34,4.57)	1.57 (-1.30,4.44)	1.43 (-1.04,3.89)	1.42 (-1.01,3.85)	1.37 (-1.07,3.80)	1.20 (-1.27,3.68)	0.90 (-1.56,3.37)	0.70 (-1.69,3.09)	MMG	
***1.65 (0.45,2.86)**	***1.52 (0.47,2.56)**	1.49 (-0.23,3.21)	***1.22 (0.45,1.98)**	***1.23 (0.19,2.27)**	1.08 (-0.79,2.95)	1.04 (-0.69,2.77)	***0.90 (0.04,1.75)**	***0.89 (0.13,1.64)**	***0.84 (0.13,1.54)**	0.67 (-0.28,1.62)	0.38 (-0.51,1.26)	0.17 (-0.54,0.88)	-0.53 (-3.03,1.97)	MLR

Pairwise (upper-right portion) and network (lower-left portion) meta-analysis results are presented as estimated effect sizes for the outcome of improvement of cognition in patients with tinnitus. Interventions are reported in order of mean ranking of cognition improvement, and outcomes are expressed as mean difference (MD) (95% confidence intervals). For the pairwise meta-analyses, MD of more than 0 indicate that the treatment specified in the row had more improvement than that specified in the column. For the network meta-analysis (NMA), MD of more than 0 indicate that the treatment specified in the column had more improvement than that specified in the row. Bold results marked with * indicate statistical significance.

eTable 7B: League table of the improvement of cognition (measured by MMSE) : subgroup of exclude concomitant medication

SHD															***1.50 (0.15,2.85)**	
0.03 (-2.15,2.21)	GMMH					0.45 (-0.85,1.75)	0.41 (-1.89,1.07)					0.82 (-0.58,2.22)				
0.10 (-1.82,2.02)	0.07 (-2.03,2.18)	MLT													***1.40 (0.17,2.63)**	
0.48 (-0.97,1.92)	0.45 (-1.23,2.12)	0.38 (-0.96,1.71)	MHD	0.15 (-0.65,0.95)								-0.37 (-1.94,1.20)			***1.06 (0.78,1.34)**	
0.45 (-1.16,2.07)	0.42 (-1.41,2.26)	0.35 (-1.17,1.87)	-0.02 (-0.82,0.77)	MMD											***1.21 (0.42,2.00)**	
0.50 (-0.99,1.99)	0.47 (-1.26,2.20)	0.40 (-0.99,1.79)	0.02 (-0.56,0.60)	0.05 (-0.88,0.98)	LHR										***1.00 (0.72,1.28)**	
0.48 (-1.70,2.66)	0.45 (-0.91,1.81)	0.38 (-1.73,2.49)	0.00 (-1.68,1.69)	0.03 (-1.81,1.86)	-0.02 (-1.76,1.72)	DMMH	-0.04 (-1.53,1.45)					0.37 (-1.04,1.78)				
0.44 (-1.86,2.74)	0.41 (-1.13,1.95)	0.34 (-1.89,2.57)	-0.04 (-1.87,1.79)	-0.01 (-1.99,1.96)	-0.06 (-1.94,1.82)	-0.04 (-1.59,1.51)	RMMH					0.41 (-1.17,1.99)				
0.70 (-2.05,3.45)	0.67 (-2.21,3.55)	0.60 (-2.09,3.29)	0.22 (-2.15,2.60)	0.25 (-2.24,2.73)	0.20 (-2.20,2.60)	0.22 (-2.66,3.10)	0.26 (-2.71,3.23)	SLT							0.80 (-1.52,3.12)	
0.77 (-0.77,2.31)	0.74 (-1.02,2.51)	0.67 (-0.76,2.11)	0.29 (-0.39,0.98)	0.32 (-0.68,1.32)	0.27 (-0.51,1.06)	0.29 (-1.48,2.07)	0.33 (-1.58,2.24)	0.07 (-2.36,2.50)	MEPR	-0.20 (-0.74,0.34)	0.10 (-0.43,0.63)				***0.90 (0.35,1.45)**	
0.78 (-0.70,2.25)	0.75 (-0.96,2.46)	0.68 (-0.69,2.05)	0.30 (-0.23,0.84)	0.32 (-0.58,1.23)	0.28 (-0.37,0.93)	0.30 (-1.42,2.02)	0.34 (-1.52,2.20)	0.08 (-2.32,2.47)	0.01 (-0.60,0.61)	MHPR	0.21 (-0.18,0.59)			0.30 (-0.23,0.83)	0.69 (-0.09,1.48)	
0.83 (-0.66,2.31)	0.80 (-0.92,2.52)	0.73 (-0.65,2.11)	0.35 (-0.21,0.91)	0.38 (-0.54,1.29)	0.33 (-0.34,1.00)	0.35 (-1.38,2.08)	0.39 (-1.48,2.26)	0.13 (-2.27,2.53)	0.06 (-0.55,0.67)	0.05 (-0.38,0.49)	MHR				***0.83 (0.39,1.26)**	***0.94 (0.24,1.64)**
0.85 (-0.77,2.47)	0.82 (-0.64,2.28)	0.75 (-0.77,2.27)	0.37 (-0.46,1.20)	0.40 (-0.71,1.50)	0.35 (-0.58,1.28)	0.37 (-1.10,1.84)	0.41 (-1.22,2.04)	0.15 (-2.33,2.63)	0.08 (-0.92,1.07)	0.07 (-0.82,0.97)	0.02 (-0.89,0.93)	MHM			0.41 (-0.40,1.22)	
1.60 (-0.83,4.03)	1.57 (-1.01,4.15)	1.50 (-0.87,3.87)	1.12 (-0.88,3.13)	1.15 (-0.99,3.28)	1.10 (-0.94,3.14)	1.12 (-1.47,3.71)	1.16 (-1.53,3.85)	0.90 (-2.18,3.98)	0.83 (-1.25,2.90)	0.82 (-1.21,2.85)	0.77 (-1.27,2.81)	0.75 (-1.38,2.89)	SMD		-0.10 (-2.04,1.84)	
1.29 (-0.25,2.83)	1.26 (-0.50,3.03)	1.19 (-0.25,2.63)	***0.82 (0.12,1.51)**	0.84 (-0.16,1.84)	***0.79 (0.00,1.58)**	0.81 (-0.96,2.59)	0.85 (-1.06,2.77)	0.59 (-1.84,3.03)	0.52 (-0.29,1.33)	0.51 (-0.11,1.13)	0.46 (-0.24,1.16)	0.44 (-0.56,1.44)	-0.31 (-2.38,1.77)	MLPR	0.00 (-0.52,0.52)	
***1.50 (0.09,2.91)**	1.47 (-0.19,3.13)	***1.40 (0.10,2.70)**	***1.02 (0.71,1.34)**	***1.05 (0.26,1.84)**	***1.00 (0.51,1.49)**	1.02 (-0.64,2.69)	1.06 (-0.75,2.87)	0.80 (-1.55,3.15)	***0.73 (0.12,1.34)**	***0.72 (0.29,1.15)**	***0.67 (0.21,1.13)**	0.65 (-0.14,1.44)	-0.10 (-2.08,1.88)	0.21 (-0.41,0.83)	Pla	0.06 (-0.66,0.78)
***1.67 (0.07,3.26)**	1.64 (-0.17,3.45)	***1.57 (0.07,3.06)**	***1.19 (0.39,1.99)**	***1.21 (0.13,2.30)**	***1.17 (0.28,2.05)**	1.19 (-0.63,3.01)	1.23 (-0.73,3.18)	0.97 (-1.50,3.44)	0.90 (-0.00,1.79)	***0.89 (0.10,1.68)**	***0.84 (0.10,1.57)**	0.82 (-0.26,1.90)	0.07 (-2.05,2.18)	0.38 (-0.56,1.31)	0.17 (-0.57,0.91)	MLR

Pairwise (upper-right portion) and network (lower-left portion) meta-analysis results are presented as estimated effect sizes for the outcome of improvement of cognition in patients with tinnitus. Interventions are reported in order of mean ranking of cognition improvement, and outcomes are expressed as mean difference (MD) (95% confidence intervals). For the pairwise meta-analyses, MD of more than 0 indicate that the treatment specified in the row had more improvement than that specified in the column. For the network meta-analysis (NMA), MD of more than 0 indicate that the treatment specified in the column had more improvement than that specified in the row. Bold results marked with * indicate statistical significance.

eTable 7C: League table of the improvement of quality of life

MLT																						***-0.63 (-1.02,-0.23)**
-0.00 (-0.82,0.82)	GMMH	-0.22 (-0.81,0.38)									-0.41 (-1.01,0.18)									-0.49 (-1.09,0.11)			
-0.17 (-0.80,0.47)	-0.17 (-0.81,0.48)	DMMH	***-0.24 (-0.46,-0.02)**								-0.20 (-0.79,0.39)									-0.28 (-0.87,0.32)			
-0.37 (-0.89,0.16)	-0.37 (-1.02,0.29)	-0.20 (-0.58,0.18)	MHD			-0.01 (-0.13,0.12)								-0.08 (-0.22,0.07)						-0.01 (-0.31,0.30)			***-0.31 (-0.59,-0.02)**
-0.34 (-0.99,0.30)	-0.34 (-1.12,0.43)	-0.18 (-0.76,0.40)	0.02 (-0.44,0.48)	SLG			-0.03 (-0.20,0.15)																***-0.29 (-0.46,-0.12)**
-0.36 (-1.05,0.34)	-0.36 (-1.18,0.47)	-0.19 (-0.84,0.45)	0.01 (-0.53,0.54)	-0.01 (-0.66,0.64)	SLT												-0.03 (-0.41,0.36)						-0.79 (-2.59,1.01)
-0.37 (-1.03,0.28)	-0.37 (-1.14,0.40)	-0.21 (-0.76,0.34)	-0.01 (-0.41,0.39)	-0.03 (-0.64,0.58)	-0.02 (-0.68,0.65)	MED																	
-0.37 (-1.02,0.28)	-0.37 (-1.15,0.41)	-0.20 (-0.79,0.38)	-0.01 (-0.47,0.46)	-0.03 (-0.44,0.39)	-0.01 (-0.67,0.64)	0.00 (-0.61,0.61)	SMG																***-0.27 (-0.45,-0.08)**
-0.40 (-1.01,0.21)	-0.40 (-1.16,0.35)	-0.24 (-0.78,0.31)	-0.04 (-0.45,0.38)	-0.06 (-0.61,0.50)	-0.04 (-0.67,0.58)	-0.03 (-0.60,0.55)	-0.03 (-0.59,0.53)	MEPR		-0.01 (-0.17,0.15)			-0.05 (-0.21,0.11)										***-0.23 (-0.39,-0.07)**
-0.39 (-1.27,0.48)	-0.39 (-1.37,0.58)	-0.23 (-1.06,0.60)	-0.03 (-0.78,0.72)	-0.05 (-0.88,0.78)	-0.04 (-0.92,0.84)	-0.02 (-0.87,0.83)	-0.02 (-0.86,0.81)	0.01 (-0.80,0.82)	LHR														-0.24 (-0.86,0.37)
-0.43 (-0.98,0.12)	-0.43 (-1.13,0.28)	-0.26 (-0.74,0.22)	-0.06 (-0.38,0.26)	-0.08 (-0.57,0.41)	-0.07 (-0.63,0.49)	-0.05 (-0.56,0.46)	-0.06 (-0.55,0.44)	-0.03 (-0.39,0.34)	-0.03 (-0.80,0.74)	MHPR			-0.01 (-0.14,0.12)						***-0.12 (-0.23,-0.01)**			***-0.21 (-0.33,-0.10)**
-0.41 (-1.23,0.40)	-0.41 (-1.12,0.29)	-0.25 (-0.89,0.40)	-0.05 (-0.70,0.61)	-0.07 (-0.85,0.71)	-0.06 (-0.88,0.77)	-0.04 (-0.81,0.73)	-0.04 (-0.82,0.74)	-0.01 (-0.76,0.74)	-0.02 (-0.99,0.96)	0.01 (-0.69,0.72)	RMMH									-0.08 (-0.67,0.51)			
-0.42 (-1.05,0.21)	-0.42 (-1.19,0.35)	-0.25 (-0.82,0.31)	-0.05 (-0.50,0.39)	-0.07 (-0.65,0.50)	-0.06 (-0.70,0.58)	-0.05 (-0.64,0.55)	-0.05 (-0.63,0.53)	-0.02 (-0.56,0.53)	-0.03 (-0.85,0.80)	0.01 (-0.47,0.48)	-0.01 (-0.77,0.76)	MHG						-0.08 (-0.30,0.14)					***-0.24 (-0.46,-0.02)**
-0.43 (-0.99,0.12)	-0.43 (-1.14,0.28)	-0.26 (-0.75,0.22)	-0.07 (-0.39,0.26)	-0.09 (-0.58,0.41)	-0.07 (-0.64,0.49)	-0.06 (-0.57,0.46)	-0.06 (-0.56,0.44)	-0.03 (-0.40,0.34)	-0.04 (-0.81,0.73)	-0.00 (-0.27,0.26)	-0.02 (-0.72,0.69)	-0.01 (-0.49,0.47)	MHR								-0.17 (-0.38,0.03)	***-0.19 (-0.32,-0.07)**
-0.45 (-1.02,0.11)	-0.45 (-1.16,0.25)	-0.29 (-0.75,0.18)	-0.09 (-0.37,0.20)	-0.11 (-0.61,0.40)	-0.10 (-0.67,0.48)	-0.08 (-0.57,0.41)	-0.08 (-0.59,0.43)	-0.05 (-0.52,0.42)	-0.06 (-0.84,0.72)	-0.03 (-0.41,0.36)	-0.04 (-0.74,0.66)	-0.03 (-0.52,0.46)	-0.02 (-0.41,0.37)	MMD								-0.14 (-0.28,0.01)
-0.49 (-1.15,0.17)	-0.49 (-1.28,0.31)	-0.32 (-0.92,0.28)	-0.12 (-0.61,0.36)	-0.14 (-0.75,0.47)	-0.13 (-0.80,0.54)	-0.11 (-0.74,0.51)	-0.12 (-0.73,0.50)	-0.09 (-0.66,0.49)	-0.09 (-0.94,0.76)	-0.06 (-0.58,0.46)	-0.07 (-0.87,0.72)	-0.07 (-0.67,0.53)	-0.06 (-0.58,0.46)	-0.03 (-0.57,0.50)	EHM							-0.15 (-0.38,0.08)
-0.55 (-1.36,0.27)	-0.55 (-1.47,0.38)	-0.38 (-1.15,0.38)	-0.18 (-0.86,0.49)	-0.20 (-0.98,0.57)	-0.19 (-1.01,0.63)	-0.17 (-0.96,0.61)	-0.18 (-0.95,0.60)	-0.15 (-0.90,0.60)	-0.15 (-1.13,0.82)	-0.12 (-0.82,0.58)	-0.13 (-1.06,0.79)	-0.13 (-0.89,0.64)	-0.12 (-0.82,0.59)	-0.10 (-0.81,0.62)	-0.06 (-0.85,0.73)	SHR						-0.09 (-0.62,0.44)

