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## Original Article

# The efficacy and safety of anti-amyloid monoclonal antibody versus acetylcholinesterase inhibitor with an in-depth analysis across genotypes and disease stages: a systematic review and meta-analysis

Chih-Wei Hsu<sup>a,1</sup>, Tien-Wei Hsu<sup>b,c,d,e,1</sup>, Yu-Chen Kao<sup>f,g</sup>, Yu-Hsuan Lin<sup>h,i,j</sup>, Trevor Thompson<sup>k</sup>, Andre F. Carvalho<sup>l</sup>, Brendon Stubbs<sup>m</sup>, Ping-Tao Tseng<sup>n,o,p,q</sup>, Fu-Chi Yang<sup>r</sup>, Chia-Kuang Tsai<sup>r</sup>, Chia-Ling Yu<sup>s</sup>, Yu-Kang Tu<sup>t,u,\*</sup>, Chih-Sung Liang<sup>f,g,\*\*</sup>

<sup>a</sup> Department of Psychiatry, Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan

<sup>b</sup> Department of Psychiatry, E-DA Dachang Hospital, I-Shou University, Kaohsiung, Taiwan

<sup>c</sup> Department of Psychiatry, E-DA Hospital, I-Shou University, Kaohsiung, Taiwan

<sup>d</sup> Graduate Institute of Clinical Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan

<sup>e</sup> School of Medicine, College of Medicine, I-Shou University, Kaohsiung, Taiwan

<sup>f</sup> Department of Psychiatry, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan

<sup>g</sup> Department of Psychiatry, Beitou Branch, Tri-Service General Hospital, Taipei, Taiwan

<sup>h</sup> Institute of Population Health Sciences, National Health Research Institutes, Miaoli, Taiwan

<sup>i</sup> Department of Psychiatry, National Taiwan University Hospital, Taipei, Taiwan

<sup>j</sup> Department of Psychiatry, College of Medicine, National Taiwan University, Taipei, Taiwan

<sup>k</sup> Centre for Chronic Illness and Ageing, University of Greenwich, London, UK

<sup>l</sup> IMPACT (Innovation in Mental and Physical Health and Clinical Treatment) Strategic Research Centre, School of Medicine, Barwon Health, Deakin University, Geelong, VIC, Australia

<sup>m</sup> Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK

<sup>n</sup> Institute of Biomedical Sciences, National Sun Yat-sen University, Kaohsiung, Taiwan

<sup>o</sup> Department of Psychology, College of Medical and Health Science, Asia University, Taichung, Taiwan

<sup>p</sup> Prospect Clinic for Otorhinolaryngology & Neurology, Kaohsiung, Taiwan

<sup>q</sup> Institute of Precision Medicine, National Sun Yat-sen University, Kaohsiung City, Taiwan

<sup>r</sup> Department of Neurology, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan

<sup>s</sup> Department of Pharmacy, Chang Gung Memorial Hospital Linkou, Taoyuan, Taiwan

<sup>t</sup> Institute of Epidemiology & Preventive Medicine, College of Public Health, National Taiwan University, Taipei, Taiwan

<sup>u</sup> Department of Dentistry, National Taiwan University Hospital, Taipei, Taiwan

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## ABSTRACT

**Background:** To date, studies have not compared the efficacy and safety of monoclonal antibodies (mABs) with acetylcholinesterase inhibitors (AChEIs).

**Methods:** Five electronic databases were systematically searched from inception to 10 November 2024 for double-blinded randomized controlled trial (RCT) of patients diagnosed with MCI or mild AD treated with mABs or AChEIs for at least 6 months. The primary outcome was change in cognitive function, measured by the Alzheimer's Disease Assessment Scale–cognitive subscale 14-item (ADAS-Cog) and Clinical Dementia Rating Scale–Sum of Boxes (CDR-SOB). The secondary outcomes were acceptability, tolerability, serious adverse events (SAE), and all-cause mortality. For mABs, amyloid-related imaging abnormalities–edema (ARIA-E), and amyloid-related imaging abnormalities–hemorrhage (ARIA-H) were also assessed. Subgroup analyses included (i) MCI versus mild AD; (ii) with versus without concomitant AD medications; and (iii) Apolipoprotein E (ApoE4) carriers versus non-carriers. Data were pooled using a random effects model within a Bayesian framework.

\* Corresponding author at: Institute of Epidemiology & Preventive Medicine, College of Public Health, National Taiwan University, No. 17, Xuzhou Road, Zhongzheng District, Taipei City 100, Taiwan.

