SYSTEMATIC REVIEW

Comparative Efficacy and Safety of Monoclonal Antibodies for Cognitive Decline in Patients with Alzheimer's Disease: A Systematic Review and Network Meta-Analysis

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Abstract

Background Recent clinical trials of anti-Aβ monoclonal antibodies (mAbs) in the treatment of early Alzheimer's disease (AD) have produced encouraging cognitive and clinical results. The purpose of this network meta-analysis (NMA) was to compare and rank mAb drugs according to their efficacy and safety.

Methods PubMed, Embase, Web of Science, and the Cochrane Library were searched for randomized controlled trials testing various mAbs for the treatment of cognitive decline in patients with AD, up to March 31, 2023. R software (version 4.2.3) along with JAGS and STATA software (version 15.0) were used for statistical analysis. Odds ratio (OR) for binary variables, mean difference (MD) for continuous variables, and their 95% confidence intervals (CI) were utilized to estimate treatment effects and rank probabilities for each mAb in terms of safety and efficacy outcomes. We calculated the surface under the cumulative ranking area (SUCRA) to evaluate each mAb, with higher SUCRA values indicating better efficacy or lower likelihood of adverse events.

Results Thirty-three randomized controlled trials with a total of 21,087 patients were included in the current NMA, involving eight different mAbs. SUCRA values showed that aducanumab (87.01% and 99.37%, respectively) was the most likely to achieve the best therapeutic effect based on the changes of Mini-Mental State Examination (MMSE) and Clinical Dementia Rating scale Sum of Boxes (CDR-SB) scores. Donanemab (88.50% and 99.00%, respectively) performed better than other therapies for Alzheimer's Disease Assessment Scale–cognitive subscale (ADAS-cog) and Positron Emission Tomography-Standardized Uptake Value ratio (PET-SUVr). Lecanemab (87.24%) may be the most promising way to slow down the decrease of Alzheimer's Disease Cooperative Study–Activities of Daily Living (ADCS-ADL) score. In the analysis of the incidence of adverse events (subjects with any treatment-emergent adverse event), gantenerumab (89.12%) had the least potential for adverse events, while lecanemab (0.79%) may cause more adverse events. Solanezumab (95.75% and 80.38%, respectively) had the lowest incidence of amyloid-related imaging abnormalities characterized by edema and effusion (ARIA-E) and by cerebral microhemorrhages (ARIA-H) of the included immunotherapies. While SUCRA values provided a comprehensive measure of treatment efficacy, the inherent statistical uncertainty required careful analysis in clinical application.

Conclusion Despite immunotherapies significantly increasing the risks of adverse events and ARIA, the data suggest that mAbs can effectively improve the cognitive function of patients with mild and moderate AD. According to the NMA, aducanumab was the most likely to achieve significant improvements in different cognitive and clinical assessments (statistically improved MMSE and CDR-SB), followed by donanemab (statistically improved ADAS-Cog, and PET-SUVr) and lecanemab (statistically improved ADCS-ADL).

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1 Introduction

Alzheimer's disease (AD) is characterized by relentlessly progressive neurodegeneration resulting in symptoms that affect language and motivation, and cause behavioral and cognitive disorders that gradually lead to patient mortality [1, 2]. It is the most common type of dementia, accounting for 60–70% of cases [3]. It is estimated that the number of

Key Points

Among individual drugs, aducanumab was the most likely to achieve significant improvements in different cognitive and clinical assessments (statistically improved MMSE and CDR-SB) followed by donanemab (statistically improved ADAS-Cog, and PET-SUVr) and lecanemab (statistically improved ADCS-ADL).

These treatments also increase the risk of adverse events, such as amyloid-related imaging abnormalities. Thus, their use requires careful consideration and further research.

patients diagnosed with AD will increase to 65.7 million by 2030 and 115.4 million by 2050, which has attracted worldwide attention [4, 5].

New diagnostic methods, including advanced neuroimaging technology and biochemical biomarkers, are steadily becoming available as accurate methods for detecting AD. However, there is no effective treatment, and prevention is still the priority [6]. Therefore, it is essential to understand the underlying pathology of AD and develop disease-modifying therapies that not only improve symptoms but also alter the disease course.

AD is characterized by three neuropathological features including extracellular amyloid beta-peptide (Aβ) plaques, intraneuronal neurofibrillary tangles (NFT) composed of hyper-phosphorylated tau protein, and loss of synapses as well as neurons, but the exact mechanisms by which they ultimately cause cognitive deficits are still unclear [1, 7].

The treatment scheme for AD remains limited. The established US Food and Drug Administration (FDA) approved pharmacological interventions, such as donepezil, galantamine, rivastigmine, and memantine, have only modest and transient effects, and do not stop the progression of dementia [8]. The amyloid cascade hypothesis is the most widely accepted hypothesis so far, which proposes that the imbalance between the deposition of neurotoxic Aβ protein and the production and elimination of Aβ triggers a series of pathological changes, including amyloid plaques, neurofibrillary tangles, neuronal dysfunction, and dementia [9, 10]. In the past two decades, strategies targeted at the amyloid cascade hypothesis have included drugs that focus on reducing amyloid-β production (β-secretase 1 inhibitor or α-secretase modulator) or increasing amyloid-β clearance (anti-amyloid-β antibodies or active immunotherapy) [11]. However, unfortunately, due to adverse effects and a lack of therapeutic effect, most compounds have been unsuccessful in phase II/III trials [12, 13]. Recent studies have provided evidence that different therapeutic strategies for clearing brain Aβ may be effective for altering disease course, and monoclonal antibodies (mAbs) against Aβ have attracted more and more attention.

Mounting evidence suggests that mAbs demonstrate potential in improving outcomes for the treatment of patients at early stages of AD. For example, bapineuzumab was the first N-terminus-directed anti-Aβ antibody tested in humans, reducing Aβ level, but demonstrating little improvement in cognition for AD patients [14]. Subsequently, several anti-Aβ mAb drugs were tested in clinical trials. With the recent approval of lecanemab, the first mAb for Alzheimer's disease, via the accelerated approval pathway in the US, attention now moves to understanding the efficacy and safety profile of this and the other mAbs. Previous paired meta-analysis had evaluated efficacy and safety of all types of immunotherapy drugs against Aβ within a narrow observation range [15]. Therefore, the objective of this network meta-analysis (NMA) was to compare and rank mAbs according to their efficacy and safety in patients with possible or probable AD, in order to provide additional evidence for clinical decision makers to choose the most appropriate treatment.

2 Methods

The study protocol was prospectively registered with the International Prospective Register for Systematic Reviews (CRD42023416047). This NMA was performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [16] and Cochrane guidelines [17].

2.1 Literature Search

In this NMA, randomized controlled trials investigating the treatment of AD with anti-Aβ mAbs were identified through PubMed, Embase, Cochrane Library, and Web of Science with a search deadline of March 31, 2023. The reference lists of pertinent meta-analyses, reviews, pooled analyses, and included trials were carefully reviewed manually in order to identify any additional studies using all relevant combinations of the following search terms: 'aducanumab', 'bapineuzumab', 'crenezumab', 'donanemab', 'gantenerumab', 'lecanemab', 'ponezumab' 'solanezumab', and 'Alzheimer Disease', see Supplementary Material S1 in the electronic supplementary material (ESM) for the specific search strategy.

2.2 Selection Criteria

Upon initial screening, we included published randomized controlled trials (RCTs) that recruited patients diagnosed

with mild cognitive impairment (MCI) or AD at any disease stage, in order to compare the efficacy and safety of all mAbs (aducanumab, bapineuzumab, crenezumab, donanemab, gantenerumab, lecanemab, ponezumab, and solanezumab) in this target population.

Reported outcomes included at least one of the following outcome indicators: Mini-Mental State Examination (MMSE), Clinical Dementia Rating scale–Sum of Boxes (CDR-SB), Alzheimer's Disease Assessment Scale–cognitive subscale (ADAS-cog), Alzheimer's Disease Cooperative Study–Activities of Daily Living (ADCS-ADL), standardized uptake value ratio of amyloid positron emission tomography (PET-SUVr), adverse events (AEs; subjects with any treatment-emergent AE [TEAE]); and amyloid-related imaging abnormalities characterized by edema and effusion (ARIA-E) or cerebral microhemorrhages (ARIA-H).

The exclusion criteria are (i) non-RCT research, such as meeting abstracts, agreements, letters, case reports, systematic reviews, and animal experiments; (ii) unavailability of full text or unavailability of usable data; and (iii) studies not including patients with AD. In the case of multiple publications based on the same RCT, we only included articles with the richest information and the largest sample source. Articles were included for review only after a consensus was reached among all three investigators.

2.3 Data Extraction

To ensure accuracy of the data collected, two evaluators independently extracted the relevant data from the retrieved literature, and any conflict was resolved through discussion between the first two evaluators or adjudication by a third author. The following data were extracted from each study: the author, publication year, clinical trial number, country, sample size, sex, age, severity of AD, MMSE baseline, ApoE allele carrying status, follow-up, and results. At the same time, we recorded the incidence of adverse events such as ARIA-E and ARIA-H, so as to evaluate the safety of anti-Aβ mAbs.

2.4 Risk of Bias

Literature quality assessment of the included studies was performed by two independent reviewers through the risk-of-bias analysis assessment tool provided by the Cochrane Handbook for Systematic Reviews of Interventions 5.4.0 [17], and any discrepancies were resolved by consensus. The evaluation included random sequence generation (selective bias), distribution concealment (selective bias), method of blinding implementers and participants (implementation bias), method of blinding result evaluation (detection bias), data result integrity (loss bias), selective report of research results (reporting bias) and other biases.

2.5 Data Analysis

The Bayesian network meta-data analysis was performed using R software (version 4.2.3) along with JAGS software and STATA software (version 15.0). We used mean differences (MD) from baseline with 95% confidence intervals (CI) to calculate the continuous data, such as the change from baseline of MMSE, as reported. As for the binary data, including AE, ARIA-E and ARIA-H, the odds ratio (OR) analysis of 95% CI is calculated. If there was no raw data (e.g., without standard deviations [SDs], only p values or ranges are reported), SDs and 95% CIs provided in the publication were calculated using established methods for estimation [18]. The use of a random effects model or fixed effects model depended on the statistical value of each result heterogeneity. If there was significant heterogeneity, $I^2 > 50$, a random effects model was carried out, if $I^2 \leq 50$, a fixed effects model was carried out.