-0.55 (-1.27,0.17)	-0.55 (-1.40,0.30)	-0.38 (-1.05,0.29)	-0.19 (-0.75,0.38)	-0.21 (-0.88,0.47)	-0.19 (-0.72,0.34)	-0.18 (-0.87,0.52)	-0.18 (-0.86,0.50)	-0.15 (-0.80,0.50)	-0.16 (-1.05,0.74)	-0.12 (-0.72,0.47)	-0.14 (-0.98,0.71)	-0.13 (-0.80,0.53)	-0.12 (-0.72,0.47)	-0.10 (-0.70,0.51)	-0.06 (-0.76,0.63)	-0.00 (-0.84,0.84)	SHT					0.08 (-0.30,0.47)
-0.52 (-1.07,0.02)	-0.52 (-1.23,0.18)	-0.36 (-0.83,0.12)	-0.16 (-0.47,0.15)	-0.18 (-0.66,0.30)	-0.17 (-0.72,0.39)	-0.15 (-0.66,0.36)	-0.15 (-0.64,0.34)	-0.12 (-0.57,0.32)	-0.13 (-0.89,0.63)	-0.10 (-0.45,0.26)	-0.11 (-0.81,0.59)	-0.10 (-0.50,0.30)	-0.09 (-0.46,0.27)	-0.07 (-0.45,0.31)	-0.04 (-0.55,0.47)	0.02 (-0.67,0.72)	0.03 (-0.56,0.61)	MMG				-0.11 (-0.22,0.00)
-0.54 (-1.13,0.04)	-0.54 (-1.28,0.19)	-0.38 (-0.90,0.14)	-0.18 (-0.56,0.20)	-0.20 (-0.73,0.33)	-0.19 (-0.78,0.41)	-0.17 (-0.72,0.38)	-0.17 (-0.71,0.36)	-0.14 (-0.58,0.30)	-0.15 (-0.94,0.64)	-0.12 (-0.40,0.16)	-0.13 (-0.86,0.60)	-0.12 (-0.64,0.39)	-0.11 (-0.47,0.25)	-0.09 (-0.53,0.34)	-0.06 (-0.61,0.50)	0.00 (-0.72,0.73)	0.01 (-0.62,0.63)	-0.02 (-0.43,0.39)	MLPR			-0.11 (-0.28,0.06)
***-0.54 (-1.07,-0.01)**	-0.54 (-1.18,0.11)	-0.37 (-0.79,0.04)	-0.17 (-0.42,0.07)	-0.19 (-0.66,0.27)	-0.18 (-0.72,0.36)	-0.17 (-0.64,0.30)	-0.17 (-0.64,0.30)	-0.14 (-0.56,0.28)	-0.15 (-0.90,0.61)	-0.11 (-0.44,0.21)	-0.13 (-0.77,0.52)	-0.12 (-0.57,0.33)	-0.11 (-0.44,0.22)	-0.09 (-0.43,0.25)	-0.05 (-0.54,0.44)	0.01 (-0.67,0.69)	0.01 (-0.56,0.58)	-0.02 (-0.33,0.30)	0.00 (-0.38,0.39)	MHM		-0.05 (-0.36,0.26)
-0.56 (-1.19,0.08)	-0.56 (-1.33,0.22)	-0.39 (-0.96,0.19)	-0.19 (-0.64,0.26)	-0.21 (-0.80,0.37)	-0.20 (-0.84,0.45)	-0.18 (-0.78,0.42)	-0.18 (-0.77,0.40)	-0.15 (-0.71,0.40)	-0.16 (-0.99,0.67)	-0.13 (-0.61,0.36)	-0.14 (-0.92,0.63)	-0.14 (-0.71,0.44)	-0.12 (-0.61,0.36)	-0.10 (-0.60,0.40)	-0.07 (-0.67,0.54)	-0.01 (-0.78,0.76)	-0.00 (-0.68,0.67)	-0.03 (-0.51,0.45)	-0.01 (-0.54,0.51)	-0.02 (-0.47,0.44)	MEM	-0.08 (-0.24,0.07)
-0.60 (-1.23,0.03)	-0.60 (-1.37,0.17)	-0.43 (-1.00,0.13)	-0.23 (-0.67,0.20)	-0.25 (-0.83,0.32)	-0.24 (-0.88,0.39)	-0.23 (-0.82,0.36)	-0.23 (-0.81,0.35)	-0.20 (-0.70,0.31)	-0.21 (-1.03,0.62)	-0.17 (-0.61,0.26)	-0.19 (-0.95,0.58)	-0.18 (-0.74,0.38)	-0.17 (-0.56,0.23)	-0.15 (-0.63,0.34)	-0.11 (-0.71,0.48)	-0.05 (-0.81,0.71)	-0.05 (-0.71,0.61)	-0.08 (-0.54,0.39)	-0.06 (-0.54,0.43)	-0.06 (-0.50,0.38)	-0.04 (-0.61,0.52)	MLR	-0.04 (-0.23,0.15)
***-0.64 (-1.13,-0.15)**	-0.64 (-1.30,0.02)	***-0.47 (-0.88,-0.07)**	***-0.27 (-0.46,-0.09)**	-0.29 (-0.71,0.12)	-0.28 (-0.78,0.22)	-0.26 (-0.71,0.18)	-0.27 (-0.69,0.16)	-0.24 (-0.60,0.13)	-0.24 (-0.97,0.48)	-0.21 (-0.47,0.05)	-0.22 (-0.88,0.43)	-0.22 (-0.62,0.18)	-0.21 (-0.47,0.06)	-0.19 (-0.47,0.10)	-0.15 (-0.60,0.30)	-0.09 (-0.74,0.56)	-0.09 (-0.62,0.45)	-0.11 (-0.36,0.13)	-0.09 (-0.42,0.23)	-0.10 (-0.30,0.10)	-0.08 (-0.49,0.33)	-0.04 (-0.43,0.35)	Pla

Pairwise (upper-right portion) and network (lower-left portion) meta-analysis results are presented as estimated effect sizes for the outcome of improvement of quality of life in patients with tinnitus. Interventions are reported in order of mean ranking of quality of life improvement, and outcomes are expressed as standardized mean difference (StMD) (95% confidence intervals). For the pairwise meta-analyses, StMD of less than 0 indicate that the treatment specified in the row had more improvement than that specified in the column. For the network meta-analysis (NMA), StMD of less than 0 indicate that the treatment specified in the column had more improvement than that specified in the row. Bold results marked with * indicate statistical significance.