\*\* Corresponding author at: Department of Psychiatry, Tri-Service General Hospital, National Defense Medical Centre, No. 60, Xinmin Road, Beitou District, Taipei, Taiwan.

E-mail addresses: [yukangtu@ntu.edu.tw](mailto:yukangtu@ntu.edu.tw) (Y.-K. Tu), [lcsyfw@gmail.com](mailto:lcsyfw@gmail.com) (C.-S. Liang).

<sup>1</sup> contributed equally to this article as first authors.

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**Results:** There were 8010 participants (mean age: 71.5 years) across seven mAB trials, and 4993 participants (mean age: 70.7 years) in nine AChEI trials. When compared to placebo, only mABs, not AChEIs, were associated with a slower progression of cognitive decline on CDR-SOB (mean difference -0.41 (95 % credible interval -0.61 to -0.22); minimally important difference (MID) -1) and ADAS-Cog (-1.35 (-2.36 to -0.36), MID -2); however, these benefits of mABs did not reach MID across the two cognitive measurements. Besides, mABs were associated with a slower progression of cognitive decline on CDR-SOB (-0.30 (-0.60 to -0.001)) than AChEIs, although mABs and AChEIs did not differ across safety outcomes, including acceptability, tolerability, SAE, and all-cause mortality. Further analysis of mABs indicated that their efficacy did not differ by disease stage, concomitant AD medications, or APOE4 carrier status. However, APOE4 homozygotes carriers were associated with a 5.53-fold (2.48 to 13.07) increased odds of developing ARIA-E compared to non-carriers. Finally, lecanemab demonstrated relatively better efficacy and a more favorable profile on ARIA-E compared to aducanumab and donanemab.

**Conclusions:** mABs were associated with a slower progression of cognitive decline than AChEIs; however, this effect did not reach the MID. The incidence of ARIA-E with mABs was associated with APOE4 carrier status and was not indicative of treatment efficacy.

## 1. Background

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by memory loss, cognitive decline, and behavioural changes, which significantly impair daily functioning and contribute to a substantial disease burden [1]. AD often develops following mild cognitive impairment (MCI), and it is the most common cause of dementia. As of 2018, it affects an estimated 50 million people worldwide, with projections suggesting this number may triple by 2050 [1]. According to the cholinergic hypothesis, the loss of cholinergic neurons in the brain leads to impaired cholinergic transmission, resulting in cognitive dysfunction [2]. Acetylcholinesterase inhibitors (AChEIs) which increase acetylcholine levels in the brain have been approved as a symptomatic treatment for AD over the past 20 years [3]. However, this class of medications does not modify the course of the disease [4]. Cummings suggested disease-modifying treatments for Alzheimer's disease as those that demonstrate significant differences in clinical outcomes compared to a placebo, along with biomarker outcomes that show a correlational relationship with the clinical outcomes. Examples of such biomarkers include the effect on cortical atrophy observed through magnetic resonance imaging (MRI) or reduced levels of tau or phosphorylated tau in cerebrospinal fluid [5]. A Cochrane Review reported that AChEIs are effective for mild to moderate AD demonstrating benefits in cognitive function, daily living activities, and behavioural symptoms [6]. A meta-analysis including both randomized controlled trials (RCTs) and non-randomized studies found that donepezil, a AChEI, was beneficial for patients with MCI. Another meta-analysis found that AChEIs were associated with a lower incidence of dementia progression compared to placebo in patients with MCI, although the treatment effect on cognitive measurement scores remained uncertain [7]. These findings support AChEIs as a first-line pharmacological treatment for AD in clinical practice.

Recently, the United States Food and Drug Administration (FDA) has accelerated the approval of monoclonal antibody (mABs) including aducanumab, lecanemab, and donanemab for MCI due to AD and mild AD [8,9]. These mABs target amyloid- $\beta$  plaques which was seen as disease-modifying therapies based on the amyloid hypothesis of AD [9,10]. Indeed, RCTs have shown that mABs can significantly reduce amyloid- $\beta$  burden, as measured by positron emission tomography (PET) scans [11–13]. However, some concerns have been raised. Firstly, although mABs compared to placebo produced a slower progression of cognitive decline [11,13,14], few studies have discussed whether these findings meet the threshold for a minimally important difference (MID) in clinical practice [15]. Secondly, amyloid-related imaging abnormalities (ARIA) occurred in a significant proportion of patients receiving mABs. Certain brain injury-related adverse effects, such as symptomatic and ventricular enlargement, are also more frequent compared to placebo [15].