In order to verify the consistency between direct comparisons and indirect comparisons, we used the node splitting method through the design-by-treatment interaction model in the closed loop in the evidence network [19]. A p value higher than 0.05 ($p > 0.05$) indicates that there is no significant inconsistency between direct and indirect comparisons, on the contrary, the difference is statistically significant [20].

We calculated the surface under the cumulative ranking area (SUCRA) to rank the charts and the priority of the different interventions, in which the larger the SUCRA value, the better the efficacy or safety [21]. For the results of each trial, the potential retrieval bias was assessed using funnel plots to represent individual studies against some measure of each study's size or precision.

3 Results

3.1 Literature Search Results

We found 1058 articles from PubMed, Embase, Cochrane Library and Web of Science, of which 400 studies were discarded because of duplication. We excluded a further 609 articles after reviewing the titles and abstracts. Finally, after reviewing the full text of 51 papers, 33 studies were found to fulfil the inclusion criteria. A PRISMA flowchart illustrating the specific screening process is shown in Fig. 1.

3.2 Eligible Studies and Patient Characteristics

A total of 33 randomized controlled trials [14, 22–53] were included, including 17,686 patients who received eight different mAbs (aducanumab, bapineuzumab, crenezumab, donanemab, gantenerumab, lecanemab, ponezumab, and solanezumab), and placebo was the most common

Fig. 1 PRISMA flow diagram of current network meta-analysis. *PRISMA* Preferred Reporting Items for Systematic review and Meta-analysis
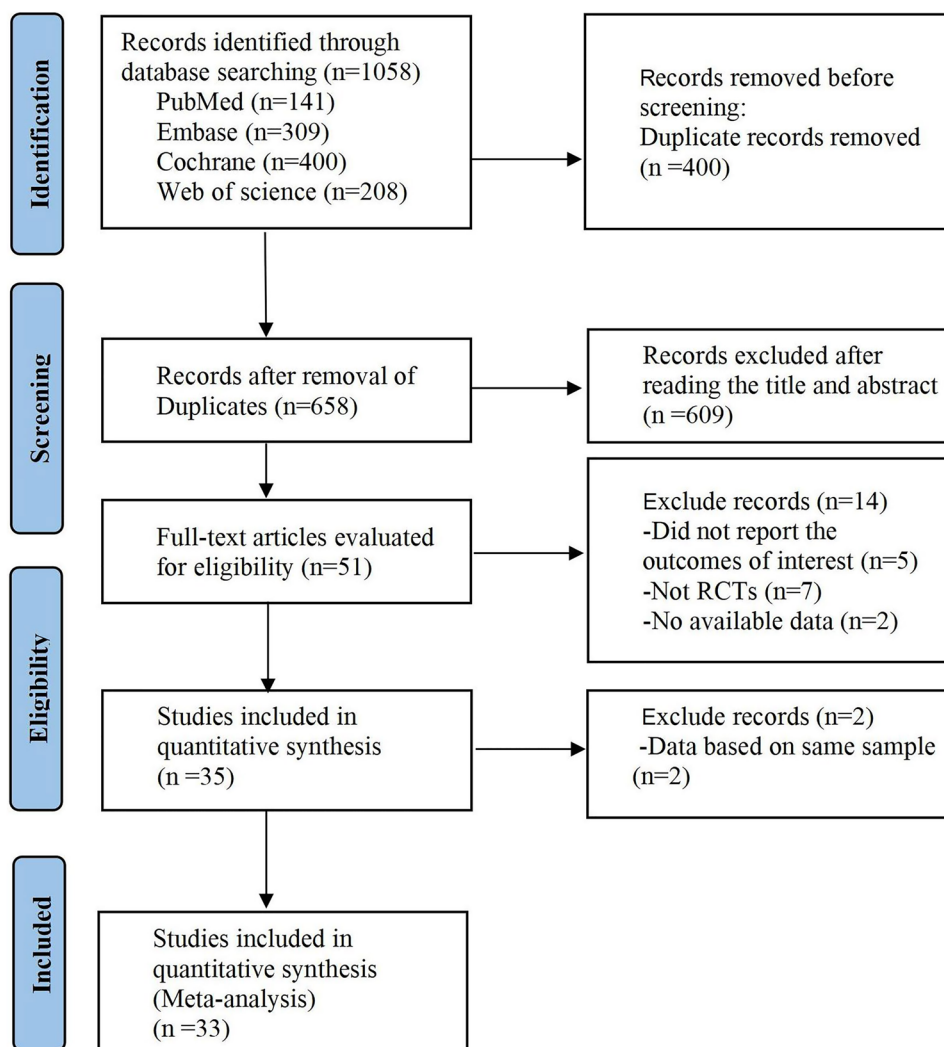
comparison. Of the 33 included trials, 32 were two-group trials and one was a three-group clinical trial. See Table 1 for the baseline characteristics and design features of trials included in this NMA.

3.3 Risk of Bias

The overall risk included in the bias assessment of the studies is low to moderate. All the RCTs used the random number acquisition method, but only 19 papers provided a detailed description. Consideration should be given to the lack of information on the randomization process and allocation procedure, which were judged to have ambiguous risk of bias. One study was considered to have a high risk of bias in terms of "incomplete result data" [28]. Almost all studies are funded by large pharmaceutical companies. The risk-of-bias assessment of the included literature is shown in Fig. 2.

The network diagram of qualified comparisons of all result measurements is shown in Figs. 3 and 4, which includes nine interventions. RCTs are connected by a network diagram composed of points and lines. The dots represent different interventions, and their sizes represent the number of participants in each intervention. The straight lines indicate that there is direct comparison evidence between two interventions, and the thickness of the lines indicates the number of studies directly compared between the two interventions. In this study, there was a closed loop of indirect evidence and the node-split model was used to test the inconsistency. When using the node splitting method to evaluate MMSE and CDR-SB analysis, there is no obvious inconsistencies between direct evidence and indirect evidence (see Table 2 and Supplementary table S10 in the ESM).

Table 1 Trial features and baseline characteristics of participants for 33 trials included in the network meta-analysis

Study	Country	Phase	Sample size		Gender (M/F)		Mean age (years)		Severity of AD	MMSE (baseline)		ApoE e4 carriers (%)		Follow-up	Outcome
			EG	CG	EG	CG	EG	CG		EG	CG	EG	CG		
Treatment: Aducanumab															
Ferrero et al. 2016 [33] NCT01397539	United States	I	0.3 mg/kg: 6	14	12/27	5/9	72.0 ± 8.4	66.9 ± 8.7	Mild to moderate probable AD	23.0 ± 1.9	22.1 ± 2.4	2 (33)	4 (29)	6 mo	F1,F5
			1 mg/kg: 6				67.0 ± 8.8			22.0 ± 3.4		2 (33)			
			3 mg/kg: 6				63.0 ± 5.0			18.3 ± 2.7		1 (17)			
			10 mg/kg: 6				72.7 ± 4.5			18.3 ± 4.9		4 (67)			
			20 mg/kg: 6				66.8 ± 8.9			23.0 ± 3.1		2 (33)			
			30 mg/kg: 6				63.3 ± 9.0			19.8 ± 4.6		3 (50)			
			60 mg/kg: 3				73.7 ± 9.5			24.7 ± 1.5		1 (33)			
Sevigny et al. 2016 [24] NCT01677572	United States	I	1 mg/kg: 31	40	65/60	17/23	72.6 ± 7.8	72.8 ± 7.2	Prodromal or mild AD	23.6 ± 3.3	24.7 ± 3.6	19 (61)	26 (65)	54 wk	F1,F2,F3,F4,F8
			3 mg/kg: 32				70.5 ± 8.2			23.2 ± 4.2		21 (66)			
			6 mg/kg: 30				73.3 ± 9.3			24.4 ± 2.9		21 (70)			
			10 mg/kg: 32				73.7 ± 8.3			24.8 ± 3.1		20 (63)			
Haeberlein et al. 2022 [53] NCT02484547	United States	III	3 mg/kg or 6 mg/kg (low dose): 543	548	510/553	258/290	70.6 ± 7.4	70.8 ± 7.4	Mild/MCI	26.3 ± 1.7	26.4 ± 1.8	362 (67)	368 (67)	78 wk	F1,F2,F3,F4,F5,F6,F7
			10 mg/kg (high dose): 547				70.6 ± 7.5			26.3 ± 1.7		365 (67)			
Haeberlein et al. 2022 [53] NCT02477800	United States	III	3 mg/kg or 6 mg/kg (low dose): 547	545	526/576	258/287	70.4 ± 7.0	69.8 ± 7.7	Mild/MCI	26.4 ± 1.8	26.4 ± 1.7	391 (71)	176 (69)		
			10 mg/kg (high dose): 555				70.0 ± 7.7			26.4 ± 1.8		378 (68)			

Table 1 (continued)