eTable 7D: League table of the improvement of behavioral disturbance

SHM																	***-0.55 (-0.90,-0.21)**	
-0.10 (-0.73,0.52)	SLT															***-0.50 (-0.88,-0.11)**	***-0.45 (-0.83,-0.07)**	
-0.25 (-0.81,0.31)	-0.14 (-0.73,0.44)	DMMH										***-0.26 (-0.48,-0.04)**						
-0.36 (-0.87,0.16)	-0.25 (-0.80,0.29)	-0.11 (-0.58,0.36)	MEM														***-0.20 (-0.35,-0.04)**	
-0.35 (-0.88,0.18)	-0.25 (-0.80,0.31)	-0.10 (-0.58,0.38)	0.01 (-0.42,0.44)	SMG		-0.07 (-0.24,0.11)											***-0.20 (-0.39,-0.02)**	
-0.35 (-1.07,0.38)	-0.24 (-0.99,0.50)	-0.10 (-0.79,0.59)	0.01 (-0.65,0.67)	0.00 (-0.66,0.67)	SHR												-0.21 (-0.74,0.32)	
-0.42 (-0.94,0.10)	-0.31 (-0.86,0.24)	-0.17 (-0.65,0.30)	-0.06 (-0.48,0.36)	-0.07 (-0.37,0.24)	-0.07 (-0.73,0.59)	SLG											-0.14 (-0.31,0.03)	
-0.45 (-0.98,0.07)	-0.35 (-0.90,0.20)	-0.21 (-0.68,0.27)	-0.10 (-0.52,0.33)	-0.10 (-0.54,0.33)	-0.11 (-0.77,0.55)	-0.04 (-0.47,0.39)	MMG										-0.10 (-0.28,0.08)	
-0.48 (-0.97,0.01)	-0.38 (-0.89,0.14)	-0.23 (-0.67,0.21)	-0.12 (-0.51,0.26)	-0.13 (-0.53,0.27)	-0.13 (-0.77,0.50)	-0.06 (-0.45,0.33)	-0.03 (-0.42,0.37)	MHR	0.01 (-0.15,0.17)					-0.06 (-0.18,0.07)			-0.04 (-0.20,0.12)	
-0.49 (-0.99,0.02)	-0.38 (-0.92,0.15)	-0.24 (-0.70,0.22)	-0.13 (-0.53,0.27)	-0.14 (-0.55,0.28)	-0.14 (-0.79,0.51)	-0.07 (-0.48,0.34)	-0.03 (-0.44,0.38)	-0.01 (-0.28,0.27)	MEPR					-0.05 (-0.21,0.11)			-0.05 (-0.21,0.11)	
-0.50 (-1.04,0.04)	-0.39 (-0.96,0.17)	-0.25 (-0.72,0.22)	-0.14 (-0.59,0.30)	-0.15 (-0.61,0.31)	-0.15 (-0.83,0.52)	-0.08 (-0.53,0.37)	-0.04 (-0.50,0.41)	-0.02 (-0.43,0.40)	-0.01 (-0.45,0.42)	MMD		-0.07 (-0.35,0.22)					0.00 (-0.28,0.28)	
***-0.51 (-0.95,-0.06)**	-0.40 (-0.88,0.08)	-0.26 (-0.64,0.13)	-0.15 (-0.48,0.18)	-0.16 (-0.50,0.19)	-0.16 (-0.76,0.44)	-0.09 (-0.42,0.25)	-0.05 (-0.39,0.28)	-0.03 (-0.31,0.26)	-0.02 (-0.33,0.29)	-0.01 (-0.37,0.35)	MHM	-0.00 (-0.31,0.30)					-0.04 (-0.14,0.06)	
***-0.51 (-0.96,-0.06)**	-0.40 (-0.89,0.08)	-0.26 (-0.59,0.07)	-0.15 (-0.48,0.18)	-0.16 (-0.50,0.19)	-0.16 (-0.77,0.44)	-0.09 (-0.43,0.25)	-0.05 (-0.39,0.29)	-0.03 (-0.31,0.26)	-0.02 (-0.33,0.29)	-0.01 (-0.34,0.33)	-0.00 (-0.19,0.19)	MHD					-0.04 (-0.31,0.24)	
-0.52 (-1.06,0.02)	-0.42 (-0.99,0.15)	-0.27 (-0.77,0.22)	-0.16 (-0.61,0.28)	-0.17 (-0.63,0.29)	-0.17 (-0.85,0.50)	-0.10 (-0.55,0.35)	-0.07 (-0.52,0.39)	-0.04 (-0.46,0.37)	-0.03 (-0.47,0.40)	-0.02 (-0.50,0.45)	-0.02 (-0.38,0.35)	-0.01 (-0.38,0.35)	EHM				-0.03 (-0.26,0.19)	
***-0.53 (-1.00,-0.06)**	-0.42 (-0.92,0.08)	-0.28 (-0.70,0.13)	-0.17 (-0.53,0.18)	-0.18 (-0.55,0.19)	-0.18 (-0.80,0.44)	-0.11 (-0.47,0.25)	-0.07 (-0.44,0.29)	-0.05 (-0.26,0.16)	-0.04 (-0.31,0.22)	-0.03 (-0.42,0.36)	-0.02 (-0.27,0.22)	-0.02 (-0.27,0.23)	-0.01 (-0.40,0.38)	MHPR			-0.02 (-0.14,0.09)	-0.08 (-0.19,0.03)
-0.54 (-1.11,0.02)	-0.44 (-1.03,0.15)	-0.29 (-0.82,0.23)	-0.18 (-0.66,0.29)	-0.19 (-0.68,0.29)	-0.19 (-0.89,0.50)	-0.12 (-0.60,0.36)	-0.09 (-0.57,0.40)	-0.06 (-0.51,0.38)	-0.05 (-0.52,0.41)	-0.04 (-0.54,0.46)	-0.04 (-0.43,0.36)	-0.03 (-0.44,0.37)	-0.02 (-0.52,0.48)	-0.01 (-0.44,0.41)	SHD		-0.01 (-0.29,0.26)	
-0.60 (-1.22,0.03)	***-0.49 (-0.96,-0.03)**	-0.35 (-0.94,0.24)	-0.24 (-0.79,0.30)	-0.25 (-0.81,0.31)	-0.25 (-1.00,0.49)	-0.18 (-0.73,0.37)	-0.14 (-0.70,0.41)	-0.12 (-0.64,0.40)	-0.11 (-0.65,0.42)	-0.10 (-0.67,0.47)	-0.09 (-0.57,0.39)	-0.09 (-0.58,0.39)	-0.08 (-0.65,0.49)	-0.07 (-0.57,0.43)	-0.06 (-0.65,0.53)	SHT	0.05 (-0.34,0.43)	
***-0.55 (-0.98,-0.13)**	-0.45 (-0.91,0.01)	-0.31 (-0.67,0.06)	-0.20 (-0.49,0.10)	-0.20 (-0.52,0.11)	-0.21 (-0.79,0.38)	-0.14 (-0.44,0.17)	-0.10 (-0.41,0.21)	-0.07 (-0.32,0.17)	-0.07 (-0.34,0.21)	-0.06 (-0.39,0.28)	-0.05 (-0.19,0.09)	-0.05 (-0.20,0.10)	-0.03 (-0.37,0.30)	-0.03 (-0.22,0.17)	-0.01 (-0.39,0.36)	0.05 (-0.41,0.51)	Pla	0.00 (-0.17,0.17)
***-0.59 (-1.08,-0.11)**	-0.49 (-1.01,0.03)	-0.35 (-0.79,0.09)	-0.24 (-0.62,0.14)	-0.24 (-0.64,0.15)	-0.25 (-0.88,0.39)	-0.18 (-0.56,0.21)	-0.14 (-0.53,0.25)	-0.11 (-0.39,0.16)	-0.11 (-0.43,0.21)	-0.10 (-0.51,0.32)	-0.09 (-0.37,0.19)	-0.09 (-0.37,0.20)	-0.07 (-0.49,0.34)	-0.07 (-0.27,0.14)	-0.05 (-0.50,0.39)	0.00 (-0.52,0.52)	-0.04 (-0.28,0.20)	MLPR

Pairwise (upper-right portion) and network (lower-left portion) meta-analysis results are presented as estimated effect sizes for the outcome of improvement of behavioral disturbance in patients with tinnitus. Interventions are reported in order of mean ranking of behavioral disturbance improvement, and outcomes are expressed as standardized mean difference (StMD) (95% confidence intervals). For the pairwise meta-analyses, StMD of less than 0 indicate that the treatment specified in the row had more improvement than that specified in the column. For the network meta-analysis (NMA), StMD of less than 0 indicate that the treatment specified in the column had more improvement than that specified in the row. Bold results marked with * indicate statistical significance.

eTable 7E: League table of the acceptability in aspect of drop-out rate

SLT								0.30 (0.05,1.75)		0.22 (0.02,2.05)																	
1.66 (0.04,61.40)	SMD							0.18 (0.01,4.25)																			
0.48 (0.07,3.09)	0.29 (0.01,7.19)	DMMH		3.13 (0.12,83.33)					3.14 (0.12,81.35)				***0.51 (0.31,0.84)**					0.57 (0.07,4.74)									
0.46 (0.07,3.18)	0.28 (0.01,7.16)	0.95 (0.35,2.60)	SHD					0.67 (0.31,1.41)																			
0.99 (0.03,37.76)	0.60 (0.01,52.88)	2.06 (0.09,48.45)	2.16 (0.08,57.90)	GMMH					1.00 (0.02,52.63)									0.18 (0.01,4.02)									
0.36 (0.06,2.18)	0.22 (0.01,5.22)	0.76 (0.40,1.44)	0.80 (0.34,1.88)	0.37 (0.02,9.00)	MMD			0.94 (0.71,1.23)					***0.60 (0.38,0.97)**														
0.35 (0.06,2.19)	0.21 (0.01,5.14)	0.72 (0.32,1.61)	0.76 (0.29,2.00)	0.35 (0.01,8.88)	0.95 (0.52,1.76)	MLR		1.09 (0.65,1.84)																***0.34 (0.22,0.53)**			
0.33 (0.05,1.97)	0.20 (0.01,4.72)	0.68 (0.34,1.36)	0.72 (0.30,1.72)	0.33 (0.01,8.16)	0.90 (0.57,1.41)	0.94 (0.50,1.78)	EMG	0.93 (0.77,1.12)																			
0.30 (0.05,1.78)	0.18 (0.01,4.31)	0.63 (0.35,1.15)	0.67 (0.30,1.49)	0.31 (0.01,7.46)	0.84 (0.62,1.12)	0.88 (0.51,1.50)	0.93 (0.66,1.31)	Pla	1.05 (0.83,1.31)	1.25 (0.32,4.95)	0.92 (0.63,1.34)	1.11 (0.70,1.74)	0.84 (0.66,1.07)	0.70 (0.34,1.43)	0.66 (0.23,1.85)	***0.68 (0.53,0.88)**	0.68 (0.46,1.01)		***0.65 (0.46,0.91)**	***0.66 (0.43,1.00)**	***0.60 (0.40,0.91)**	***0.53 (0.34,0.82)**	***0.38 (0.27,0.53)**	***0.40 (0.25,0.64)**		***0.21 (0.05,0.97)**	***0.21 (0.09,0.45)**
0.30 (0.05,1.76)	0.18 (0.01,4.25)	0.62 (0.33,1.17)	0.65 (0.28,1.51)	0.30 (0.01,7.31)	0.82 (0.57,1.18)	0.86 (0.48,1.54)	0.91 (0.60,1.38)	0.98 (0.77,1.24)	MHM				1.35 (0.78,2.34)					0.18 (0.01,4.02)								
0.34 (0.05,2.47)	0.21 (0.01,6.52)	0.72 (0.16,3.24)	0.75 (0.15,3.74)	0.35 (0.01,11.25)	0.95 (0.23,3.90)	0.99 (0.23,4.38)	1.05 (0.25,4.39)	1.13 (0.28,4.52)	1.16 (0.28,4.71)	SHT																
0.28 (0.05,1.73)	0.17 (0.01,4.09)	0.58 (0.27,1.25)	0.61 (0.24,1.56)	0.28 (0.01,7.08)	0.77 (0.44,1.34)	0.80 (0.39,1.65)	0.85 (0.47,1.54)	0.92 (0.57,1.48)	0.94 (0.55,1.60)	0.81 (0.19,3.50)	MEM															
0.28 (0.04,1.74)	0.17 (0.01,4.08)	0.57 (0.26,1.28)	0.60 (0.23,1.59)	0.28 (0.01,7.06)	0.76 (0.41,1.40)	0.79 (0.37,1.70)	0.84 (0.44,1.60)	0.90 (0.53,1.55)	0.92 (0.51,1.66)	0.80 (0.18,3.53)	0.99 (0.48,2.03)	EHM														
0.26 (0.04,1.52)	0.16 (0.01,3.67)	***0.54 (0.30,0.95)**	0.56 (0.25,1.29)	0.26 (0.01,6.30)	***0.71 (0.53,0.95)**	0.74 (0.42,1.32)	0.79 (0.53,1.17)	0.85 (0.70,1.03)	0.87 (0.65,1.15)	0.75 (0.18,3.03)	0.92 (0.55,1.55)	0.94 (0.53,1.66)	MHD												***0.47 (0.37,0.60)**		
0.21 (0.03,1.46)	0.13 (0.00,3.30)	0.44 (0.17,1.18)	0.47 (0.15,1.42)	0.21 (0.01,5.71)	0.58 (0.26,1.34)	0.61 (0.24,1.57)	0.65 (0.28,1.51)	0.70 (0.32,1.51)	0.71 (0.32,1.60)	0.62 (0.13,3.01)	0.76 (0.31,1.89)	0.77 (0.30,1.98)	0.82 (0.37,1.83)	SHM												
0.20 (0.03,1.56)	0.12 (0.00,3.35)	0.42 (0.12,1.40)	0.44 (0.12,1.65)	0.20 (0.01,5.80)	0.55 (0.18,1.64)	0.58 (0.18,1.88)	0.61 (0.20,1.85)	0.66 (0.23,1.89)	0.67 (0.23,1.98)	0.58 (0.10,3.31)	0.71 (0.22,2.28)	0.72 (0.22,2.37)	0.77 (0.26,2.27)	0.94 (0.25,3.48)	MLT											