Although several meta-analyses of mABs have been published [16–19], the comparisons between disease-modifying therapy mABs and traditional symptomatic treatment AChEIs remain unexplored. Given that

early cognitive intervention during the prodromal to mild stages of AD is essential for slowing disease progression, this study compared the efficacy and safety of mABs with AChEIs in patients with MCI or mild AD. Additionally, we conducted an in-depth analysis of the efficacy and safety of mABs across various conditions, including (i) MCI versus mild AD; (ii) the moderating effect of concomitant AD medications; and (iii) Apolipoprotein E (ApoE4) carriers versus non-carriers. We also assessed whether the observed efficacy and safety outcomes met the threshold for MID. Our findings may provide new insights into the practical utility of mABs for prodromal to mild AD.

## 2. Methods

The study protocol was registered with PROSPERO (CRD42024606860). We followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) extension statement for reporting systematic reviews incorporating network meta-analysis (appendix 1) [20].

### 2.1. Data sources and searches

Two reviewers independently searched the PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), Embase, and PsycINFO, and ClinicalTrials.gov databases without language restrictions from database inception to 10 November 2024. The reviewers also searched the grey literature and reviewed reference lists of the included studies and related systematic reviews [17,21].

### 2.2. Inclusion and exclusion criteria

The inclusion criteria were: (i) double-blinded RCT; (ii) patients diagnosed with MCI or mild AD [22]; (iii) treated with FDA-approved mAB or AChEI; and (iv) the treatment duration needed to be at least 6 months (24 weeks). The exclusion criteria include: (i) non-randomized studies; (ii) AD without clear stage or severity; (iii) moderate or severe AD; (iv) other types of dementia (e.g., vascular dementia); and (v) studies only reporting results of pharmacodynamics or pharmacokinetics, (vi) MCI due to non-AD etiologies (e.g., vascular dementia or Parkinson's disease), and (vii) RCTs without providing primary outcomes. In the case of multiple publications based on the same RCT, we only included articles with the richest information and the largest sample source. Two reviewers independently screened the retrieved studies for eligibility, and discrepancies were resolved by consulting the corresponding authors. Appendix 2 shows the complete search strategies, and appendix 3 presents the reasons for exclusion.

### 2.3. Definition of outcomes and risk of bias

The study evaluated both cognitive function and safety outcomes. The primary outcome focused on cognitive function, measured through

three validated assessment tools: the Alzheimer's Disease Assessment Scale–cognitive subscale 14-Item (ADAS-Cog), the Clinical Dementia Rating scale–Sum of Boxes (CDR-SOB), and the Mini-Mental State Examination (MMSE). To ensure standardization, different versions of ADAS-Cog (such as 11-item or 13-item) were converted to the 14-Item version using validated methods [23].

Secondary outcomes encompassed six safety parameters: acceptability (all-cause discontinuation), tolerability (discontinuation due to adverse events), serious adverse events, all-cause mortality, and two types of amyloid-related imaging abnormalities–edema (ARIA-E) and –hemorrhage (ARIA-H).

Data were extracted from intention-to-treat or last observation carrying forward analyses, along with estimates from mixed-effect models for repeated measures. Numerical data from figures were extracted using WebPlotDigitizer (<https://automeris.io/WebPlotDigitizer/>). For trials involving mAB, only data from FDA-approved recommended doses were included.

To ensure data quality and minimize bias, two authors independently conducted data extraction and review, with additional verification by a third author. The risk of bias assessment utilized the Cochrane randomized trial risk of bias tool (version 2.0), with any discrepancies resolved through consensus discussion among the authors [24].

#### 2.4. Minimally important difference (MID)

To ensure practical clinical relevance, we also considered minimally important difference (MID) for the efficacy and safety outcomes in MCI or mild AD. We defined efficacy threshold for cognitive measures based on recent review findings [25]. A treatment was considered efficacious if it achieved a decrease of at least 2 points for the ADAS-Cog, a decrease of at least 1 point for the CDR-SOB, or an increase of at least 1 point for the MMSE. For safety outcomes, we established a threshold odds ratio of 1.15 based on clinical consensus, which approximates a relative risk of 1.1 when assuming baseline incidences between 10 % and 30 %.

#### 2.5. Data synthesis

We computed the mean difference with a 95 % credible interval (CrI) for continuous outcomes, defined as the difference between the change scores of the active and placebo arms, and calculated the odds ratio (OR) for categorical outcomes. We focused only on results where the 95 % CrI for the mean difference did not cross zero or where the 95 % CrI for the OR did not cross one. We conducted a random-effects contrast-based network meta-analysis within a Bayesian framework [26,27]. The posterior probabilities were calculated. We initially compared the overall effects of mABs and AChEIs, and then we evaluated the effects of individual mABs and individual AChEIs. The transitivity assumption was assessed by visual comparisons of the distribution of potential effect modifiers across treatment comparisons. The consistency assumption was not examined, as all included studies were two-armed, placebo-controlled RCTs without direct comparisons between active treatments. We calculated the surface under the cumulative ranking area (SUCRA) to rank the priority of the different interventions, with higher SUCRA values indicating greater benefits for both efficacy and safety. To provide a clear comparison of treatment effects and safety across multiple outcomes, we used spie charts to present a comprehensive overview of each treatment's relative benefits and risks [28].