Study	Country	Phase	Sample size EG	CG	Gender (M/F) EG	CG	Mean age (years) EG	CG	Severity of AD	MMSE (baseline) EG	CG	ApoE e4 carriers (%) EG	CG	Follow-up	Outcome
Treatment: Bapineuzumab															
Lu and Brashear 2019 [37] NCT02484547	United States	I	5 mg/kg: 6	10	15/15	6/4	65.8 ± 11.63	71.0 ± 10.16	Mild to moderate AD	19.0 ± 4.10	19.9 (5.24)			6 mo	F1
			10 mg/kg: 6				74.2 ± 10.70			19.7 ± 4.32					
			20 m/kg: 6				69.0 ± 9.49			20.3 ± 4.27					
			40 mg/kg: 6				79.3 ± 4.03			17.3 ± 3.88					
			80 mg/kg: 6				66.8 ± 9.47			19.5 ± 2.59					
Arai et al. 2016 [44] NCT00397891	Japan	I	0.15 mg/kg: 6	8	14/11	4/4	60.7 ± 5.2	68.8 ± 8.9	Mild to moderate AD	16.8 ± 2.9	20.6 ± 3.0			52 wk	F1,F4
			0.5 mg/kg: 6				72.2 ± 8.4			21.0 ± 3.6					
			1 mg/kg: 6				72.2 ± 10.9			21.0 ± 4.6					
			2 mg/kg: 6				64.8 ± 5.2			20.2 ± 2.8					
Black et al. 2010 [49]	United States	I	0.5 mg/kg: 6	8	15/7	1/7	74.67 ± 5.65	69.88 ± 10.71	Mild to moderate AD	21.8	20.8			2 y	F1
			1.5 mg/kg: 6				72.33 ± 9.85			21.3					
			5 mg/kg: 10				74.70 ± 7.44			22.3					
Brody et al. 2016 [39] NCT01254773	United States	II	2 mg/kg: 37	36	49/61	13/23	73.5 ± 8.34	73.3 ± 8.79	Mild to moderate AD	22.3 ± 2.78	22.3 ± 2.84	22 (59.5)	22 (61.1)	13 mo	F1,F4,F8
			7 mg/kg: 36				74.1 ± 9.26			21.5 ± 2.47		22 (61.1)			
			20 mg/kg: 37				70.5 ± 8.68			21.9 ± 2.99		22 (59.5)			
Rinne et al. 2010 [27]	Finland	II	(0.5, 1, or 2 mg/kg): 19	7	11/8	3/4	67.26 ± 8.60	70.0 ± 8.81	Mild to moderate AD	21 ± 2.33	22.29 ± 2.69	12 (63)	5 (71)	78 wk	F2,F3,F5,F7

Table 1 (continued)

Study	Country	Phase	Sample size		Gender (M/F)		Mean age (years)		Severity of AD	MMSE (baseline)		ApoE e4 carriers (%)		Follow-up	Outcome
			EG	CG	EG	CG	EG	CG		EG	CG	EG	CG		
Salloway et al. 2009 [14] NCT00112073	United States	II	0.15 mg/kg: 31 0.5 mg/kg: 33 1.0 mg/kg: 29 2.0 mg/kg: 29	25 28 26 27	61/61	43/64	70.1 ± 0.82	67.9 ± 0.85	Mild to moderate AD	20.9 ± 0.29	20.7 ± 0.30	72 (60.5)	74 (69.8)	78 wk	F6
Salloway et al. 2014 [52] NCT00575055	United States	III	0.5 mg/kg: 658	432	300/358	190/242	72.0 ± 8.0	72.3 ± 8.4	Mild	20.8 ± 3.1	20.7 ± 3.2	658 (100)	658 (100)	78 wk	F2,F4,F5,F6
Salloway et al. 2014 [52] NCT00574132		III	0.5 mg/kg: 314 1.0 mg/kg: 307 0.5 mg/kg: 6 1.0 mg/kg: 6	493	289/344	245/248	73.1 ± 9.3 73.5 ± 9.1 72.2 ± 8.4 72.2 ± 10.9	71.9 ± 10.1	Mild	21.2 ± 3.4 21.2 ± 3.3 21.0 ± 3.6 21.0 ± 4.6	21.2 ± 3.2	0 0 0 0	0 0 0 0	78 wk	F2,F4,F5,F6
Vandenberghe et al. 2016 [26] NCT00667810	Belgium	III	0.5 mg/kg: 650	431	231/419	168/263	70.9	70.2	Mild to moderate AD	20.9 ± 3.1	21.0 ± 3.0	100	100	78 wk	F2,F6
Vandenberghe et al. 2016 [26] NCT00676143		III	0.5 mg/kg: 255 1 mg/kg: 253	328	221/287	138/190	71.1 70.7	69.7	Mild to moderate AD	20.8 ± 3.2 20.8 ± 3.1	20.8 ± 3.1	0 0	0	78 wk	F2,F6
Brashear et al. 2018 [28] NCT00575055	United States	III	0.5 mg/kg: 337 1 mg/kg: 329 2 mg/kg: 141	524	368/439	258/266	73.0 ± 9.47 73.2 ± 9.30 73.7 ± 9.53	71.8 ± 10.10	Mild to moderate AD	21.2 ± 3.36 21.2 ± 3.27 21.0 ± 3.09	21.3 ± 3.21	0 0 0	0	83 wk	F1,F2

Table 1 (continued)

Study	Country	Phase	Sample size EG	CG	Gender (M/F) EG	CG	Mean age (years) EG	CG	Severity of AD	MMSE (baseline) EG	CG	ApoE e4 carriers (%) EG	CG	Follow-up	Outcome
Treatment: Crenezumab															
Guthrie et al. 2020 [48] NCT02353598	United States	Ib	30 mg/kg: 10	14	33/28	6/8	73.4 ± 6.75	71.4 ± 6.75	Mild to moderate AD	23.3 ± 3.8	20.9 ± 2.8	6 (60)	10 (71.4)	133 wk	F1,F3
			45 mg/kg: 11				73.3 ± 7			22.2 ± 2.7		10 (90.9)			
			60 mg/kg: 21				72.9 ± 6.25			23.2 ± 3.3		17 (81)			
			120 mg/kg: 19				69.4 ± 8.5			22.9 ± 3.1		12 (63.2)			
Cummings et al. 2018 [22] NCT01343966	Germany	II	300 mg: 122	103	56/66	32/30	71.2 ± 6.3	70.3 ± 7.2	Mild to moderate AD	21.7 ± 2.8	21.5 ± 2.6	78 (63.9)	66 (64.5)	73 wk	F1, F2,F5,F6,F7
			15 mg/kg: 165	84	81/84	36/48	70.9 ± 6.9	69.9 ± 7.1		21.9 ± 2.7	21.6 ± 2.5	117 (70.9)	60 (71.4)		
Salloway et al. 2018 [23] NCT01397578	United States	II	300 mg: 26	13	12/14	5/8	66.7 ± 9.5	68.9 ± 8.3	Mild to moderate AD	21.5 ± 2.4	22.3 ± 2.4	22 (84.6)	12 (92.3)	73 wk	F1,F5,F6,F8
			15 mg/kg: 35	17	11/24	11/6	71.4 ± 7.1	69.8 ± 7.7		20.8 ± 2.3	20.5 ± 2.2	24 (68.6)	12 (70.6)		
Ostrowitzki et al. 2022 [32] NCT02670083	Switzerland	III	60 mg/kg (CREAD): 404	409	168/236	162/247	71.0 ± 7.9	70.3 ± 8.4	Mild	23.7 ± 3.0	23.4 ± 2.9	293 (72.7)	292 (71.7)	105 wk	F1,F2,F3,F5,F6,F7
Ostrowitzki et al. 2022 [32] NCT03114657			60 mg/kg (CREAD2): 407	399	176/231	174/225	71.1 ± 7.5	70.7 ± 7.9		23.6 ± 2.8	23.5 ± 2.9	271 (66.9)	263 (65.9)		
Treatment: Donanemab															
Lowe et al. 2021 [30] NCT02624778	Singapore	Ib	10 mg/kg (single dose): 7	15	3/4	4/15	78.3 ± 8.4	74.5 ± 10.1	Mild to moderate	21.71 ± 4.23	21.67 ± 4.81	5 (71.4)	10 (66.7)	84 wk	F11
			20 mg/kg (single dose): 7		4/3		75.6 ± 6.4			23.57 ± 4.5		5 (71.4)			
			40 mg/kg (single dose): 4		2/2		75.3 ± 6.7			23.25 ± 3.86		4 (100)			
			10 mg/kg (Q2W): 10		6/4		66.8 ± 8.6			20 ± 3.4		8 (80.0)			
			10 mg/kg (Q4W): 8		4/4		73 ± 7.8			18.86 ± 2.41		6 (75.0)			
			20 mg/kg (Q4W): 10		3/7		71.7 ± 9.2			19.5 ± 2.93		9 (90.0)			

Table 1 (continued)

Study	Country	Phase	Sample size EG	Sample size CG	Gender (M/F) EG	Gender (M/F) CG	Mean age (years) EG	Mean age (years) CG	Severity of AD	MMSE (baseline) EG	MMSE (baseline) CG	ApoE e4 carriers (%) EG	ApoE e4 carriers (%) CG	Follow-up	Outcome
Mintun et al. 2021 [31] NCT03367403	United States	II	700–1400 mg: 131	126	63/68	61/65	75.0 ± 5.6	75.4 ± 5.4	Mild	23.6 ± 3.1	23.7 ± 2.9	95 (72.5)	92 (74.2)	76 wk	F1,F2,F3,F4,F5,F6,F7
Shcherbinin et al. 2022 [25] NCT03367403	United States	II	700–1400 mg: 115	120	68/63	65/61	75.0 ± 5.6	75.4 ± 5.4	Prodromal (MCI) or mild AD	23.5 ± 3	23.77 ± 2.9	85 (73.9)	88 (73.9)	72 wk	F2,F3,F8
Treatment: Lecanemab															
Logovinsky et al. 2016 [47] NCT01230853	United States	I	0.1, 0.3, 1, 3, 10, 15 mg/kg (SAD): 36	12	18/18	7/5	70.9 ± 10.0	72.1 ± 9.2	Mild to moderate AD	23.8	23.5			180 d	F1,F2,F3
			0.3, 1, 3, 10 mg/kg (MAD): 24	8	11/13	6/2	70.0 ± 9.97	70.0 ± 11.70		23.3	24.1				
Swanson et al. 2021 [42] NCT01767311	United States	IIb	2.5 mg/kg biweekly: 52	238	315/272	101/137	71	72	Mild	25.7 ± 2.5	26.0 ± 2.3	38 (73)	169 (71)	18 mo	F1,F2,F5,F6
			5 mg/kg monthly: 48				71			25.3 ± 2.6		37 (77)			
			5 mg/kg biweekly: 89				72			25.6 ± 2.3		81 (91)			
			10 mg/kg monthly: 246				71			25.7 ± 2.4		218 (89)			
			10 mg/kg biweekly: 152				73			25.6 ± 2.4		46 (30)			
van Dyck et al. 2023 [34] NCT03887455	United States	III	10 mg/kg: 859	875	416/443	411/464	71.4 ± 7.9	71.0 ± 7.8	Mild	25.5 ± 2.2	25.6 ± 2.2	592 (68.9)	600 (68.6)	18 mo	F1,F2,F3,F5,F6,F7,F8
Treatment: Gantenerumab															
Ostrowitzki et al. 2012 [35] NCT00531804	United States	I	60 mg: 8	4	9/5	1/3	70.9 ± 8.1	62.8 ± 3.5	Mild to moderate AD	21.8 ± 3.6	21.0 ± 2.5	4 (57.1)	4 (100)	28 wk	F8
			200 mg: 6				66.5 ± 8.4			22.0 ± 1.6		5 (83.3)			