0.21 (0.03,1.24)	0.13 (0.01,2.97)	***0.43 (0.22,0.83)**	0.45 (0.19,1.06)	0.21 (0.01,5.14)	***0.57 (0.38,0.85)**	0.60 (0.33,1.09)	***0.63 (0.41,0.98)**	***0.68 (0.52,0.89)**	0.70 (0.49,1.00)	0.60 (0.15,2.47)	0.74 (0.43,1.29)	0.75 (0.41,1.38)	0.81 (0.58,1.12)	0.98 (0.43,2.22)	1.04 (0.35,3.10)	MMG							***0.69 (0.51,0.93)**				
0.20 (0.03,1.26)	0.12 (0.01,2.98)	***0.42 (0.20,0.90)**	0.45 (0.18,1.13)	0.21 (0.01,5.16)	***0.56 (0.33,0.96)**	0.59 (0.29,1.19)	0.62 (0.35,1.10)	0.67 (0.43,1.05)	0.69 (0.41,1.14)	0.59 (0.14,2.54)	0.73 (0.38,1.41)	0.74 (0.37,1.50)	0.79 (0.48,1.30)	0.96 (0.39,2.35)	1.02 (0.32,3.23)	0.98 (0.58,1.66)	SLG		0.98 (0.68,1.41)								
0.18 (0.01,2.61)	0.11 (0.00,4.57)	0.37 (0.05,2.67)	0.39 (0.05,3.43)	0.18 (0.01,4.08)	0.49 (0.07,3.74)	0.52 (0.07,4.14)	0.55 (0.07,4.22)	0.59 (0.08,4.40)	0.60 (0.08,4.52)	0.52 (0.05,5.99)	0.65 (0.08,5.08)	0.65 (0.08,5.22)	0.70 (0.09,5.17)	0.85 (0.10,7.28)	0.90 (0.09,8.73)	0.87 (0.11,6.57)	0.88 (0.11,6.90)	RMMH								
0.20 (0.03,1.20)	0.12 (0.00,2.85)	***0.41 (0.20,0.84)**	0.43 (0.18,1.05)	0.20 (0.01,4.94)	***0.54 (0.33,0.88)**	0.57 (0.29,1.10)	0.60 (0.36,1.01)	***0.65 (0.44,0.95)**	0.66 (0.42,1.04)	0.57 (0.14,2.41)	0.71 (0.38,1.31)	0.71 (0.37,1.39)	0.76 (0.49,1.18)	0.93 (0.39,2.20)	0.99 (0.32,3.04)	0.95 (0.59,1.52)	0.96 (0.62,1.50)	1.09 (0.14,8.43)	SMG								***0.40 (0.21,0.77)**
0.17 (0.03,1.04)	0.10 (0.00,2.47)	***0.35 (0.17,0.72)**	***0.37 (0.15,0.91)**	0.17 (0.01,4.27)	***0.47 (0.29,0.76)**	***0.49 (0.26,0.91)**	***0.52 (0.31,0.88)**	***0.56 (0.38,0.83)**	***0.57 (0.36,0.90)**	0.49 (0.12,2.08)	0.61 (0.33,1.13)	0.62 (0.32,1.20)	0.66 (0.43,1.02)	0.80 (0.34,1.90)	0.85 (0.28,2.63)	0.82 (0.51,1.32)	0.83 (0.46,1.51)	0.94 (0.12,7.30)	0.86 (0.50,1.50)	MLPR	1.03 (0.81,1.31)						
0.17 (0.03,1.00)	0.10 (0.00,2.39)	***0.35 (0.17,0.68)**	***0.36 (0.15,0.86)**	0.17 (0.01,4.13)	***0.46 (0.29,0.70)**	***0.48 (0.27,0.84)**	***0.51 (0.32,0.81)**	***0.54 (0.40,0.75)**	***0.56 (0.37,0.83)**	0.48 (0.12,1.99)	0.59 (0.33,1.06)	0.60 (0.32,1.13)	***0.64 (0.44,0.94)**	0.78 (0.34,1.80)	0.83 (0.28,2.51)	0.80 (0.53,1.21)	0.81 (0.47,1.41)	0.92 (0.12,7.02)	0.84 (0.51,1.39)	0.97 (0.71,1.33)	MHPR	0.92 (0.62,1.36)		0.94 (0.70,1.25)			
***0.16 (0.03,0.98)**	0.10 (0.00,2.33)	***0.33 (0.16,0.70)**	***0.35 (0.14,0.88)**	0.16 (0.01,4.03)	***0.44 (0.25,0.75)**	***0.46 (0.24,0.88)**	***0.49 (0.28,0.86)**	***0.52 (0.33,0.83)**	***0.53 (0.32,0.89)**	0.46 (0.11,1.99)	0.57 (0.29,1.11)	0.58 (0.29,1.17)	0.62 (0.38,1.01)	0.75 (0.31,1.84)	0.80 (0.25,2.53)	0.77 (0.45,1.30)	0.78 (0.41,1.48)	0.88 (0.11,6.92)	0.81 (0.45,1.47)	0.94 (0.56,1.57)	0.96 (0.62,1.49)	MEPR		0.96 (0.64,1.42)			
***0.13 (0.02,0.79)**	0.08 (0.00,1.89)	***0.27 (0.14,0.55)**	***0.29 (0.12,0.69)**	0.13 (0.01,3.26)	***0.36 (0.23,0.57)**	***0.38 (0.20,0.72)**	***0.40 (0.24,0.65)**	***0.43 (0.30,0.61)**	***0.44 (0.29,0.67)**	0.38 (0.09,1.58)	***0.47 (0.26,0.85)**	***0.47 (0.25,0.90)**	***0.51 (0.34,0.76)**	0.62 (0.26,1.44)	0.66 (0.21,2.00)	***0.63 (0.45,0.88)**	0.64 (0.36,1.14)	0.73 (0.09,5.56)	0.66 (0.39,1.12)	0.77 (0.45,1.30)	0.79 (0.49,1.27)	0.82 (0.46,1.46)	MHG				
***0.13 (0.02,0.81)**	0.08 (0.00,1.93)	***0.28 (0.14,0.55)**	***0.29 (0.12,0.70)**	0.14 (0.01,3.34)	***0.37 (0.24,0.58)**	***0.39 (0.23,0.64)**	***0.41 (0.25,0.66)**	***0.44 (0.32,0.61)**	***0.45 (0.30,0.68)**	0.39 (0.09,1.62)	***0.48 (0.27,0.86)**	***0.49 (0.26,0.92)**	***0.52 (0.35,0.77)**	0.63 (0.27,1.46)	0.67 (0.22,2.04)	***0.65 (0.42,0.99)**	0.66 (0.37,1.15)	0.74 (0.10,5.69)	0.68 (0.41,1.14)	0.79 (0.52,1.20)	0.81 (0.59,1.11)	0.84 (0.54,1.31)	1.03 (0.63,1.67)	MHR			
***0.12 (0.02,0.74)**	0.07 (0.00,1.76)	***0.25 (0.13,0.49)**	***0.27 (0.11,0.65)**	0.12 (0.00,3.02)	***0.33 (0.21,0.52)**	***0.35 (0.18,0.68)**	***0.37 (0.22,0.62)**	***0.40 (0.27,0.59)**	***0.41 (0.26,0.63)**	0.35 (0.08,1.48)	***0.43 (0.24,0.80)**	***0.44 (0.23,0.85)**	***0.47 (0.34,0.66)**	0.57 (0.24,1.36)	0.61 (0.20,1.88)	***0.58 (0.37,0.93)**	0.59 (0.33,1.08)	0.67 (0.09,5.13)	0.62 (0.36,1.07)	0.71 (0.41,1.23)	0.73 (0.44,1.21)	0.76 (0.42,1.38)	0.93 (0.55,1.57)	0.91 (0.54,1.51)	MED		
***0.06 (0.01,0.67)**	0.04 (0.00,1.31)	***0.13 (0.03,0.70)**	***0.14 (0.02,0.81)**	0.07 (0.00,2.25)	***0.18 (0.04,0.85)**	***0.19 (0.04,0.95)**	***0.20 (0.04,0.96)**	***0.21 (0.05,0.99)**	0.22 (0.05,1.03)	0.19 (0.02,1.49)	0.23 (0.05,1.16)	0.23 (0.05,1.20)	0.25 (0.05,1.19)	0.30 (0.05,1.71)	0.32 (0.05,2.10)	0.31 (0.06,1.49)	0.32 (0.06,1.58)	0.36 (0.03,4.51)	0.33 (0.07,1.61)	0.38 (0.08,1.87)	0.39 (0.08,1.88)	0.41 (0.08,2.03)	0.49 (0.10,2.41)	0.48 (0.10,2.34)	0.53 (0.11,2.61)	SHR	
***0.07 (0.01,0.49)**	0.04 (0.00,1.12)	***0.15 (0.06,0.39)**	***0.16 (0.05,0.47)**	0.07 (0.00,1.94)	***0.20 (0.09,0.44)**	***0.21 (0.09,0.52)**	***0.22 (0.10,0.50)**	***0.24 (0.12,0.49)**	***0.25 (0.12,0.52)**	0.21 (0.04,1.01)	***0.26 (0.11,0.62)**	***0.27 (0.11,0.65)**	***0.28 (0.13,0.60)**	***0.34 (0.12,0.99)**	0.37 (0.10,1.32)	***0.35 (0.16,0.76)**	***0.36 (0.16,0.78)**	0.41 (0.05,3.42)	***0.37 (0.19,0.73)**	***0.43 (0.19,0.97)**	***0.44 (0.20,0.97)**	0.46 (0.20,1.08)	0.56 (0.25,1.25)	0.55 (0.25,1.21)	0.60 (0.27,1.36)	1.13 (0.21,6.22)	SHG

Pairwise (upper-right portion) and network (lower-left portion) meta-analysis results are presented as estimated effect sizes for the outcome of drop-out rate in patients with tinnitus. Interventions are reported in order of mean ranking of acceptability, and outcomes are expressed as odds ratio (OR) (95% confidence intervals). For the pairwise meta-analyses, OR of less than 1 indicate that the treatment specified in the row had better acceptability than that specified in the column. For the network meta-analysis (NMA), OR of less than 1 indicate that the treatment specified in the column had better acceptability than that specified in the row. Bold results marked with * indicate statistical significance.

eTable 7F: League table of the rate of any adverse event reported

MLR		0.96 (0.64,1.42)																	***0.25 (0.15,0.41)**				
0.88 (0.53,1.47)	MEM	0.95 (0.70,1.30)																					
0.84 (0.57,1.23)	0.95 (0.68,1.33)	Pla	0.99 (0.81,1.20)	0.84 (0.53,1.34)	0.88 (0.63,1.24)	***0.80 (0.68,0.96)**	***0.71 (0.54,0.93)**	0.77 (0.32,1.82)	0.88 (0.17,4.50)	0.69 (0.44,1.07)		***0.56 (0.36,0.86)**	0.69 (0.46,1.05)	0.58 (0.24,1.40)	***0.60 (0.49,0.72)**	***0.55 (0.39,0.78)**	0.46 (0.15,1.36)			***0.36 (0.24,0.54)**	***0.37 (0.19,0.70)**	***0.44 (0.32,0.61)**		***0.33 (0.16,0.67)**	***0.06 (0.01,0.30)**
0.82 (0.53,1.27)	0.93 (0.63,1.38)	0.98 (0.80,1.20)	MHM								0.78 (0.20,3.09)							0.51 (0.14,1.93)	0.63 (0.16,2.41)					
0.71 (0.38,1.30)	0.80 (0.45,1.43)	0.84 (0.53,1.35)	0.86 (0.52,1.44)	EHM																				
0.70 (0.42,1.18)	0.80 (0.50,1.28)	0.84 (0.60,1.17)	0.85 (0.58,1.27)	0.99 (0.55,1.77)	SLG											0.72 (0.50,1.04)								
0.67 (0.43,1.05)	0.77 (0.52,1.14)	***0.80 (0.65,0.99)**	0.82 (0.62,1.10)	0.95 (0.57,1.60)	0.96 (0.65,1.43)	EMG																		
0.65 (0.41,1.04)	0.74 (0.49,1.13)	0.78 (0.60,1.01)	0.79 (0.57,1.10)	0.92 (0.54,1.58)	0.93 (0.61,1.42)	0.97 (0.69,1.35)	MMD								***0.61 (0.44,0.85)**									
0.65 (0.25,1.67)	0.73 (0.29,1.86)	0.77 (0.32,1.84)	0.79 (0.32,1.92)	0.91 (0.34,2.45)	0.92 (0.36,2.34)	0.96 (0.39,2.34)	0.99 (0.40,2.45)	SHT						0.75 (0.30,1.87)										
0.74 (0.14,3.97)	0.84 (0.16,4.46)	0.88 (0.17,4.52)	0.90 (0.17,4.67)	1.04 (0.19,5.73)	1.05 (0.20,5.59)	1.10 (0.21,5.70)	1.14 (0.22,5.94)	1.15 (0.18,7.30)	LHR															
***0.61 (0.39,0.97)**	0.70 (0.46,1.05)	***0.73 (0.57,0.94)**	0.75 (0.54,1.03)	0.87 (0.51,1.48)	0.87 (0.58,1.32)	0.91 (0.66,1.26)	0.94 (0.66,1.35)	0.95 (0.38,2.35)	0.83 (0.16,4.33)	MMG										0.71 (0.45,1.09)				
0.53 (0.15,1.86)	0.61 (0.18,2.09)	0.64 (0.19,2.09)	0.65 (0.20,2.13)	0.75 (0.21,2.71)	0.76 (0.22,2.62)	0.79 (0.24,2.65)	0.82 (0.24,2.75)	0.83 (0.19,3.61)	0.72 (0.10,5.45)	0.87 (0.26,2.93)	GMMH							0.66 (0.18,2.36)	0.80 (0.22,2.94)					
***0.55 (0.33,0.90)**	***0.62 (0.39,0.99)**	***0.65 (0.47,0.91)**	***0.67 (0.45,0.98)**	0.77 (0.43,1.37)	0.78 (0.49,1.24)	0.81 (0.55,1.20)	0.84 (0.55,1.28)	0.85 (0.33,2.15)	0.74 (0.14,3.92)	0.89 (0.60,1.33)	1.02 (0.30,3.52)	MLPR	0.95 (0.72,1.25)											
***0.54 (0.35,0.84)**	***0.62 (0.41,0.94)**	***0.65 (0.50,0.83)**	***0.66 (0.48,0.91)**	0.77 (0.45,1.31)	0.77 (0.51,1.17)	0.80 (0.58,1.11)	0.83 (0.58,1.19)	0.84 (0.34,2.08)	0.73 (0.14,3.83)	0.88 (0.63,1.24)	1.02 (0.30,3.43)	0.99 (0.75,1.31)	MHPR								***0.62 (0.49,0.79)**	***0.53 (0.38,0.73)**			
0.48 (0.18,1.28)	0.55 (0.21,1.42)	0.58 (0.24,1.41)	0.59 (0.24,1.47)	0.68 (0.25,1.87)	0.69 (0.26,1.79)	0.72 (0.29,1.79)	0.74 (0.29,1.88)	0.75 (0.30,1.88)	0.65 (0.10,4.20)	0.79 (0.31,1.99)	0.90 (0.20,4.00)	0.88 (0.34,2.29)	0.89 (0.35,2.25)	SLT										
***0.49 (0.32,0.75)**	***0.56 (0.38,0.82)**	***0.58 (0.48,0.71)**	***0.60 (0.45,0.79)**	0.69 (0.42,1.15)	0.70 (0.47,1.03)	***0.73 (0.55,0.96)**	***0.75 (0.57,0.99)**	0.76 (0.31,1.85)	0.66 (0.13,3.43)	0.80 (0.58,1.09)	0.92 (0.28,3.01)	0.90 (0.61,1.31)	0.90 (0.66,1.24)	1.02 (0.41,2.53)	MHD				0.72 (0.46,1.14)				***0.61 (0.49,0.75)**		