Several subgroup analyses were conducted to examine the efficacy and safety of mABs across different conditions, including (i) MCI versus mild AD; (ii) the moderating effect of concomitant AD medications; and (iii) ApoE4 carriers versus non-carriers. The interaction between treatment and placebo was assumed to be independent. For the risk of ARIA-E and ARIA-H, we performed subgroup analyses stratified by (i) ApoE4 non-carriers versus ApoE4 carriers and (ii) ApoE4 non-carriers, heterozygotes, and homozygotes.

Publication bias was assessed by visual inspection of a comparison adjusted funnel plots with placebo as the comparator. Additionally, we conducted the Egger test, Begg test, and Thompson test to examine the asymmetry of the funnel plot. We conducted sensitivity analyses using separate Bayesian models: a base model with treatment effects only, five individual models each incorporating one covariate (baseline score of cognitive function (e.g., ADAS-Cog), trial duration, proportion of MCI patients, proportion of combined AD medications, or publication year) as random effects, and a final model including all covariates simultaneously for the primary outcomes.

Four Markov chains were implemented. 50,000 iterations occurred per chain and the first 20,000 iterations for each chain were discarded as a warm-up. Convergence was assessed by visual inspection of the trace plots of the key parameters for each analysis. The prior settings and convergence results are shown in appendix 4. All statistical analyses were done using R version 4.3.1. The network meta-analysis within a Bayesian framework was fitted using the Bayesian statistical software called Stan within R package multinma and brms [27]. Reasons for protocol changes are in Appendix 5.

### 3. Results

#### 3.1. Characteristics of included study

After searching the database and excluding duplicated records, we identified 3360 unique potential studies. We then screened the titles and abstracts of these studies for eligibility and excluded 3126 of them, in which 234 studies remained. 224 studies were excluded after an assessment of the full text for various reasons (appendix 3). We identified four additional studies through a manual search resulting in total 14 eligible studies (efigure 1). Details of the characteristics of the included studies are shown in eTable 1. Overall, 6479 people (mean age of 71.5 years, 53.4 % (3366/6309) were women) were included in mABs trials (7 trials, 6 articles) [11,13,14,29–31], and 4993 participants (mean age of 70.7 years, 56.8 % (2748/4839) were women) were included in AChEI trials (9 trials, 8 articles) [32–39].

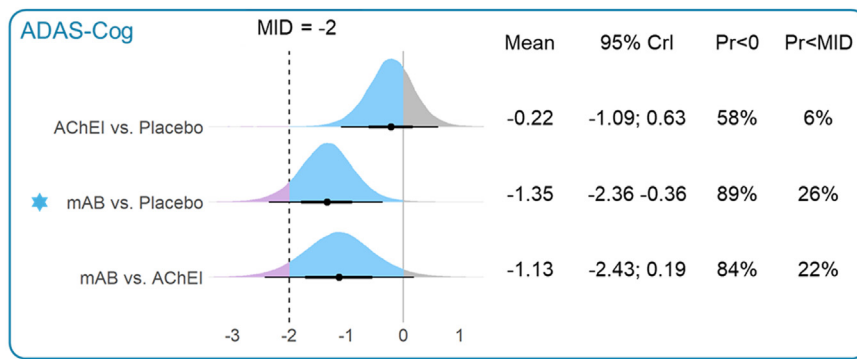
#### 3.2. Risk of bias of the included studies