Table 1 (continued)

Study	Country	Phase	Sample size		Gender (M/F)		Mean age (years)		Severity of AD	MMSE (baseline)		ApoE e4 carriers (%)		Follow-up	Outcome
			EG	CG	EG	CG	EG	CG		EG	CG	EG	CG		
Ostrowitzki et al. 2017 [40] NCT01224106	United States	III	105 mg: 271 225 mg: 260	266	NA	NA	70.3 ± 7.0 71.3 ± 7.1	69.5 ± 7.5	Mild to moderate AD	25.7 ± 2.3 25.7 ± 2.2	25.7 ± 2.1	70.5 (13.6) 70.1 (12.5)	69.8 (12.9)	104 wk	F1,F2,F3,F4,F5,F6,F8
Salloway et al. 2021 [50] NCT01760005	United States	III	Gantenerumab 225–1200 mg: 52 Solanezumab 400–1600 mg: 50	40	31/21 21/29	18/22	46.0 ± 10.8 42.5 ± 9.5	44.2 ± 9.6	DIAD	27.10 ± 3.45 26.72 ± 4.11	26.68 ± 3.97	16 (31) 14 (28)	13 (32)	4 y	F2,F3,F4,F5,F8
Treatment: Ponezumab															
Landen et al. 2013 [46] NCT00455000	United States	I	0.1 mg/kg: 4 0.3 mg/kg: 4 1 mg/kg: 4 3 mg/kg: 6 10 mg/kg: 8	11	15/11	8/3	69.0 ± 8.1 70.0 ± 3.7 72.0 ± 7.5 66.5 ± 11.8 72.1 ± 8.0	71.8 ± 7.0	Mild to moderate AD	22.5 ± 2.5 24.3 ± 1.7 21.3 ± 3.6 22.7 ± 3.3 21.9 ± 2.8	21.5 ± 3.4	1 (25) 2 (50) 3 (75) 2 (33) 1 (12.5)	1 (9.1)	1 y	F1
Miyoshi et al. 2013 [45] NCT00607308	Japan	I	0.1 mg/kg: 3 0.5 mg/kg: 3 1 mg/kg: 3 5 mg/kg: 3 10 mg/kg: 3	5	7/8	2/3	65.7 ± 6.4 67.7 ± 8.1 72.3 ± 11.5 61.3 ± 18.4 50.3 ± 7.5	72.2 ± 7.1	Mild to moderate AD	16.33 ± 3.21 19.67 ± 1.53 18.33 ± 1.53 20.67 ± 6.11 24.67 ± 1.53	21.2 ± 3.56	2 (66.7) 1 (33.3) 0 1 (33.3) 2 (66.7)	4 (80)	1 y	F1

Table 1 (continued)

Study	Country	Phase	Sample size EG	CG	Gender (M/F) EG	CG	Mean age (years) EG	CG	Severity of AD	MMSE (baseline) EG	CG	ApoE e4 carriers (%) EG	CG	Follow-up	Outcome
Landen et al. 2017(a) [36] NCT00722046	United States	II	0.1 mg/kg: 25	24	13/12	11/13	70.8 ± 8.2	70.0 ± 7.8	Mild to moderate AD	21.5 ± 2.9	21.0 ± 3.4	N	N	24 mo	F2,F6
			0.5 mg/kg: 25		10/15		71.9 ± 9.4			21.4 ± 3.6					
			1 mg/kg: 25		14/11		72.2 ± 8.4			20.8 ± 3.0					
			3 mg/kg: 32	32	12/20	15/17	70.5 ± 8.9	70.4 ± 10.3		22.5 ± 2.5	21.9 ± 3.4				
			8.5 mg/kg: 31		14/17		71.8 ± 7.3			20.9 ± 3.1					
Landen et al. 2017(b) [41] NCT00945672	United States	II	10 mg/kg (Cohort Q): 12	6	8/4	3/3	65.1 ± 7.4	71.3 ± 8.5	Mild to moderate AD	22.5 ± 2.75	20.8 ± 2.99	10 (83)	3 (50)	18 mo	F3,F4,F6
			10 mg/kg/ 7.5 mg/kg (Cohort M): 12	6	9/3	1/5	69.8 ± 7.5	65.8 ± 8.3		21.2 ± 3.04	22.5 ± 4.04	11 (92)	5 (83)		
Treatment: Solanezumab															
Farlow et al. 2012 [43] NCT00329082	United States	II	100 mg Q4W: 10	10	24/28		71.2 ± 9.2		Mild to moderate AD	20.2 ± 3.8		39 (75)		1 y	F6
			100 mg QW: 11												
			400 mg Q4W: 10												
			400 mg QW: 11												

Table 1 (continued)

Study	Country	Phase	Sample size		Gender (M/F)		Mean age (years)		Severity of AD	MMSE (baseline)		ApoE e4 carriers (%)		Follow-up	Outcome
			EG	CG	EG	CG	EG	CG		EG	CG	EG	CG		
Doody et al. 2014 [38] NCT00905372	United States	III	400 mg Q4W (EXPEDITION 1): 506	506	207/299	219/287	75.0 ± 7.9	74.4 ± 8.0	Mild to moderate AD	21 ± 4	21 ± 3	266 (57.3)	288 (61.3)	18 mo	F1,F2,F3,F5,F6,F7
Doody et al. 2014 [38] NCT00904683			400 mg Q4W (EXPEDITION 2): 521	519	397/446	377/467	72.5 ± 8.0	72.4 ± 7.8		21 ± 3	21 ± 3	263 (56.8)	281 (59.5)		
			400 mg Q4W (EXPEDITION 2-mild): 322	325			71.5 ± 7.9	72.5 ± 7.9	Mild	22 ± 3	23 ± 3	155 (54.6)	183 (61.4)		
Honig et al. 2018 [51] NCT01900665	11 countries	III	400 mg IV every 4 weeks: 1057	1072	457/600	441/631	72.7 ± 7.8	73.3 ± 8.0	Mild	22.8 ± 2.8	22.6 ± 2.9	712 (69.3)	685 (66.3)	76 wk	F4,F5,F6
Nakamura et al. 2017 [29] NCT00905372, NCT00904683, NCT00904683	Japan	III	400 mg IV every 4 weeks: 65	61	18/47	22/39	75.2 ± 7.1	73.2 ± 7.2	Mild	22.5 ± 2.9	21.6 ± 2.5	50.8	61	184 wk	F2,F3,F4,F5

AD Alzheimer's disease, *ADAS-cog14* Alzheimer's Disease Assessment Scale, *ADCS-ADL* Alzheimer's Disease Cooperative Study–Activities of Daily Living, *AE* adverse event, *ARIA-E* amyloid-related imaging abnormalities characterized by edema and effusion, *ARIA-H* amyloid-related imaging abnormalities characterized by cerebral microhemorrhages, *CDR-SB* Clinical Dementia Rating scale–Sum of Boxes, *CG* control group, *DIAD* dominantly inherited Alzheimer's disease, *EG* experimental group, *F1*: any AE, *F2* ARIA-E, *F3* ARIA-H, *F4* MMSE, *F5* CDR-SB, *F6* ADAS-cog14, *F7* ADCS-ADL, *F8* PET-SUVr, *IV* intravenously, *MAD* multiple ascending dose, *MCI* mild cognitive impairment, *MMSE* Mini–Mental State Examination, *PET-SUVr* standardized uptake value ratio of amyloid positron emission tomography, *NA* not available, *QW* every week, *Q2W* every 2 weeks, *Q4W* every 4 weeks, *SAD* single ascending dose, *SD* standard deviation

a

b

Fig. 2 Risk of bias graph and risk of bias summary

4 Network Analysis of Outcomes

4.1 Change in MMSE

In the evaluation of the change in MMSE from baseline, 11 studies were included with a total of 9897 patients, with higher scores indicating better mental performance. There were seven interventions including aducanumab, bapineuzumab, crenezumab, donanemab, gantenerumab, placebo, and solanezumab. In terms of MMSE score, aducanumab was significantly more effective than placebo (MD 0.93, 95% CI 0.39–1.41), as shown in Supplementary table S2 (see ESM). No significant differences were found among the other meta-analysis pairs. The results of the ranking according to SUCRA values were that aducanumab (87.01%) ranked first in MMSE score change, followed by solanezumab (64.03%) and donanemab (63.80%) (Table 3). The cumulative probability showed that aducanumab was associated with the greatest benefit on MMSE score, as shown in Fig. 5a.