***0.47 (0.29,0.77)**	***0.54 (0.34,0.84)**	***0.56 (0.41,0.77)**	***0.57 (0.40,0.83)**	0.67 (0.38,1.17)	***0.67 (0.47,0.96)**	0.70 (0.48,1.01)	0.72 (0.48,1.08)	0.73 (0.29,1.84)	0.64 (0.12,3.36)	0.77 (0.52,1.13)	0.88 (0.26,3.02)	0.86 (0.55,1.35)	0.87 (0.59,1.28)	0.98 (0.38,2.51)	0.96 (0.67,1.39)	SMG								0.56 (0.29,1.09)	
0.38 (0.12,1.22)	0.44 (0.14,1.37)	0.46 (0.15,1.37)	0.47 (0.15,1.42)	0.54 (0.16,1.78)	0.55 (0.17,1.72)	0.57 (0.19,1.73)	0.59 (0.19,1.81)	0.59 (0.15,2.40)	0.52 (0.07,3.71)	0.63 (0.20,1.92)	0.72 (0.14,3.62)	0.70 (0.22,2.20)	0.71 (0.23,2.17)	0.79 (0.19,3.26)	0.78 (0.26,2.38)	0.81 (0.26,2.54)	MLT								
0.35 (0.11,1.16)	0.40 (0.12,1.30)	0.42 (0.13,1.30)	0.43 (0.14,1.33)	0.49 (0.14,1.69)	0.50 (0.15,1.63)	0.52 (0.16,1.65)	0.54 (0.17,1.71)	0.54 (0.13,2.27)	0.47 (0.06,3.46)	0.57 (0.18,1.83)	0.66 (0.18,2.37)	0.64 (0.20,2.09)	0.65 (0.20,2.07)	0.73 (0.17,3.08)	0.71 (0.23,2.22)	0.74 (0.23,2.41)	0.91 (0.19,4.42)	RMMH	1.22 (0.35,4.27)						
***0.37 (0.20,0.68)**	***0.42 (0.23,0.75)**	***0.44 (0.27,0.71)**	***0.45 (0.27,0.74)**	0.52 (0.27,1.02)	***0.52 (0.29,0.94)**	***0.55 (0.32,0.92)**	***0.57 (0.34,0.95)**	0.57 (0.21,1.54)	0.50 (0.09,2.73)	0.60 (0.35,1.03)	0.69 (0.21,2.24)	0.67 (0.38,1.20)	0.68 (0.39,1.17)	0.76 (0.28,2.10)	0.75 (0.48,1.17)	0.78 (0.44,1.38)	0.96 (0.29,3.17)	1.05 (0.34,3.23)	DMMH						
***0.34 (0.20,0.59)**	***0.39 (0.23,0.65)**	***0.41 (0.28,0.60)**	***0.42 (0.27,0.65)**	***0.48 (0.26,0.89)**	***0.49 (0.29,0.82)**	***0.51 (0.33,0.79)**	***0.53 (0.33,0.84)**	0.53 (0.20,1.38)	0.46 (0.09,2.49)	***0.56 (0.37,0.87)**	0.64 (0.18,2.25)	0.63 (0.38,1.04)	0.63 (0.40,1.00)	0.71 (0.27,1.88)	0.70 (0.45,1.08)	0.73 (0.44,1.20)	0.89 (0.28,2.86)	0.98 (0.29,3.25)	0.93 (0.50,1.72)	MHG					
***0.33 (0.22,0.51)**	***0.38 (0.25,0.58)**	***0.40 (0.30,0.52)**	***0.41 (0.29,0.57)**	***0.47 (0.27,0.81)**	***0.48 (0.31,0.73)**	***0.49 (0.35,0.69)**	***0.51 (0.35,0.74)**	0.52 (0.21,1.29)	0.45 (0.09,2.37)	***0.54 (0.38,0.77)**	0.63 (0.18,2.12)	***0.61 (0.43,0.86)**	***0.62 (0.48,0.78)**	0.69 (0.27,1.76)	***0.68 (0.49,0.95)**	0.71 (0.47,1.06)	0.87 (0.28,2.69)	0.95 (0.30,3.06)	0.91 (0.52,1.57)	0.97 (0.61,1.56)	MHR	0.89 (0.63,1.24)			
***0.32 (0.19,0.51)**	***0.36 (0.22,0.57)**	***0.38 (0.27,0.52)**	***0.38 (0.26,0.56)**	***0.45 (0.25,0.79)**	***0.45 (0.28,0.72)**	***0.47 (0.32,0.69)**	***0.48 (0.32,0.73)**	0.49 (0.19,1.24)	0.43 (0.08,2.26)	***0.51 (0.34,0.77)**	0.59 (0.17,2.03)	***0.58 (0.39,0.86)**	***0.58 (0.42,0.80)**	0.65 (0.25,1.69)	***0.64 (0.44,0.94)**	0.67 (0.43,1.04)	0.82 (0.26,2.58)	0.90 (0.28,2.94)	0.86 (0.48,1.53)	0.92 (0.55,1.53)	0.94 (0.68,1.31)	MEPR			
***0.30 (0.18,0.48)**	***0.34 (0.22,0.53)**	***0.35 (0.26,0.48)**	***0.36 (0.25,0.52)**	***0.42 (0.24,0.73)**	***0.42 (0.27,0.66)**	***0.44 (0.31,0.63)**	***0.46 (0.32,0.65)**	0.46 (0.18,1.15)	0.40 (0.08,2.11)	***0.48 (0.33,0.71)**	0.56 (0.17,1.87)	***0.54 (0.35,0.84)**	***0.55 (0.37,0.80)**	0.61 (0.24,1.58)	***0.61 (0.48,0.76)**	***0.63 (0.41,0.97)**	0.77 (0.25,2.41)	0.85 (0.27,2.70)	0.81 (0.49,1.33)	0.86 (0.53,1.41)	0.89 (0.60,1.32)	0.94 (0.61,1.46)	MED		
***0.27 (0.12,0.58)**	***0.30 (0.14,0.64)**	***0.32 (0.16,0.62)**	***0.32 (0.16,0.66)**	***0.38 (0.17,0.86)**	***0.38 (0.18,0.78)**	***0.40 (0.20,0.80)**	***0.41 (0.20,0.84)**	0.41 (0.14,1.24)	0.36 (0.06,2.11)	***0.43 (0.21,0.89)**	0.50 (0.13,1.96)	0.49 (0.23,1.03)	0.49 (0.24,1.01)	0.55 (0.18,1.69)	0.54 (0.27,1.10)	0.57 (0.29,1.09)	0.70 (0.19,2.52)	0.76 (0.20,2.85)	0.72 (0.32,1.66)	0.78 (0.36,1.70)	0.80 (0.39,1.65)	0.85 (0.40,1.79)	0.90 (0.43,1.88)	SHG	
***0.06 (0.01,0.26)**	***0.06 (0.01,0.30)**	***0.07 (0.01,0.30)**	***0.07 (0.01,0.31)**	***0.08 (0.02,0.38)**	***0.08 (0.02,0.37)**	***0.08 (0.02,0.38)**	***0.09 (0.02,0.40)**	***0.09 (0.02,0.49)**	***0.08 (0.01,0.70)**	***0.09 (0.02,0.42)**	***0.10 (0.02,0.71)**	***0.10 (0.02,0.48)**	***0.10 (0.02,0.47)**	***0.12 (0.02,0.67)**	***0.11 (0.02,0.52)**	***0.12 (0.03,0.55)**	***0.15 (0.02,0.94)**	0.16 (0.02,1.05)	***0.15 (0.03,0.74)**	***0.16 (0.03,0.77)**	***0.17 (0.04,0.77)**	***0.18 (0.04,0.83)**	***0.19 (0.04,0.88)**	0.21 (0.04,1.09)	SHR

Pairwise (upper-right portion) and network (lower-left portion) meta-analyses results are presented as estimated effect sizes for the outcomes of rates of any adverse events reported in patients with tinnitus. Interventions are reported in the order of the mean ranking of tolerability, and outcomes are expressed as odds ratio (OR) (95% confidence intervals). For the pairwise meta-analyses, OR of less than 1 indicate that the treatment specified in the row had better tolerability than that specified in the column. For the network meta-analysis (NMA), OR of less than 1 indicate that the treatment specified in the column had better tolerability than that specified in the row. Bold results marked with * indicate statistical significance.

Abbreviation: CI: confidence interval; DMMH: medium-term high dose memantine plus high dose donepezil; EHM: extreme-long-term high dose memantine; EMG: extreme-long-term medium dose galantamine; ES: effect size; GMMH: medium-term high dose memantine plus low dose galantamine; LHR: long-term high dose rivastigmine; LLT: long-term low dose melatonin; MA: meta-analysis; MD: mean difference; MED: medium-term extreme high dose donepezil; MEM: medium-term extreme high dose memantine; MEPR: medium-term extreme high dose rivastigmine patch; MHD: medium-term high dose donepezil; MHG: medium-term high dose galantamine; MHM: medium-term high dose memantine; MHPR: medium-term high dose rivastigmine patch; MHR: medium-term high dose rivastigmine; MLPR: medium-term low dose rivastigmine patch; MLR: medium-term low dose rivastigmine; MLT: medium-term low dose melatonin; MMD: medium-term donepezil medium dose; MMG: medium-term medium dose galantamine; MMSE: mini-mental status examination;

NMA: network meta-analysis; OR: odds ratio; Pla: Placebo; PRISMA: preferred reporting items for systematic reviews and meta-analyses; RCT: randomized controlled trial; RMMH: medium-term high dose memantine plus medium dose rivastigmine; SHD: short-term high dose donepezil; SHG: short-term high dose galantamine; SHM: short-term high dose memantine; SHR: short-term high dose rivastigmine; SHT: short-term high dose melatonin; SLG: short-term low dose galantamine; SLT: short-term low dose melatonin; SMD: short-term medium dose donepezil; SMG: short-term medium dose galantamine; SMT: short-term medium dose melatonin; StMD: standardized mean difference; SUCRA: surface under the cumulative ranking curve

eTable 8: Inconsistency of different intervention: design-by-treatment and loop inconsistency

Inconsistency	chi2	Prob>chi2
Changes of cognition		
design-by-treatment	6.69	0.3504
loop	1.50	0.4721
Changes of quality of life		
design-by-treatment	8.44	0.4907
loop	0.71	0.9499
Changes of behavioral disturbance		
design-by-treatment	0.36	0.9964
loop	0.12	0.9893
Drop-out rate		
design-by-treatment	13.32	0.3460
loop	3.23	0.5202
Rate of any adverse event		
design-by-treatment	20.87	0.0220
loop	0.84	0.8408

eTable 9: Inconsistency of different intervention: side-splitting inconsistency

changes of cognition

Side	symmetric		nosymmetric		Treatments used	
	P>z	tau	P>z	tau		
A B	.	.	.	.	A (reference):	Pla
A C *	0.54	0.171287	.	.	B:	SLT
A D	.	.	.	.	C:	SHT
A E	.	.	.	.	D:	MLT
A F *	0.546	0.184451	.	.	E:	SHM
A G	.	.	.	.	F:	MLR
A I	.	.	.	.	G:	EMG
A J	.	.	.	.	H:	MED
A L	.	.	.	.	I:	EHM
A M	.	.	.	.	J:	SHD
A N	0.217	0.159703	0.217	0.159703	K:	GMMH
A O *	0.217	0.159703	0.217	0.159703	L:	MMG
A P *	0.451	0.18414	.	.	M:	LHR
A Q *	0.64	0.193659	0.858	0.204768	N:	MHM
A R *	0.03	8.89E-08	.	.	O:	MHD
A S *	0.182	0.135242	0.858	0.20478	P:	MMD
A U *	0.188	0.114576	.	.	Q:	MHPR