4.2 Change in CDR-SB

In the evaluation of the CDR-SB, 14 RCTs were included with a total of 13,835 patients. The higher the score, the greater the damage. There were eight interventions: aducanumab, bapineuzumab, crenezumab, donanemab, gantenerumab, lecanemab, placebo and solanezumab. A total of 28 direct or indirect comparisons were generated by the NMA, which revealed that aducanumab (MD −0.58, 95% CI −0.69 to −0.48), lecanemab (MD −0.34, 95% CI −0.49 to −0.18), and solanezumab (MD −0.34, 95% CI −0.35 to −0.33) had significantly lower CDR-SB scores compared with placebo, indicating a statistically significant difference (Supplementary table S3, see ESM). According to the SUCRA values, aducanumab (99.37%) had the highest likelihood of being the best treatment for decreasing CDR-SB score, followed by solanezumab (74.69%), whereas donanemab (5.38%) had the lowest probability (Table 3). The cumulative probability showed
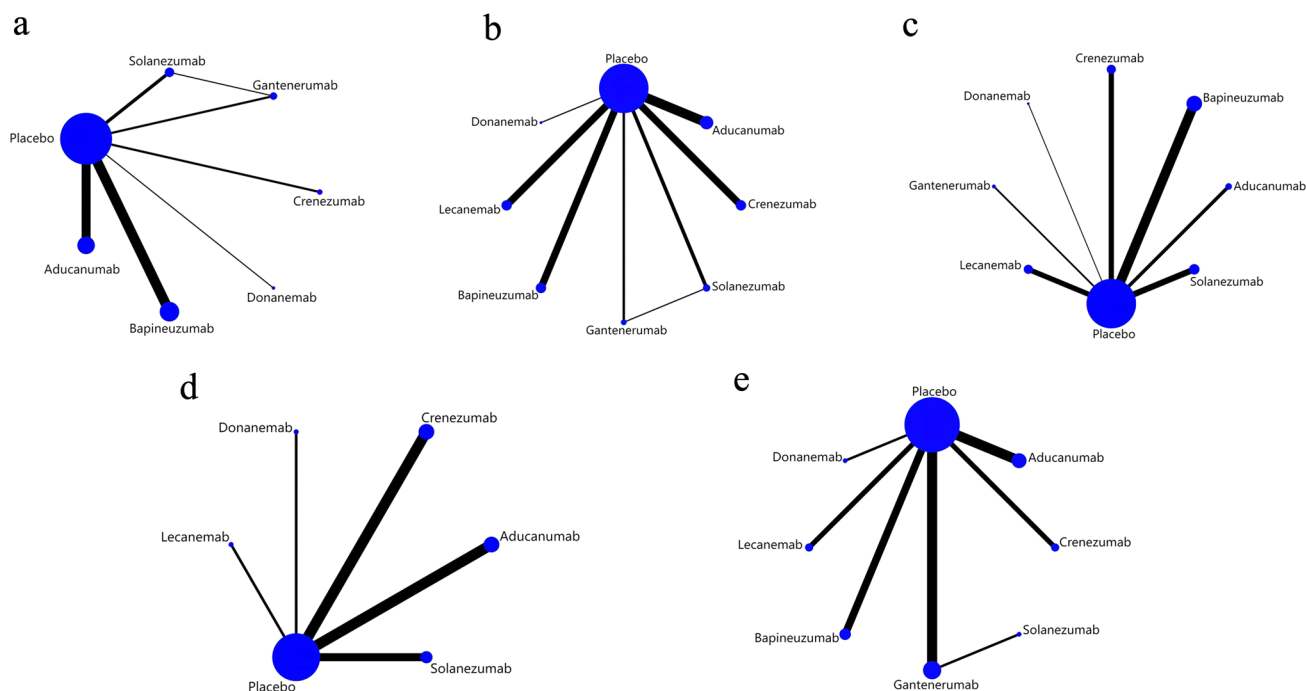
Fig. 3 Network graphs of randomized controlled trials comparing the efficacy of monoclonal antibodies (mAbs) in the treatment of Alzheimer's disease: **a** Mini-Mental State Examination (MMSE), **b** Clinical Dementia Rating scale–Sum of Boxes (CDR-SB), **c** Alzheimer's Disease Assessment Scale–cognitive subscale (ADAS-cog), **d** Alzheimer's Disease Cooperative Study–Activities of Daily Living (ADCS-ADL), **e** standardized uptake value ratio of amyloid positron emission tomography (PET-SUVr)

that aducanumab is related to the maximum benefit on CDR-SB, as shown in Fig. 5b.

4.3 Change in ADAS-cog

Results for change in ADAS-cog score were obtained from 14 RCTs covering eight treatment regimens and involving 12,252 participants, with higher scores indicating greater impairment. The eight interventions were aducanumab, bapineuzumab, crenezumab, donanemab, gantenerumab, lecanemab, placebo, and solanezumab. A total of 28 direct or indirect comparisons were generated by the NMA, which revealed that aducanumab (MD -0.82, 95% CI -1.35 to -0.29), donanemab (MD -1.78, 95% CI -3.52 to -0.01), gantenerumab (MD -0.94, 95% CI -1.35 to -0.53), lecanemab (MD -1.09, 95% CI -1.69 to -0.49) and solanezumab (MD -0.9, 95% CI -1.63 to -0.17) were associated with a significant decrease in ADAS-cog compared with placebo (Supplementary table S4, see ESM). According to SUCRA curve analysis, donanemab (88.5%) was the most effective in terms of ADAS-cog score, and crenezumab (16.17%) was the least effective of the treatments examined (Table 3). The cumulative probability showed that donanemab was associated with the greatest benefit on ADAS-cog, as shown in Fig. 5c.

4.4 Change in ADCS-ADL

Seven of the included articles including a total of 8931 participants reported the change in ADCS-ADL score of six interventions: aducanumab, crenezumab, donanemab, lecanemab, placebo, and solanezumab, with a lower score meaning greater functional loss. A total of 15 direct or indirect comparisons were generated by the NMA, which revealed that aducanumab (MD 0.91, 95% CI 0.16–1.66), lecanemab (MD 2.00, 95% CI 0.39–3.59), and solanezumab (MD 1.35, 95% CI 1.31–1.39) were more effective than placebo according to ADAS-cog (Supplementary table S5, see ESM). The results of the ranking according to SUCRA values were that lecanemab (87.24%) exhibited the highest efficiency on ADCS-ADL, whereas crenezumab (9.83%) exhibited the lowest efficiency (Table 3). The cumulative probability showed that lecanemab was associated with the greatest benefit on ADCS-ADL, as shown in Fig. 5d.

4.5 Change in *Amyloid PET SUVr*

Nine articles providing data on the changes of amyloid protein PET SUVr from baseline, including a total of 1095 participants in eight interventions (aducanumab, bapineuzumab, crenezumab, donanemab, gantenerumab, lecanemab,
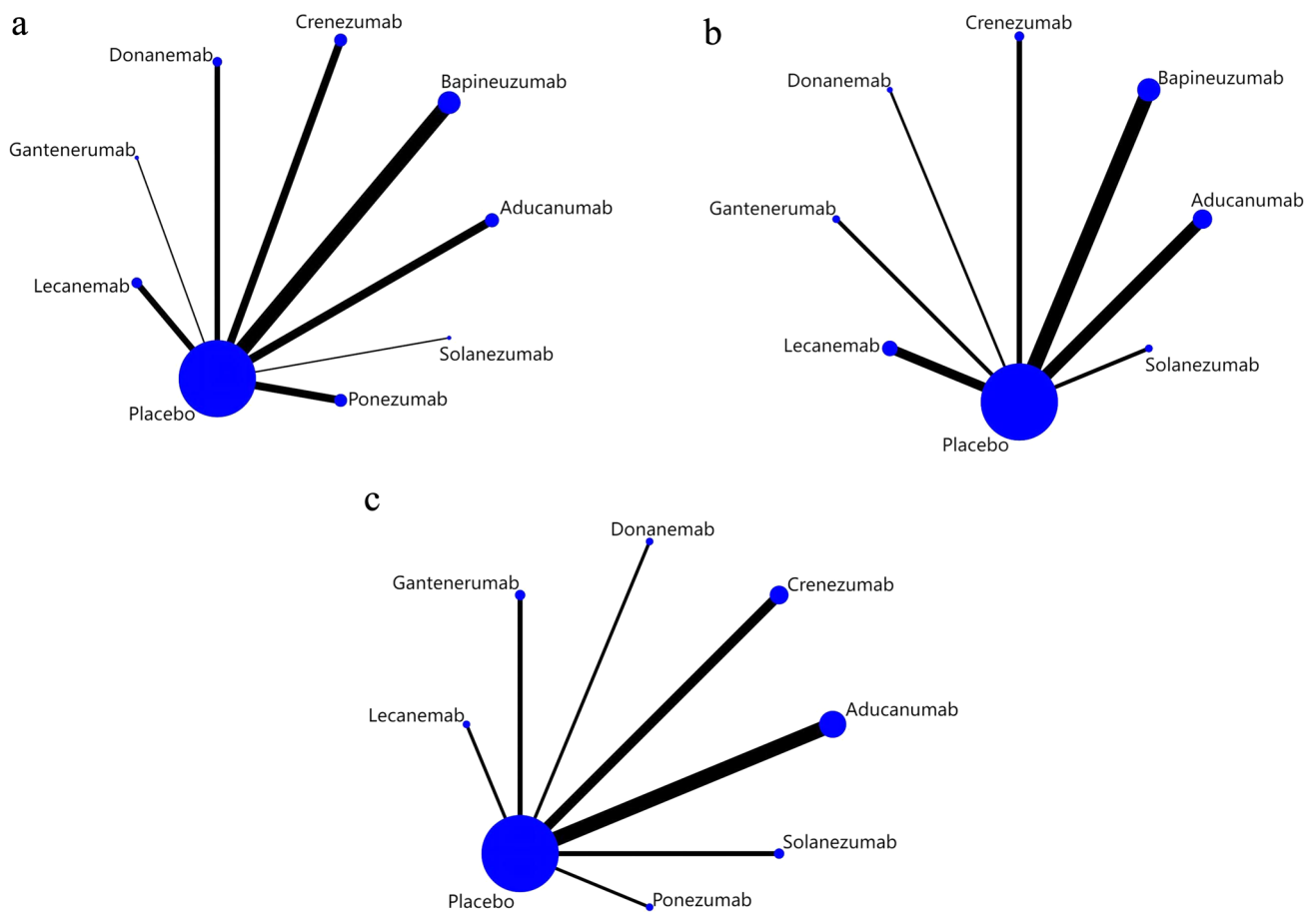
Fig. 4 Network graphs of randomized controlled trials comparing the safety of monoclonal antibodies (mAbs) in the treatment of Alzheimer's disease: **a** adverse events (AE), **b** amyloid-related imaging abnormalities characterized by edema and effusion (ARIA-E) and **c** cerebral microhemorrhages (ARIA-H)

Table 2 Assessment of local inconsistency by node-split method

Outcomes	Comparisons	Direct comparisons results (OR 95% CrI)	Indirect comparisons results (OR 95% CrI)	Network comparisons results (OR 95% CrI)	p values
MMSE	Gantenerumab vs placebo	−0.0548 (−1.12, 1.02)	−1.47 (−6.48, 3.45)	−0.113 (−1.18, 0.927)	0.580
	Solanezumab vs gantenerumab	−0.892 (5.59, 3.86)	0.516 (−0.863, 1.91)	0.416 (−0.923, 1.73)	0.576
	Solanezumab vs placebo	0.569 (−0.296, 1.44)	−0.865 (−5.82, 4.09)	0.531 (−0.329, 1.38)	0.576
CDR-SB	Gantenerumab vs placebo	−0.066 (−0.57, 0.45)	0.87 (−2.2, 4)	−0.043 (−0.54, 0.47)	0.550
	Solanezumab vs gantenerumab	0.64 (−2.5, 3.8)	−0.28 (−0.95, 0.39)	−0.25 (−0.88, 0.42)	0.571
	Solanezumab vs placebo	−0.22 (−0.62, 0.22)	0.68 (−2.4, 3.8)	−0.20 (−0.60, 0.23)	0.582

CDR-SB Clinical Dementia Rating scale–Sum of Boxes, *CrI* credible interval, *MMSE* Mini Mental State Examination, *OR* odds ratio

placebo, and solanezumab). At first glance, one can conclude that aducanumab (MD −0.17, 95% CI −0.27 to −0.07) and donanemab (MD −0.37, 95% CI −0.57 to −0.17) were more effective than placebo. On the contrary, solanezumab (MD 0.55, 95% CI 0.14–0.95) was associated with a significant increase in the risk of abnormal imaging of amyloid PET (Supplementary table S6, see ESM). In the analysis of the curative effect of SUCRA, donanemab scored the highest in SUCRA (99.00%) in the amyloid protein PET SUVr, ranking first, while solanezumab (0.6%) performed worst (Table 3). The cumulative probability showed that donanemab was associated with the greatest benefit on amyloid PET SUVr, as shown in Fig. 5e.

Table 3 The SUCRA values of each treatment

Treatment	AE (%)	Rank	ARIA-E (%)	Rank	ARIA-H (%)	Rank	MMSE (%)	Rank	CDR-SB (%)	Rank	ADAS-cog (%)	Rank	ADCS-ADL (%)	Rank	Amyloid PET SUVr (%)	Rank
Aducanumab	55.34	5	27.71	7	14.55	7	87.01	1	99.37	1	64.40	3	50.97	4	82.81	2
Bapineuzumab	22.89	8	2.92	8		-	43.38	4	30.03	6	21.26	6			24.30	7
Crenezumab	36.65	7	66.38	3	67.14	3	29.53	6	58.47	4	16.17	8	9.83	6	37.43	6
Donanemab	47.85	6	38.26	5	4.93	8	63.80	3	5.38	8	88.50	1	62.24	3	99.00	1
Gantenerumab	89.12	1	29.75	6	45.90	5	37.43	5	25.66	7	45.21	5			69.61	3
Lecanemab	0.79	9	56.57	4	37.05	6			74.19	3	79.80	2	87.24	1	42.28	5
Placebo	56.02	4	95.75	1	80.38	2	24.82	7	32.22	5	21.04	7	17.61	5	43.97	4
Ponezumab	84.91	2			60.80	4										
Solanezumab	56.43	3	82.67	2	89.26	1	64.03	2	74.69	2	63.62	4	71.11	2	0.60	8

ADAS-cog14 Alzheimer's Disease Assessment Scale, *ADCS-ADL* Alzheimer's Disease Cooperative Study–Activities of Daily Living, *AE* any adverse event, *ARIA-E* amyloid-related imaging abnormalities characterized by edema and effusion, *ARIA-H* amyloid-related imaging abnormalities characterized by cerebral microhemorrhages, *CDR-SB* Clinical Dementia Rating scale–Sum of Boxes, *MMSE* Mini Mental State Examination, *PET-SUVr* standardized uptake value ratio of positron emission tomography, *SUCRA* surface under the cumulative ranking area

4.6 Adverse Events (Subjects With Any TEAE)

Discontinuation rates for adverse events were reported in 19 trials, involving 12,867 patients with nine treatments (aducanumab, bapineuzumab, crenezumab, donanemab, gantenerumab, lecanemab, ponezumab, placebo, and solanezumab). Relative to the other types of mAbs, bapineuzumab (OR 1.3; 95% CI 1.05–1.6) and lecanemab (OR 2.16; 95% CI 1.83–2.55) can increase the significant risk of adverse events during treatment compared with placebo. However, regarding gantenerumab (OR 0.61; 95% CI 0.38–0.97), there was a significantly reduced risk for adverse events (Supplementary table S7, see ESM) and lecanemab (OR 2.16; 95% CI 1.83–2.55) exhibited the lowest safety (Table 3). The results of the ranking according to SUCRA values were that gantenerumab (89.12%) exhibited the highest safety, followed by ponezumab (84.91%), solanezumab (56.43%), placebo (56.02%), aducanumab (55.34%), donanemab (47.85%), crenezumab (36.65%), bapineuzumab (22.89%), and lecanemab (0.79%) (Table 3). The cumulative probability showed that gantenerumab was associated with minimal adverse effects, as shown in Fig. 6a.

4.7 ARIA-E

In total, 16 studies with 18,300 patients were included in the analysis of the events with ARIA-E, involving eight treatments—aducanumab, bapineuzumab, crenezumab, donanemab, gantenerumab, lecanemab, placebo, and solanezumab. The incidence of ARIA-E associated with mAbs against Aβ was significantly higher in bapineuzumab (OR 30.29; 95% CI 19.88–48.89), aducanumab (OR 15.09; 95% CI 11.51–20.20), gantenerumab (OR 14.78; 95% CI 6.36–43.88), donanemab (OR 12.26; 95% CI 6.58–25.19), and lecanemab (OR 8.32; 95% CI 5.50–13.15) compared with placebo in the treatment of AD (Supplementary table S8, see ESM). According to SUCRA curve analysis, placebo (95.75%) exhibited the lowest risk of ARIA-E, followed by solanezumab (82.67%), and bapineuzumab (2.92%) exhibited the highest risk of ARIA-E (Table 3). The cumulative probability showed that solanezumab was associated with the least ARIA-E adverse effects except placebo, as shown in Fig. 6b.

4.8 ARIA-H

Fourteen articles were included in the analysis for the events of ARIA-H, involving 10,565 patients and eight interventions—aducanumab, crenezumab, donanemab, gantenerumab, lecanemab, ponezumab, placebo, and solanezumab. The NMA revealed that a higher risk of ARIA-H in aducanumab (OR 4.44; 95% CI 3.75–5.28), donanemab (OR
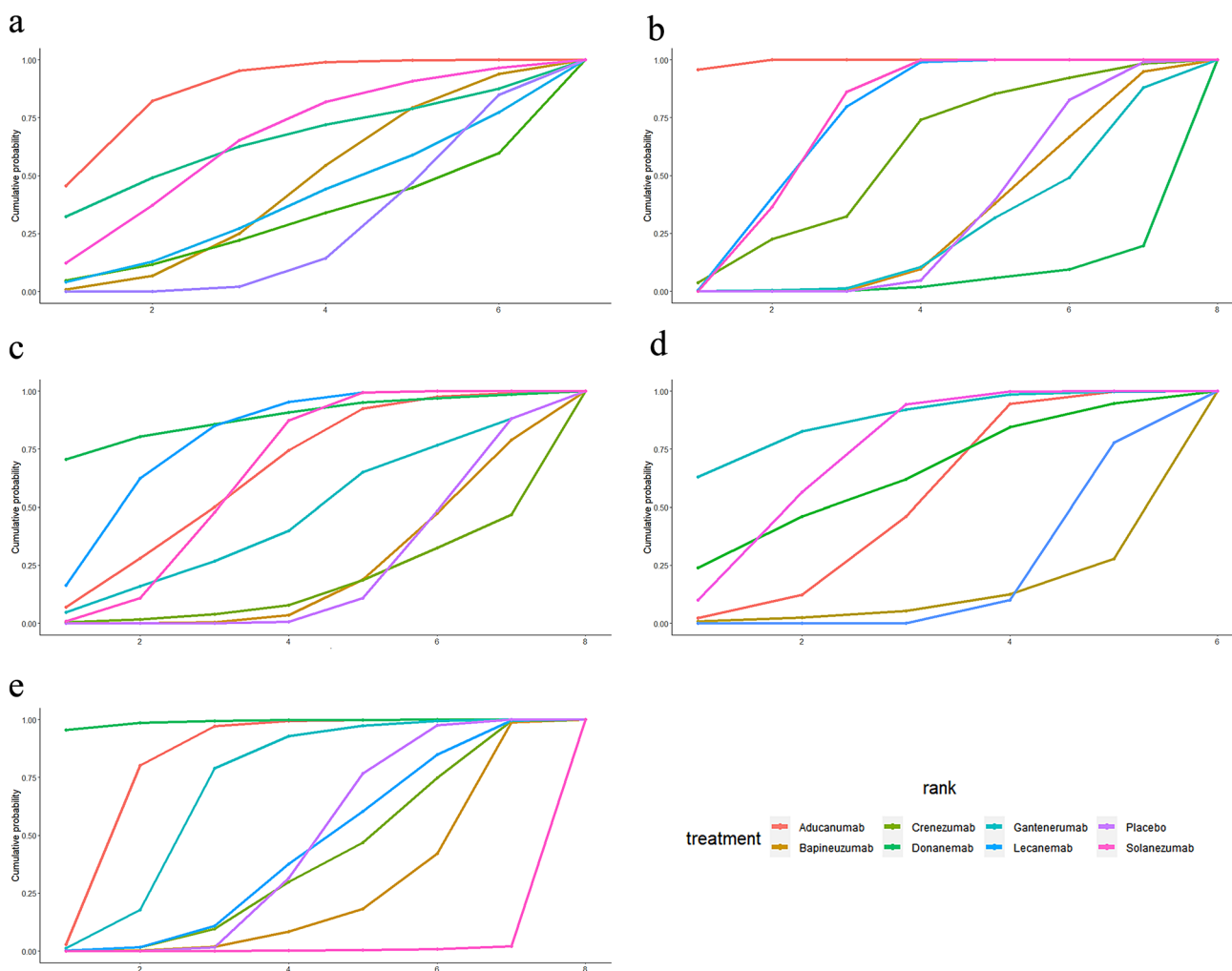
Fig. 5 Rank of the cumulative probabilities for basic parameters: **a** Mini-Mental State Examination (MMSE), **b** Clinical Dementia Rating scale–Sum of Boxes (CDR-SB), **c** Alzheimer's Disease Assessment Scale–cognitive subscale (ADAS-cog), **d** Alzheimer's Disease Cooperative Study–Activities of Daily Living (ADCS-ADL), **e** standardized uptake value ratio of amyloid positron emission tomography (PET-SUVr)