A V	.	.	.	.	R:	MLPR
B C *	0.54	0.171297	.	.	S:	MHR
F S *	0.546	0.184452	0.546	0.184452	T:	RMMH
H O *	0.999	0.168423	0.999	0.168424	U:	MEPR
K N *	0.999	0.168423	0.999	0.168424	V:	SMD
K T	.	.	.	.	W:	DMMH
K W	.	.	.	.		
N O	0.217	0.159703	0.217	0.159703		
N T *	0.999	0.168424	.	.		
N W *	0.999	0.168424	.	.		
O P *	0.451	0.184138	.	.		
Q R *	0.03	3.19E-06	.	.		
Q S *	0.06	2.53E-05	0.546	0.184452		
Q U *	0.11	0.097626	.	.		
S U *	0.764	0.20209	.	.		
T W	.	.	.	.		

changes of quality of life

Side	symmetric		nosymmetric		Treatments used	
	P>z	tau	P>z	tau		
A B	.	.	.	.	A (reference):	Pla

A C *	0.004	0.17792	.	.	B:	SLT
A D	.	.	.	.	C:	SHT
A E	.	.	.	.	D:	MLT
A F *	0.978	0.20592	.	.	E:	MEM
A H	.	.	.	.	F:	MLR
A I	.	.	.	.	G:	MED
A J	.	.	.	.	H:	EHM
A K *	0.817	0.204964	.	.	I:	SLG
A L	.	.	.	.	J:	SMG
A M	.	.	.	.	K:	MHG
A N	0.364	0.195847	0.364	0.195847	L:	MMG
A O *	0.364	0.195847	0.364	0.195847	M:	LHR
A P *	0.561	0.200465	.	.	N:	MHM
A Q *	0.971	0.206068	0.944	0.206334	O:	MHD
A R	0.921	0.206444	0.897	0.206491	P:	MMD
A S *	0.879	0.205842	0.826	0.205423	Q:	MHPR
A T	.	.	.	.	R:	MLPR
A U *	0.957	0.206376	.	.	S:	MHR
B C *	0.004	0.17792	.	.	T:	SHR
F S *	0.978	0.20592	0.978	0.20592	U:	MEPR
G O *	0.993	0.194133	0.993	0.194133	V:	GMMH
I J	.	.	.	.	W:	DMMH
K L *	0.817	0.204964	0.817	0.204964	X:	RMMH

N O	0.443	0.197537	0.443	0.197537
N V *	0.739	0.19988	.	.
N W *	0.739	0.19988	0.739	0.19988
N X *	0.739	0.19988	.	.
O P *	0.561	0.200465	.	.
O W	0.739	0.19988	0.739	0.19988
Q R *	0.973	0.206398	.	.
Q S *	0.996	0.20607	0.978	0.20592
Q U *	0.877	0.206135	.	.
S U *	0.832	0.205662	.	.
V W *	0.739	0.19988	0.739	0.19988
V X	.	.	.	.
W X *	0.739	0.19988	.	.

changes of behavioral disturbance

Side	symmetric		nosymmetric		Treatments used	
	P>z	tau	P>z	tau		
A B	.	.	.	.	A (reference):	Pla
A C	.	.	.	.	B:	SLT
A D	.	.	.	.	C:	SHT
A E	.	.	.	.	D:	MEM

A F	.	.	.	.	E:	SHM
A G	.	.	.	.	F:	EHM
A I	.	.	.	.	G:	SHD
A J	.	.	.	.	H:	DMMH
A K *	0.742	0.141315	.	.	I:	SLG
A L	.	.	.	.	J:	SMG
A M	.	.	.	.	K:	MEPR
A N	0.999	0.13734	0.999	0.13734	L:	MMG
A O *	0.999	0.137339	0.999	0.137339	M:	SHR
A P *	0.527	0.132967	.	.	N:	MHM
A Q *	0.953	0.14274	0.953	0.14274	O:	MHD
A R	0.681	0.140629	0.748	0.141756	P:	MMD
A S *	0.711	0.140413	0.801	0.141248	Q:	MHPR
B C	.	.	.	.	R:	MLPR
H O *	1	0.127712	1	0.127712	S:	MHR
I J	.	.	.	.		
K Q *	0.939	0.14266	0.939	0.142659		
K S *	0.801	0.141248	0.801	0.141248		
N O	0.999	0.13734	0.999	0.137339		
O P *	0.527	0.132968	.	.		
Q R *	0.742	0.141316	.	.		
Q S *	0.742	0.141316	.	.		

drop-out rate

Side	symmetric		nosymmetric		Treatments used	
	P>z	tau	P>z	tau		
AA AB	.	.	.	.	AA (reference):	Pla
AA AC	0.421	0.148016	.	.	AB:	SLT
AA AD	.	.	.	.	AC:	SHT
AA AE	.	.	.	.	AD:	MLT
AA AF	0.486	0.154004	.	.	AE:	MEM
AA AG	.	.	.	.	AF:	SHG
AA AH	0.09	0.117708	.	.	AG:	SHM
AA AI	0.866	0.15756	.	.	AH:	MLR
AA AJ	.	.	.	.	AI:	SLG
AA AK	0.156	0.137482	.	.	AJ:	SMG
AA AL	.	.	.	.	AK:	MHG
AA AM	.	.	.	.	AL:	MMG
AA AN	0.154	0.122623	0.154	0.122623	AM:	EMG
AA AO	0.282	0.131738	0.154	0.122622	AN:	MHM
AA AP	0.084	0.133255	.	.	AO:	MHD
AA AQ	0.35	0.152952	0.902	0.165202	AP:	MMD
AA AR	0.39	0.156284	0.983	0.166734	AQ:	MHPR
AA AS	0.326	0.150152	0.883	0.163604	AR:	MLPR

AA AT	.	.	.	.	AS:	MHR
AA AU	0.968	0.16197	.	.	AT:	SHR
AA AV	.	.	.	.	AU:	MEPR
AA AZ	.	.	.	.	AV:	SMD
AA BA	.	.	.	.	AW:	DMMH
AB AC	0.421	0.148016	.	.	AX:	RMMH
AF AJ	0.486	0.154004	0.486	0.154003	AY:	GMMH
AH AS	0.09	0.117708	0.09	0.117707	AZ:	SHD
AI AJ	0.866	0.15756	0.866	0.15756	BA:	EHM
AK AL	0.156	0.137482	0.156	0.137482	BB:	MED
AN AO	0.098	0.120552	0.098	0.120552		
AN AW	0.321	0.148743	0.321	0.148743		
AN AX	0.321	0.148742	.	.		
AN AY	0.321	0.148743	.	.		
AO AP	0.093	0.135922	0.574	0.156415		
AO AW	0.321	0.148743	0.321	0.148743		
AO BB	0.99	0.147801	.	.		
AQ AR	0.13	0.127517	.	.		
AQ AS	0.044	0.099812	0.09	0.117708		
AQ AU	0.251	0.141945	.	.		
AS AU	0.223	0.140457	.	.		
AW AX	0.321	0.148743	.	.		
AW AY	0.321	0.148743	.	.		

AX AY	.	.	.	.

rate of any adverse event reported

Side	symmetric		nosymmetric		Treatments used	
	P>z	tau	P>z	tau		
A B	.	.	.	.	A (reference):	Pla
A C	.	.	.	.	B:	SLT
A D	.	.	.	.	C:	SHT
A E	.	.	.	.	D:	MLT
A F *	0.849	0.076541	.	.	E:	MEM
A G *	0.057	1.21E-06	.	.	F:	SHG
A H	.	.	.	.	G:	MLR
A I *	0.387	0.06915	.	.	H:	EMG
A J	.	.	.	.	I:	SLG
A K *	0.015	2.60E-07	.	.	J:	SMG
A L	.	.	.	.	K:	MHG
A M	.	.	.	.	L:	MMG
A N	0.592	0.0621	0.592	0.0621	M:	LHR
A O	0.306	0.036676	0.592	0.062096	N:	MHM
A P *	0.057	0.035501	.	.	O:	MHD
A Q *	0.103	1.12E-06	0.432	0.068297	P:	MMD

A R	0.272	0.021718	0.581	0.069833	Q:	MHPR
A S *	0.732	0.077726	0.619	0.083076	R:	MLPR
A T	.	.	.	.	S:	MHR
A U *	0.016	5.65E-06	.	.	T:	SHR
A Z	.	.	.	.	U:	MEPR
B C	.	.	.	.	V:	MED
F J *	0.849	0.076543	0.849	0.076544	W:	DMMH
G S *	0.057	5.41E-06	0.057	1.68E-05	X:	RMMH
I J *	0.387	0.06915	0.387	0.069149	Y:	GMMH
K L *	0.015	1.23E-06	0.015	4.25E-06	Z:	EHM
N W *	0.592	0.062097	0.592	0.062102		
N X *	0.592	0.062102	.	.		
N Y *	0.592	0.062097	.	.		
O P	0.017	1.12E-06	0.073	3.75E-05		
O V *	0	0.058301	.	.		
O W	0.592	0.062092	0.592	0.0621		
Q R *	0.226	1.94E-05	.	.		
Q S *	0.77	0.082411	0.057	1.68E-05		
Q U *	0.159	0.00039	.	.		
S U *	0.404	0.079998	.	.		
W X *	0.592	0.062097	.	.		
W Y *	0.592	0.062097	.	.		
X Y	.	.	.	.		

eTable 10: Estimated between-studies standard deviations of different outcome

Outcome	Estimated between-studies standard deviation
Changes of cognition	0.1684
Changes of quality of life	0.1941
Changes of behavioral disturbance	0.1277
Drop-out rate	0.1478
Rate of any adverse event	0.0583

eTable 11: Quality of evidence for primary outcome: changes of cognition

Comparisons	GRADE		
	Direct	Indirect	Network meta-analysis
	Mean difference (95% CI) and the final rating of direct evidence	Co-efficiency (Standard error) and the final rating of indirect evidence	Mean difference (95% CI)and overall quality of evidence
MLT vs MED			0.14 (-1.10,1.37) ⊕◯◯◯ very low
MLT vs SHD			-0.02 (-1.72,1.68) ⊕◯◯◯ very low
MLT vs GMMH			0.16 (-1.68,2.01) ⊕◯◯◯ very low
MLT vs SHM			0.08 (-2.21,2.38) ⊕◯◯◯ very low
MLT vs MHD			0.44 (-0.58,1.45) ⊕◯◯◯ very low
MLT vs MMD			0.43 (-0.81,1.66) ⊕◯◯◯ very low
MLT vs LHR			0.48 (-0.58,1.55) ⊕◯◯◯ very low
MLT vs RMMH			0.57 (-1.41,2.56) ⊕◯◯◯ very low
MLT vs DMMH			0.61 (-1.24,2.47) ⊕◯◯◯ very low
MLT vs EMG			0.75 (-0.35,1.85) ⊕◯◯◯ very low
MLT vs MHPR			0.77 (-0.29,1.82) ⊕◯◯◯ very low
MLT vs MEPR			0.76 (-0.37,1.89) ⊕◯◯◯ very low
MLT vs MHR			0.82 (-0.25,1.88) ⊕◯◯◯ very low
MLT vs MHM			0.98 (-0.18,2.14) ⊕◯◯◯ very low
MLT vs SLT			1.35 (-0.04,2.74) ⊕◯◯◯ very low
MLT vs EHM			1.37 (-0.00,2.75) ⊕◯◯◯ very low
MLT vs MLPR			***1.28 (0.15,2.41)** ⊕⊕⊕◯ medium