5.77; 95% CI 3.39–10.26), gantenerumab (OR 1.81; 95% CI 1.32–2.49), and lecanemab (OR 2.12; 95% CI 1.60–2.83) was statistically different compared with placebo in the treatment of AD (Supplementary table S9, see ESM). According to SUCRA curve analysis, solanezumab (89.26%) exhibited the lowest risk of ARIA-H, followed by placebo (80.38%), and donanemab (4.93%) exhibited the highest risk of ARIA-H (Table 3). The cumulative probability showed that solanezumab was associated with the lowest ARIA-H adverse effects, as shown in Fig. 6c.

4.9 Publication Bias

Funnel plots are used to show the publication bias of the evaluation scales, including MMSE, CDR-SB, ADAS-cog, ADCS-ADL, the change of amyloid PET-SUVr, adverse events, ARIA-E, and ARIA-H. In this study, NMA may have a potential publication bias, as shown in Fig. 7.

5 Discussion

A total of 21,087 subjects from 33 studies were included in the network analysis in which the efficacy and safety of mAbs against Aβ in the treatment of mild or moderate AD were investigated. The results of a pairwise meta-analysis found that aducanumab exerted better efficacy compared with other interventions in improvements of MMSE and CDR-SB scores, with SUCRA values of 87.01% and 99.37%, respectively. Donanemab, with respective SUCRA values of 88.50% and 99.00%, showed superior performance over other therapies in improving ADAS-cog scores and amyloid
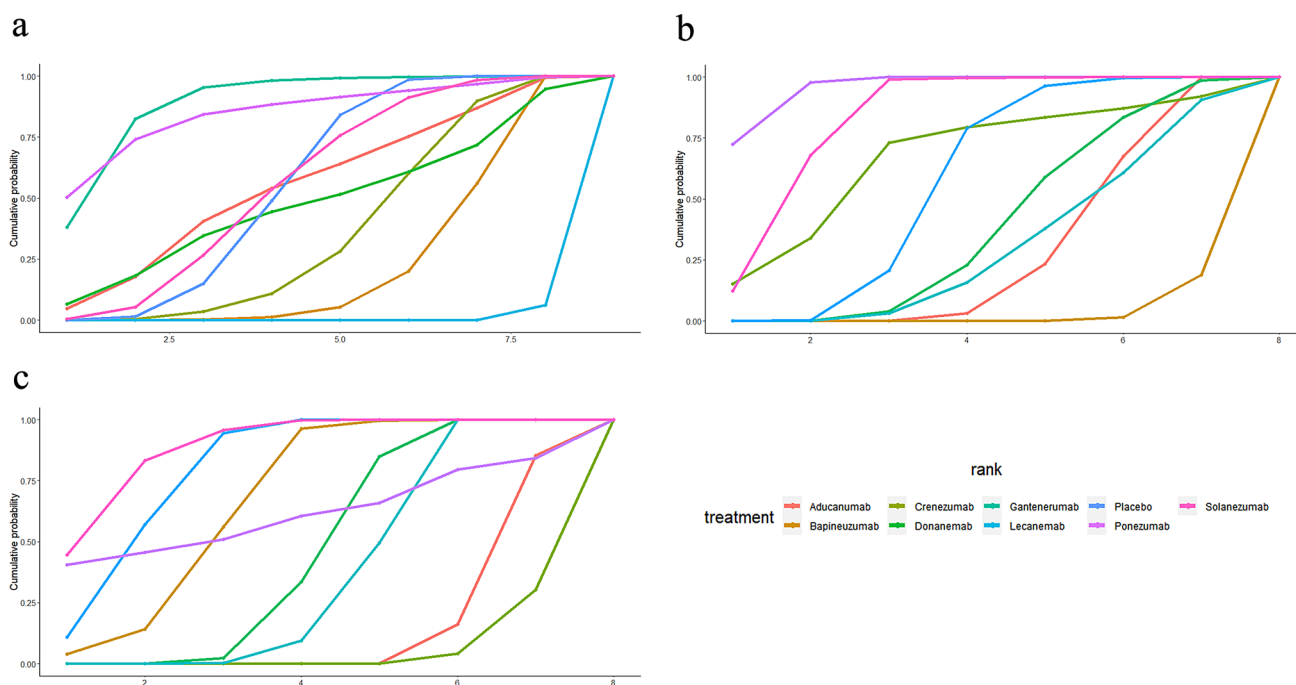
Fig. 6 Rank of the cumulative probabilities for **a** adverse events (AE), **b** amyloid-related imaging abnormalities characterized by edema and effusion (ARIA-E) and **c** cerebral microhemorrhages (ARIA-H)

PET-SUVr. Additionally, lecanemab, with a SUCRA value of 87.24%, may be the most beneficial option for slowing down the decline in ADCS-ADL scores. However, our findings also highlight the increased risk of adverse events associated with these treatments, notably ARIA. Apart from solanezumab, all other mAb therapies increased the risk of ARIA. Meanwhile, compared with the placebo group, the application of gantenerumab, ponezumab, and solanezumab did not statistically increase the risk of AEs. In interpreting SUCRA rankings, it's crucial to consider their statistical uncertainties and dependence on the quality of included studies; these rankings are relative and sensitive to methodological variations in NMA.

Considering the efficacy profile, we showed the changes in MMSE, ADAS-cog, CDR-SB, ADCS-ADL, and amyloid PET SUVr. Although the NMA was not ideal given the lack of head-to-head studies among the interventions (i.e., only against placebo; a star-shaped network), except for a three-arm experiment, interesting results were found. According to the ranking probabilities, aducanumab performed most effectively, followed by solanezumab, donanemab, and bapineuzumab, and gantenerumab was superior to crenezumab regarding MMSE scores. When we chose the improvement of CDR-SB score as the efficacy outcome, aducanumab was still ranked ahead of other anti-Aβ mAbs. In 2017, a previous meta-analysis of a total of 17 clinical studies revealed that aducanumab exerted the

most beneficial effects, followed by solanezumab, but bapineuzumab, crenezumab, and gantenerumab had no effect on the improvement of clinical outcomes [54]. A previous NMA included five interventions, involving 5141 patients; it was reported that aducanumab and solanezumab were significantly superior to placebo in MMSE [55]. These two NMAs reported similar comparative results regarding aducanumab and solanezumab. Aducanumab is a whole human IgG 1 mAb isolated from elderly donors with cognitive health as the first disease-modifying therapy (DMT) for AD [56]. Aducanumab binds to amyloid plaques and high molecular weight amyloid oligomers, and it also stimulates microglia to clear Aβ in a dose- and time-dependent manner accompanied by a slowing of cognitive impairment based on MMSE and CDR-SB [57]. The original statement discusses the approval of aducanumab and lecanemab based on their ability to reduce Aβ rather than their impact on cognitive functions. Previous analysis revealed that, despite statistically significant results, the effect of these medications on cognitive performance is relatively minor and lacks clinical significance [54, 58, 59]. In addition, a study of 196 patients with AD showed a similar result, that is, aducanumab reduced Aβ plaques, and it slowly decreased clinical indicators of patients [60]. Similarly, when assessed by ADAS-Cog, another cognitive subscale, the cognitive improvement with donanemab was more obvious than with other mAbs. ADAS-Cog was designed as a standard tool in

key clinical trials related to attention, concentration, nonverbal memory and practice, which is used to evaluate the cognitive aspects of AD [61, 62]. Only a phase II trial of donazumab was involved in our NMA, and Mintun et al. considered no definitive conclusions could be drawn regarding the difference between groups in the change in ADAS-Cog score [31]. At the same time, lecanemab, aducanumab, and solanezumab also improved ADAS-Cog scores, which had been confirmed in another meta-analysis [63, 64]. Like most measures of functioning used in AD, ADCS-ADL was developed as an interview-based, informant-reported measure of level of independence in specific tasks to assess basic as well as instrumental living skills [65]. In our study, lecanemab achieved better results on ADCS-ADL from the perspective of SUCRA rankings, followed by solanezumab, and donanemab was superior to aducanumab. A recent systematic review and meta-analysis of anti-amyloid-β mAbs in phase III clinical trials indicated that aducanumab and lecanemab significantly improved ADCS-ADL-MCI scores, consistent with our findings [66]. Lecanemab is a humanized IgG1 of the mouse mAb158, defined as the second FDA-approved anti-amyloid drug to treat AD after aducanumab, and supposedly the only one that shows a statistically significant clinical benefit [47, 67]. A multicenter, double-blind, phase III trial showed that after 18 months, according to the ADCS-MCI-ADL evaluation, compared with placebo, lecanemab delayed the progress of AD by 37%, and the gap was increasing [34]. The amyloid cascade hypothesis postulates that the amyloid precursor protein (APP) is broken down to form Aβ, and the imbalance between Aβ generation and Aβ clearance results in an abnormal accumulation of amyloid-β plaques in various regions of the brain [68, 69]. As for the data of amyloid PET-SUVr, results from our NMA showed donanemab had the highest SUCRA value in reducing the amyloid burden, followed by gantenerumab and aducanumab; other mAbs were inferior to placebo. Among these antibody molecules, donanemab was very effective in reducing florbetapir amyloid PET signal and amyloid load but depended on percent change [30, 31]. Patients with higher levels of Aβ at baseline experienced a more obvious reduction, while those with lower initial Aβ levels might achieve complete clearance of amyloid. However, according to the results of a previous meta-analysis, cognitive improvement was not found across the donanemab phase I/II trials, measured by MMSE, ADAS-Cog, and CDR-SB scores [70]. Research indicated that mAbs used in AD treatments, such as aducanumab, gantenerumab, and solanezumab, have different specificities for various forms of amyloid-β. They can influence the effectiveness at various stages or under varying conditions of amyloid-β accumulation, which might explain the variations in their therapeutic outcomes [71, 72]. Overall, the efficacy of these mAbs in improving cognitive function among patients with mild or moderate AD has been observed. At the same time, their efficacy showed considerable variation, with each mAb exhibiting a distinct profile of efficacy and associated risks for potential adverse effects.

In a safety assessment, amyloid-related imaging abnormalities (ARIA), ARIA-E, and ARIA-H, were selected for comparison between immunotherapy and placebo. Drawing on the findings of recent studies, the risk-to-benefit ratio of anti-Aβ mAbs in Alzheimer's disease continues to be unfavorable [58, 63, 73]. Several articles suggest that amyloid-β, as a barrier protein, has a unique sealant which can prevent immune-mediated brain tissue damage, and thus assume the main anti-pathogenic function. Therefore, the risk of amyloid-β deficiency can lead to a series of complications, such as downstream bleeding and edema, which should be paid attention to [74]. In addition, the risk of ARIA increased with the dose of the antibodies, suggesting a relationship between the efficacy of amyloid clearance and the imaging abnormality. In the current NMA, compared with the placebo group, most of the mAbs significantly increase the risk of ARIA-E and ARIA-H. According to the ranking results, the best alternatives were gantenerumab and solanezumab, which showed the lowest rates of adverse events (subjects with any TEAE) and ARIAs. Jeremic et al. suggested that solanezumab was the only drug that did not increase ARIA-E risk [66]. Recent studies revealed that the lack of specific targeting Aβ oligomers or blocking their toxicity is a serious defect in immune therapeutic approaches: solanezumab, ponezumab, and lecanemab are targeted to soluble Aβ; bapineuzumab and crenezumab recognize all three forms of Aβ; and aducanumab, donanemab, and gantenerumab bind AβOs and fibrils. In SCarlet RoAD, at doses of 105 and 225 mg every 4 weeks, gantenerumab was chosen to minimize the risk of any adverse events incidence [40]. However, compared with the positive results of the phase Ib trial for aducanumab [24], it shows that the dose of gantenerumab may be too low to obtain substantial clinical benefit. Because anti-amyloid treatments have been associated with ARIA with edema or hemorrhage and raised some safety concerns [75], we compared immunotherapies versus placebo. Solanezumab that also recognizes soluble, monomeric amyloid has showed the least risk of ARIA-E and ARIA-H incidence among immunotherapies. The incidence of ARIAs was 0.9% and 0.4% for solanezumab and placebo, respectively, indicating that solanezumab did not induce ARIAs, thus displaying its great tolerability and safety [38]. Lecanemab ranked lowest in terms of AEs in our study, but in clinical trials of lecanemab, the incidence of brain swelling (referred to as ARIA-E) was 12.6%, whereas in the clinical trials of donanemab, this rate was 24% [25, 34].
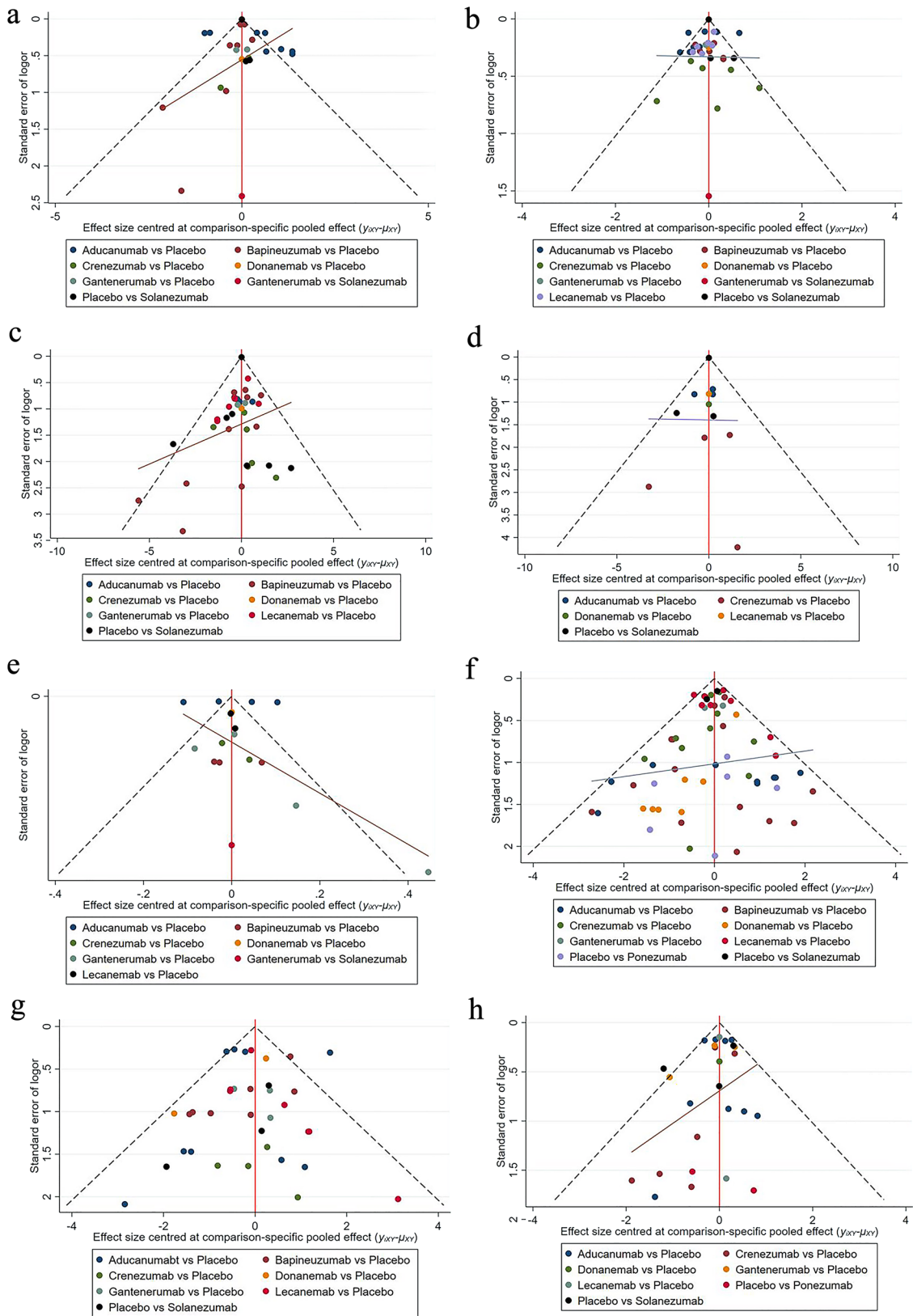
◄**Fig. 7** Funnel plots for the efficacy and safety outcomes: **a** Mini-Mental State Examination (MMSE), **b** Clinical Dementia Rating scale–Sum of Boxes (CDR-SB), **c** Alzheimer's Disease Assessment Scale–cognitive subscale (ADAS-cog), **d** Alzheimer's Disease Cooperative Study–Activities of Daily Living (ADCS-ADL), **e** standardized uptake value ratio of amyloid positron emission tomography (PET-SUVr), **f** adverse events (AE), and **g** amyloid-related imaging abnormalities characterized by edema and effusion (ARIA-E) and **h** cerebral microhemorrhages (ARIA-H)

Our study, the latest and largest evidence-based NMA, for the first time evaluated early Alzheimer's disease subjects treated with anti-Aβ mAbs. All randomized controlled trials in our study are considered to be of high quality. However, our research has some limitations. First of all, the number of head-to-head studies of mAbs is extremely limited, which might lead to mostly indirect estimates for all the comparisons in our NMA and affect the precision of the results. Secondly, we compare the changes in cognitive function mainly through clinical measurement scales. Each research variable is different in key biomarkers, so it is impossible to compare. Thirdly, we counted all the overall outcomes of the results rather than divide the evidence base by dose and mode of each drug administration, and the follow-up time ranged from 6 months to 4 years. Finally, meta-analysis data were sourced only from published scientific literature, and some negative results and non-statistical data are difficult to publish. Therefore, there is publication bias. In general, these results show that these anti-Aβ mAbs could prevent cognitive decline of patients with early AD but the curative effect on the symptoms of functional, behavioral, and systemic change in patients with severe AD is questionable. In fact, some results are difficult to evaluate today because the tools for manipulating non-cognitive results are immature [76]. We only paid attention to anti-Aβ mAbs, and more directions need to be considered in the future treatment of Alzheimer's disease, including gene therapy, immunotherapy, peptide dynamics, metal creators, and probiotics. According to the NMA of mAbs in existing research, its clinical benefits in the treatment of AD have been observed, but whether it is really worth popularizing these in clinic needs further discussion.

6 Conclusion

NMA provides effective evidence for evaluating the efficacy and safety of anti-Aβ mAbs in the treatment of AD. From the perspective of SUCRA rankings, aducanumab may be the best choice for MMSE and CDR-SB cognitive improvement. Donanemab is thought to be potentially more effective than other interventions in ADAS-cog and amyloid PET-SUVr, and lecanemab may be the most beneficial to ADCS-ADL. In terms of safety, immunotherapies significantly increase

the risks of adverse events and ARIA; gantenerumab and solanezumab might be safer than other mAbs included. Due to statistical uncertainties in SUCRA rankings, specific analysis is needed when applying them in clinical practice.

Declarations

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