MLT vs SMD			1.58 (-0.61,3.78) ⊕◯◯◯ very low
MLT vs Pla	***1.48 (0.54,2.43)** ⊕⊕⊕◯ medium		***1.48 (0.51,2.46)** ⊕⊕⊕◯ medium
MLT vs MMG			2.18 (-0.40,4.77) ⊕◯◯◯ very low
MLT vs MLR			***1.65 (0.45,2.86)** ⊕⊕⊕◯ medium
MLT vs SHT			***1.95 (0.40,3.51)** ⊕⊕⊕◯ medium
MED vs SHD			-0.15 (-1.74,1.43) ⊕◯◯◯ very low
MED vs GMMH			0.03 (-1.71,1.76) ⊕◯◯◯ very low
MED vs SHM			-0.05 (-2.27,2.16) ⊕◯◯◯ very low
MED vs MHD	0.30 (-0.32,0.92) ⊕⊕◯◯low	2.14 (2785.57) ⊕◯◯◯ very low	0.30 (-0.41,1.01) ⊕⊕⊕◯ medium
MED vs MMD			0.29 (-0.75,1.33) ⊕◯◯◯ very low
MED vs LHR			0.35 (-0.53,1.22) ⊕⊕◯◯ low
MED vs RMMH			0.44 (-1.45,2.32) ⊕◯◯◯ very low
MED vs DMMH			0.48 (-1.27,2.22) ⊕◯◯◯ very low
MED vs EMG			0.61 (-0.30,1.53) ⊕⊕◯◯ low
MED vs MHPR			0.63 (-0.23,1.49) ⊕⊕◯◯ low
MED vs MEPR			0.62 (-0.33,1.58) ⊕⊕◯◯ low
MED vs MHR			0.68 (-0.20,1.56) ⊕⊕◯◯ low
MED vs MHM			0.85 (-0.13,1.82) ⊕⊕◯◯ low
MED vs SLT			1.21 (-0.04,2.46) ⊕◯◯◯ very low
MED vs EHM			***1.24 (0.00,2.47)** ⊕⊕⊕◯ medium
MED vs MLPR			***1.14 (0.18,2.10)** ⊕⊕⊕◯ medium
MED vs SMD			1.45 (-0.67,3.56) ⊕◯◯◯ very low
MED vs Pla			***1.35 (0.59,2.11)** ⊕⊕⊕◯ medium
MED vs MMG			2.05 (-0.46,4.56) ⊕◯◯◯ very low
MED vs MLR			***1.52 (0.48,2.56)** ⊕⊕⊕◯ medium

MED vs SHT		***1.81 (0.38,3.25)** ⊕⊕⊕◯ medium
SHD vs GMMH		0.18 (-1.92,2.28) ⊕◯◯◯ very low
SHD vs SHM		0.10 (-2.40,2.60) ⊕◯◯◯ very low
SHD vs MHD		0.45 (-0.97,1.87) ⊕◯◯◯ very low
SHD vs MMD		0.44 (-1.15,2.03) ⊕◯◯◯ very low
SHD vs LHR		0.50 (-0.96,1.96) ⊕◯◯◯ very low
SHD vs RMMH		0.59 (-1.63,2.81) ⊕◯◯◯ very low
SHD vs DMMH		0.63 (-1.48,2.73) ⊕◯◯◯ very low
SHD vs EMG		0.77 (-0.72,2.25) ⊕◯◯◯ very low
SHD vs MHPR		0.78 (-0.67,2.23) ⊕◯◯◯ very low
SHD vs MEPR		0.77 (-0.73,2.28) ⊕◯◯◯ very low
SHD vs MHR		0.83 (-0.62,2.29) ⊕◯◯◯ very low
SHD vs MHM		1.00 (-0.53,2.53) ⊕◯◯◯ very low
SHD vs SLT		1.36 (-0.35,3.08) ⊕◯◯◯ very low
SHD vs EHM		1.39 (-0.31,3.09) ⊕◯◯◯ very low
SHD vs MLPR		1.30 (-0.21,2.80) ⊕◯◯◯ very low
SHD vs SMD		1.60 (-0.81,4.01) ⊕◯◯◯ very low
SHD vs Pla	***1.50 (0.15,2.85)** ⊕⊕⊕◯ medium	***1.50 (0.11,2.89)** ⊕⊕⊕◯ medium
SHD vs MMG		2.20 (-0.57,4.97) ⊕◯◯◯ very low
SHD vs MLR		***1.67 (0.11,3.23)** ⊕⊕⊕◯ medium
SHD vs SHT		***1.97 (0.12,3.81)** ⊕⊕⊕◯ medium
GMMH vs SHM		-0.08 (-2.68,2.53) ⊕◯◯◯ very low
GMMH vs MHD		0.27 (-1.31,1.86) ⊕◯◯◯ very low
GMMH vs MMD		0.26 (-1.48,2.00) ⊕◯◯◯ very low
GMMH vs LHR		0.32 (-1.31,1.95) ⊕◯◯◯ very low

GMMH vs RMMH	0.41 (-1.07,1.89) ⊕⊕◯◯ low		0.41 (-1.11,1.93) ⊕⊕◯◯ low
GMMH vs DMMH	0.45 (-0.85,1.75) ⊕⊕◯◯ low		0.45 (-0.89,1.79) ⊕⊕◯◯ low
GMMH vs EMG			0.59 (-1.06,2.24) ⊕◯◯◯ very low
GMMH vs MHPR			0.60 (-1.02,2.22) ⊕◯◯◯ very low
GMMH vs MEPR			0.60 (-1.07,2.27) ⊕◯◯◯ very low
GMMH vs MHR			0.66 (-0.97,2.28) ⊕◯◯◯ very low
GMMH vs MHM	0.82 (-0.58,2.22) ⊕⊕◯◯ low	0.65 (1605.92) ⊕◯◯◯ very low	0.82 (-0.62,2.26) ⊕⊕◯◯ low
GMMH vs SLT			1.19 (-0.67,3.04) ⊕◯◯◯ very low
GMMH vs EHM			1.21 (-0.64,3.06) ⊕◯◯◯ very low
GMMH vs MLPR			1.12 (-0.56,2.79) ⊕◯◯◯ very low
GMMH vs SMD			1.42 (-1.10,3.94) ⊕◯◯◯ very low
GMMH vs Pla			1.32 (-0.25,2.89) ⊕◯◯◯ very low
GMMH vs MMG			2.02 (-0.84,4.88) ⊕◯◯◯ very low
GMMH vs MLR			1.49 (-0.23,3.21) ⊕◯◯◯ very low
GMMH vs SHT			1.79 (-0.19,3.77) ⊕◯◯◯ very low
SHM vs MHD			0.35 (-1.74,2.45) ⊕◯◯◯ very low
SHM vs MMD			0.34 (-1.87,2.56) ⊕◯◯◯ very low
SHM vs LHR			0.40 (-1.72,2.52) ⊕◯◯◯ very low
SHM vs RMMH			0.49 (-2.22,3.19) ⊕◯◯◯ very low
SHM vs DMMH			0.53 (-2.08,3.14) ⊕◯◯◯ very low
SHM vs EMG			0.67 (-1.47,2.81) ⊕◯◯◯ very low
SHM vs MHPR			0.68 (-1.43,2.80) ⊕◯◯◯ very low
SHM vs MEPR			0.67 (-1.48,2.83) ⊕◯◯◯ very low
SHM vs MHR			0.73 (-1.39,2.86) ⊕◯◯◯ very low
SHM vs MHM			0.90 (-1.27,3.07) ⊕◯◯◯ very low

SHM vs SLT			1.26 (-1.04,3.57) ⊕◯◯◯ very low
SHM vs EHM			1.29 (-1.00,3.58) ⊕◯◯◯ very low
SHM vs MLPR			1.20 (-0.96,3.35) ⊕◯◯◯ very low
SHM vs SMD			1.50 (-1.36,4.36) ⊕◯◯◯ very low
SHM vs Pla	1.40 (-0.65,3.45) ⊕⊕◯◯ low		1.40 (-0.68,3.48) ⊕⊕◯◯ low
SHM vs MMG			2.10 (-1.07,5.27) ⊕◯◯◯ very low
SHM vs MLR			1.57 (-0.62,3.77) ⊕◯◯◯ very low
SHM vs SHT			1.87 (-0.54,4.27) ⊕◯◯◯ very low
MHD vs MMD	0.15 (-0.65,0.95) ⊕⊕◯◯ low	0.56 (0.83) ⊕⊕◯◯ low	-0.01 (-0.77,0.75) ⊕⊕⊕◯ medium
MHD vs LHR			0.05 (-0.47,0.56) ⊕⊕◯◯ low
MHD vs RMMH			0.14 (-1.61,1.89) ⊕◯◯◯ very low
MHD vs DMMH			0.18 (-1.42,1.77) ⊕◯◯◯ very low
MHD vs EMG			0.31 (-0.27,0.90) ⊕⊕◯◯ low
MHD vs MHPR			0.33 (-0.17,0.83) ⊕⊕◯◯ low
MHD vs MEPR			0.32 (-0.32,0.97) ⊕⊕◯◯ low
MHD vs MHR			0.38 (-0.14,0.90) ⊕⊕◯◯ low
MHD vs MHM	-0.37 (-1.94,1.20) ⊕⊕◯◯ low	0.74 (0.38) ⊕⊕◯◯ low	0.55 (-0.13,1.22) ⊕⊕⊕◯ medium
MHD vs SLT			0.91 (-0.13,1.95) ⊕◯◯◯ very low
MHD vs EHM			0.94 (-0.08,1.95) ⊕◯◯◯ very low
MHD vs MLPR			***0.84 (0.19,1.49)** ⊕⊕⊕◯ medium
MHD vs SMD			1.15 (-0.84,3.14) ⊕◯◯◯ very low
MHD vs Pla	***1.08 (0.83,1.34)** ⊕⊕⊕◯ medium	-0.03 (0.89) ⊕⊕◯◯ low	***1.05 (0.76,1.33)** ⊕⊕⊕◯ medium
MHD vs MMG			1.75 (-0.66,4.16) ⊕◯◯◯ very low
MHD vs MLR			***1.22 (0.46,1.98)** ⊕⊕⊕◯ medium
MHD vs SHT			***1.51 (0.27,2.76)** ⊕⊕⊕◯ medium

MMD vs LHR			0.06 (-0.82,0.93) ⊕⊕◯◯ low
MMD vs RMMH			0.15 (-1.74,2.04) ⊕◯◯◯ very low
MMD vs DMMH			0.19 (-1.56,1.94) ⊕◯◯◯ very low
MMD vs EMG			0.32 (-0.59,1.24) ⊕⊕◯◯ low
MMD vs MHPR			0.34 (-0.52,1.20) ⊕⊕◯◯ low
MMD vs MEPR			0.33 (-0.62,1.29) ⊕⊕◯◯ low
MMD vs MHR			0.39 (-0.49,1.27) ⊕⊕◯◯ low
MMD vs MHM			0.56 (-0.43,1.54) ⊕⊕◯◯ low
MMD vs SLT			0.92 (-0.33,2.18) ⊕◯◯◯ very low
MMD vs EHM			0.95 (-0.29,2.18) ⊕◯◯◯ very low
MMD vs MLPR			0.85 (-0.10,1.81) ⊕⊕◯◯ low
MMD vs SMD			1.16 (-0.95,3.27) ⊕◯◯◯ very low
MMD vs Pla	***1.21 (0.42,2.00)** ⊕⊕⊕◯ medium	0.50 (0.84) ⊕⊕◯◯ low	***1.06 (0.30,1.82)** ⊕⊕⊕◯ medium
MMD vs MMG			1.76 (-0.75,4.27) ⊕◯◯◯ very low
MMD vs MLR			***1.23 (0.19,2.27)** ⊕⊕⊕◯ medium
MMD vs SHT			***1.53 (0.10,2.96)** ⊕⊕⊕◯ medium
LHR vs RMMH			0.09 (-1.70,1.87) ⊕◯◯◯ very low
LHR vs DMMH			0.13 (-1.51,1.77) ⊕◯◯◯ very low
LHR vs EMG			0.27 (-0.40,0.94) ⊕⊕◯◯ low
LHR vs MHPR			0.28 (-0.31,0.87) ⊕⊕◯◯ low
LHR vs MEPR			0.27 (-0.44,0.99) ⊕⊕◯◯ low
LHR vs MHR			0.33 (-0.28,0.95) ⊕⊕◯◯ low
LHR vs MHM			0.50 (-0.26,1.26) ⊕⊕◯◯ low
LHR vs SLT			0.86 (-0.22,1.95) ⊕◯◯◯ very low
LHR vs EHM			0.89 (-0.17,1.95) ⊕◯◯◯ very low

LHR vs MLPR			***0.80 (0.07,1.52)** ⊕⊕⊕◯ medium
LHR vs SMD			1.10 (-0.92,3.12) ⊕◯◯◯ very low
LHR vs Pla	***1.00 (0.72,1.28)** ⊕⊕⊕◯ medium		***1.00 (0.57,1.43)** ⊕⊕⊕◯ medium
LHR vs MMG			1.70 (-0.73,4.13) ⊕◯◯◯ very low
LHR vs MLR			***1.17 (0.34,2.00)** ⊕⊕⊕◯ medium
LHR vs SHT			***1.47 (0.18,2.75)** ⊕⊕◯◯ low
RMMH vs DMMH	0.04 (-1.45,1.53) ⊕⊕◯◯ low		0.04 (-1.49,1.57) ⊕⊕◯◯ low
RMMH vs EMG			0.18 (-1.63,1.98) ⊕◯◯◯ very low
RMMH vs MHPR			0.19 (-1.58,1.97) ⊕◯◯◯ very low
RMMH vs MEPR			0.19 (-1.64,2.01) ⊕◯◯◯ very low
RMMH vs MHR			0.25 (-1.54,2.03) ⊕◯◯◯ very low
RMMH vs MHM	0.41 (-1.17,1.99) ⊕⊕◯◯ low	-1.34 (1437.04) ⊕◯◯◯ very low	0.41 (-1.20,2.02) ⊕⊕◯◯ low
RMMH vs SLT			0.78 (-1.22,2.77) ⊕◯◯◯ very low
RMMH vs EHM			0.80 (-1.19,2.79) ⊕◯◯◯ very low
RMMH vs MLPR			0.71 (-1.12,2.53) ⊕◯◯◯ very low
RMMH vs SMD			1.01 (-1.61,3.63) ⊕◯◯◯ very low
RMMH vs Pla			0.91 (-0.82,2.64) ⊕◯◯◯ very low
RMMH vs MMG			1.61 (-1.34,4.57) ⊕◯◯◯ very low
RMMH vs MLR			1.08 (-0.79,2.95) ⊕◯◯◯ very low
RMMH vs SHT			1.38 (-0.73,3.49) ⊕◯◯◯ very low
DMMH vs EMG			0.14 (-1.52,1.80) ⊕◯◯◯ very low
DMMH vs MHPR			0.15 (-1.48,1.78) ⊕◯◯◯ very low
DMMH vs MEPR			0.15 (-1.53,1.83) ⊕◯◯◯ very low
DMMH vs MHR			0.21 (-1.43,1.84) ⊕◯◯◯ very low
DMMH vs MHM	0.37 (-1.78,1.04) ⊕⊕◯◯ low	-1.46 (1533.20) ⊕◯◯◯ very low	0.37 (-1.08,1.82) ⊕⊕◯◯ low

DMMH vs SLT			0.74 (-1.13,2.60) ⊕◯◯◯ very low
DMMH vs EHM			0.76 (-1.09,2.62) ⊕◯◯◯ very low
DMMH vs MLPR			0.67 (-1.01,2.35) ⊕◯◯◯ very low
DMMH vs SMD			0.97 (-1.55,3.50) ⊕◯◯◯ very low
DMMH vs Pla			0.87 (-0.71,2.45) ⊕◯◯◯ very low
DMMH vs MMG			1.57 (-1.30,4.44) ⊕◯◯◯ very low
DMMH vs MLR			1.04 (-0.69,2.77) ⊕◯◯◯ very low
DMMH vs SHT			1.34 (-0.65,3.33) ⊕◯◯◯ very low
EMG vs MHPR			0.02 (-0.64,0.67) ⊕⊕◯◯ low
EMG vs MEPR			0.01 (-0.76,0.78) ⊕⊕◯◯ low
EMG vs MHR			0.07 (-0.60,0.74) ⊕⊕◯◯ low
EMG vs MHM			0.23 (-0.58,1.04) ⊕⊕◯◯ low
EMG vs SLT			0.60 (-0.52,1.72) ⊕◯◯◯ very low
EMG vs EHM			0.62 (-0.48,1.72) ⊕◯◯◯ very low
EMG vs MLPR			0.53 (-0.24,1.30) ⊕⊕◯◯ low
EMG vs SMD			0.83 (-1.20,2.87) ⊕◯◯◯ very low
EMG vs Pla	***0.73 (0.34,1.13)** ⊕⊕⊕◯ medium		***0.73 (0.22,1.25)** ⊕⊕⊕◯ medium
EMG vs MMG			1.43 (-1.01,3.88) ⊕◯◯◯ very low
EMG vs MLR			***0.90 (0.03,1.78)** ⊕⊕⊕◯ medium
EMG vs SHT			1.20 (-0.11,2.52) ⊕◯◯◯ very low
MHPR vs MEPR	0.20 (-0.34,0.74) ⊕⊕◯◯ low	0.83 (0.58) ⊕⊕◯◯ low	-0.01 (-0.57,0.56) ⊕⊕⊕◯ medium
MHPR vs MHR	0.21 (-0.18,0.59) ⊕⊕◯◯ low	0.70 (0.44) ⊕⊕◯◯ low	0.05 (-0.36,0.46) ⊕⊕⊕◯ medium
MHPR vs MHM			0.22 (-0.53,0.96) ⊕⊕◯◯ low
MHPR vs SLT			0.58 (-0.49,1.65) ⊕◯◯◯ very low
MHPR vs EHM			0.61 (-0.45,1.66) ⊕◯◯◯ very low

MHPR vs MLPR	0.30 (-0.23,0.83) ⊕⊕◯◯ low	-1.82 (0.65) ⊕⊕◯◯ low	0.51 (-0.07,1.09) ⊕⊕⊕◯ medium
MHPR vs SMD			0.82 (-1.19,2.83) ⊕◯◯◯ very low
MHPR vs Pla	0.69 (-0.09,1.48) ⊕⊕◯◯ low	0.95 (0.54) ⊕⊕◯◯ low	***0.72 (0.31,1.12)** ⊕⊕⊕◯ medium
MHPR vs MMG			1.42 (-1.01,3.84) ⊕◯◯◯ very low
MHPR vs MLR			***0.89 (0.14,1.64)** ⊕⊕⊕◯ medium
MHPR vs SHT			1.19 (-0.09,2.46) ⊕◯◯◯ very low
MEPR vs MHR	0.10 (-0.43,0.63) ⊕⊕◯◯ low	-0.14 (0.72) ⊕⊕◯◯ low	0.06 (-0.51,0.63) ⊕⊕⊕◯ medium
MEPR vs MHM			0.22 (-0.63,1.08) ⊕⊕◯◯ low
MEPR vs SLT			0.59 (-0.56,1.74) ⊕◯◯◯ very low
MEPR vs EHM			0.62 (-0.51,1.74) ⊕◯◯◯ very low
MEPR vs MLPR			0.52 (-0.24,1.28) ⊕⊕◯◯ low
MEPR vs SMD			0.83 (-1.23,2.88) ⊕◯◯◯ very low
MEPR vs Pla	***0.90 (0.35,1.45)** ⊕⊕⊕◯ medium	0.63 (0.93) ⊕⊕◯◯ low	***0.73 (0.15,1.30)** ⊕⊕⊕◯ medium
MEPR vs MMG			1.43 (-1.04,3.89) ⊕◯◯◯ very low
MEPR vs MLR			***0.90 (0.04,1.75)** ⊕⊕⊕◯ medium
MEPR vs SHT			1.19 (-0.15,2.53) ⊕◯◯◯ very low
MHR vs MHM			0.16 (-0.60,0.93) ⊕⊕◯◯ low
MHR vs SLT			0.53 (-0.55,1.61) ⊕◯◯◯ very low
MHR vs EHM			0.56 (-0.51,1.62) ⊕◯◯◯ very low
MHR vs MLPR			0.46 (-0.20,1.12) ⊕⊕◯◯ low
MHR vs SMD			0.77 (-1.25,2.78) ⊕◯◯◯ very low
MHR vs Pla	***0.83 (0.39,1.26)** ⊕⊕⊕◯ medium	0.43 (0.65) ⊕⊕◯◯ low	***0.67 (0.23,1.10)** ⊕⊕⊕◯ medium
MHR vs MMG			1.37 (-1.07,3.80) ⊕◯◯◯ very low
MHR vs MLR	***0.94 (0.24,1.64)** ⊕⊕⊕◯ medium	0.34 (0.90) ⊕⊕◯◯ low	***0.84 (0.14,1.54)** ⊕⊕⊕◯ medium
MHR vs SHT			1.13 (-0.15,2.42) ⊕◯◯◯ very low

MHM vs SLT			0.37 (-0.81,1.54) ⊕◯◯◯ very low
MHM vs EHM			0.39 (-0.77,1.55) ⊕◯◯◯ very low
MHM vs MLPR			0.30 (-0.56,1.15) ⊕◯◯◯ very low
MHM vs SMD			0.60 (-1.47,2.67) ⊕◯◯◯ very low
MHM vs Pla	0.33 (-0.31,0.97) ⊕⊕◯◯ low	1.45 (0.83) ⊕⊕◯◯ low	0.50 (-0.13,1.13) ⊕⊕⊕◯ medium
MHM vs MMG			1.20 (-1.27,3.68) ⊕◯◯◯ very low
MHM vs MLR			0.67 (-0.27,1.62) ⊕⊕◯◯ low
MHM vs SHT			0.97 (-0.40,2.33) ⊕◯◯◯ very low
SLT vs EHM			0.03 (-1.37,1.42) ⊕◯◯◯ very low
SLT vs MLPR			-0.07 (-1.22,1.08) ⊕◯◯◯ very low
SLT vs SMD			0.24 (-1.97,2.44) ⊕◯◯◯ very low
SLT vs Pla	0.13 (-0.83,1.08) ⊕⊕◯◯ low		0.14 (-0.86,1.13) ⊕⊕⊕◯ medium
SLT vs MMG			0.84 (-1.76,3.43) ⊕◯◯◯ very low
SLT vs MLR			0.31 (-0.91,1.53) ⊕◯◯◯ very low
SLT vs SHT	0.53 (-0.67,1.73) ⊕⊕◯◯ low	-2.15 (2.60) ⊕⊕◯◯ low	0.60 (-0.61,1.82) ⊕⊕◯◯ low
EHM vs MLPR			-0.09 (-1.23,1.04) ⊕◯◯◯ very low
EHM vs SMD			0.21 (-1.99,2.41) ⊕◯◯◯ very low
EHM vs Pla	0.11 (-0.81,1.03) ⊕⊕◯◯ low		0.11 (-0.86,1.08) ⊕⊕⊕◯ medium
EHM vs MMG			0.81 (-1.77,3.39) ⊕◯◯◯ very low
EHM vs MLR			0.28 (-0.92,1.48) ⊕◯◯◯ very low
EHM vs SHT			0.58 (-0.97,2.13) ⊕◯◯◯ very low
MLPR vs SMD			0.30 (-1.75,2.36) ⊕◯◯◯ very low
MLPR vs Pla	0.00 (-0.52,0.52) ⊕⊕◯◯ low	0.66 (-1.52) ⊕⊕◯◯ low	0.20 (-0.37,0.78) ⊕⊕⊕◯ medium
MLPR vs MMG			0.90 (-1.56,3.37) ⊕◯◯◯ very low
MLPR vs MLR			0.38 (-0.51,1.26) ⊕◯◯◯ very low

MLPR vs SHT			0.67 (-0.67,2.01) ⊕○○○ very low
SMD vs Pla	-0.10 (-2.04,1.84) ⊕⊕○○ low		-0.10 (-2.07,1.87) ⊕⊕○○ low
SMD vs MMG			0.60 (-2.50,3.70) ⊕○○○ very low
SMD vs MLR			0.07 (-2.02,2.16) ⊕○○○ very low
SMD vs SHT			0.37 (-1.94,2.68) ⊕○○○ very low
Pla vs MMG	0.70 (-1.67,3.07) ⊕⊕○○ low		0.70 (-1.69,3.09) ⊕⊕○○ low
Pla vs MLR	0.06 (-0.66,0.78) ⊕⊕○○ low	-0.66 (0.89) ⊕⊕○○ low	0.17 (-0.53,0.88) ⊕⊕⊕○ medium
Pla vs SHT	0.54 (-0.65,1.73) ⊕⊕○○ low	1.08 (2.60) ⊕⊕○○ low	0.47 (-0.74,1.68) ⊕⊕○○ low
MMG vs MLR			-0.53 (-3.02,1.97) ⊕○○○ very low
MMG vs SHT			-0.23 (-2.91,2.45) ⊕○○○ very low
MLR vs SHT			0.30 (-1.10,1.70) ⊕○○○ very low

We followed the article in BMJ [1] and previous network meta-analysis [2] for quality assessment

References:

[1] Puhan, M.A.; Schunemann, H.J.; Murad, M.H.; Li, T.; Brignardello-Petersen, R.; Singh, J.A.; Kessels, A.G.; Guyatt, G.H.; Group, G.W. A GRADE Working Group approach for rating the quality of treatment effect estimates from network meta-analysis. *BMJ*, **2014**, *349*, g5630.

[2] Cipriani, A.; Furukawa, T.A.; Salanti, G.; Chaimani, A.; Atkinson, L.Z.; Ogawa, Y.; Leucht, S.; Ruhe, H.G.; Turner, E.H.; Higgins, J.P.T.; Egger, M.; Takeshima, N.; Hayasaka, Y.; Imai, H.; Shinohara, K.; Tajika, A.; Ioannidis, J.P.A.; Geddes, J.R. Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. *Lancet*, **2018**.