No mAB study (0/7) had a high overall risk of bias (efigure 2 and efigure 3). The percentages of studies with high, some concerns, or low risk of bias in the 7 mAB trials were as follows: 0 % ( $k = 0$ ), 0 % ( $k = 0$ ), and 100 % ( $k = 7$ ) for randomisation; 0 % ( $k = 0$ ), 0 % ( $k = 0$ ), and 100 % ( $k = 7$ ) for deviations from intended Interventions; 0 % ( $k = 0$ ), 0 % ( $k = 0$ ), and 100 % ( $k = 7$ ) for missing outcome data; 0 % ( $k = 0$ ), 0 % ( $k = 0$ ), and 100 % ( $k = 7$ ) for measurements of outcomes; 0 % ( $k = 0$ ), 0 % ( $k = 0$ ), and 100 % ( $k = 7$ ) for selection of reported results. No AChEI studies (0/9) were rated as high risk of bias. The percentages of studies with high, some concerns, and low risk of bias in the 9 AChEIs studies were as follows: 0 % ( $k = 0$ ), 0 % ( $k = 0$ ), and 100 % ( $k = 9$ ) for randomisation; 0 %, ( $k = 0$ ), 11 % ( $k = 1$ ), and 89 % ( $k = 8$ ) for deviations from intended interventions; 0 %, ( $k = 0$ ), 11 % ( $k = 1$ ), and 89 % ( $k = 8$ ) for missing outcome data; 0 % ( $k = 0$ ), 0 % ( $k = 0$ ), and 100 % ( $k = 9$ ) for measurements of outcomes; 0 % ( $k = 0$ ), 78 % ( $k = 7$ ), and 22 % ( $k = 2$ ) for selection of reported results.

#### 3.3. Cognitive outcomes

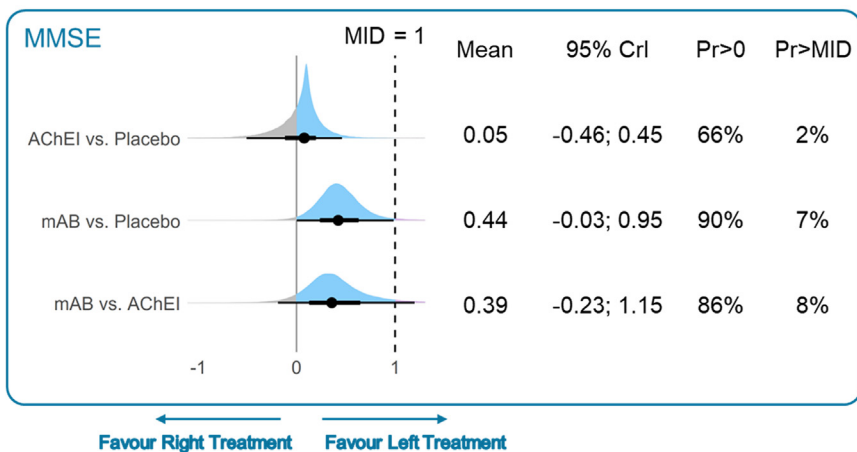
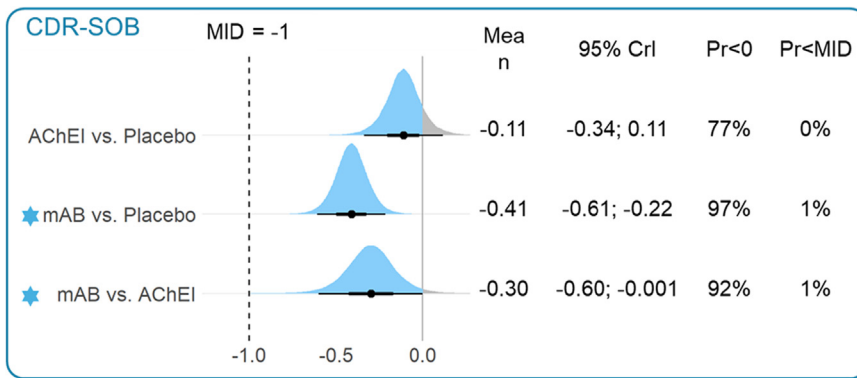
The evidence for every outcome analyzed had a star-shaped structure with placebo as the common comparator (detailed in supplement efigures 4–19). The placebo group demonstrated cognitive deterioration with pooled changes of 1.90 points (95 % CrI: 0.16 to 3.74) in ADAS-Cog, 1.37 points (95 % CrI: 0.81 to 2.01) in CDR-SOB, and –2.30 points (95 % CrI: –3.26 to –1.33) in MMSE (Fig. 1)

Compared to placebo, mABs were associated with mean differences of –1.35 points (95 % CrI: –2.36 to –0.36) on ADAS-Cog and –0.41



**Fig. 1.** Comparisons between mABs and AChEIs on Cognitive Function

Abbreviations: AChEI = acetylcholinesterase inhibitor; ADAS-Cog = Alzheimer's Disease Assessment Scale-Cognitive Subscale 14-item; CDR-SOB = Clinical Dementia Rating Scale Sum of Boxes; CrI = credible interval; mAB = anti-amyloid monoclonal antibody; MID = minimally important difference; MMSE = Mini-Mental Status Examination; Pr = posterior probability.



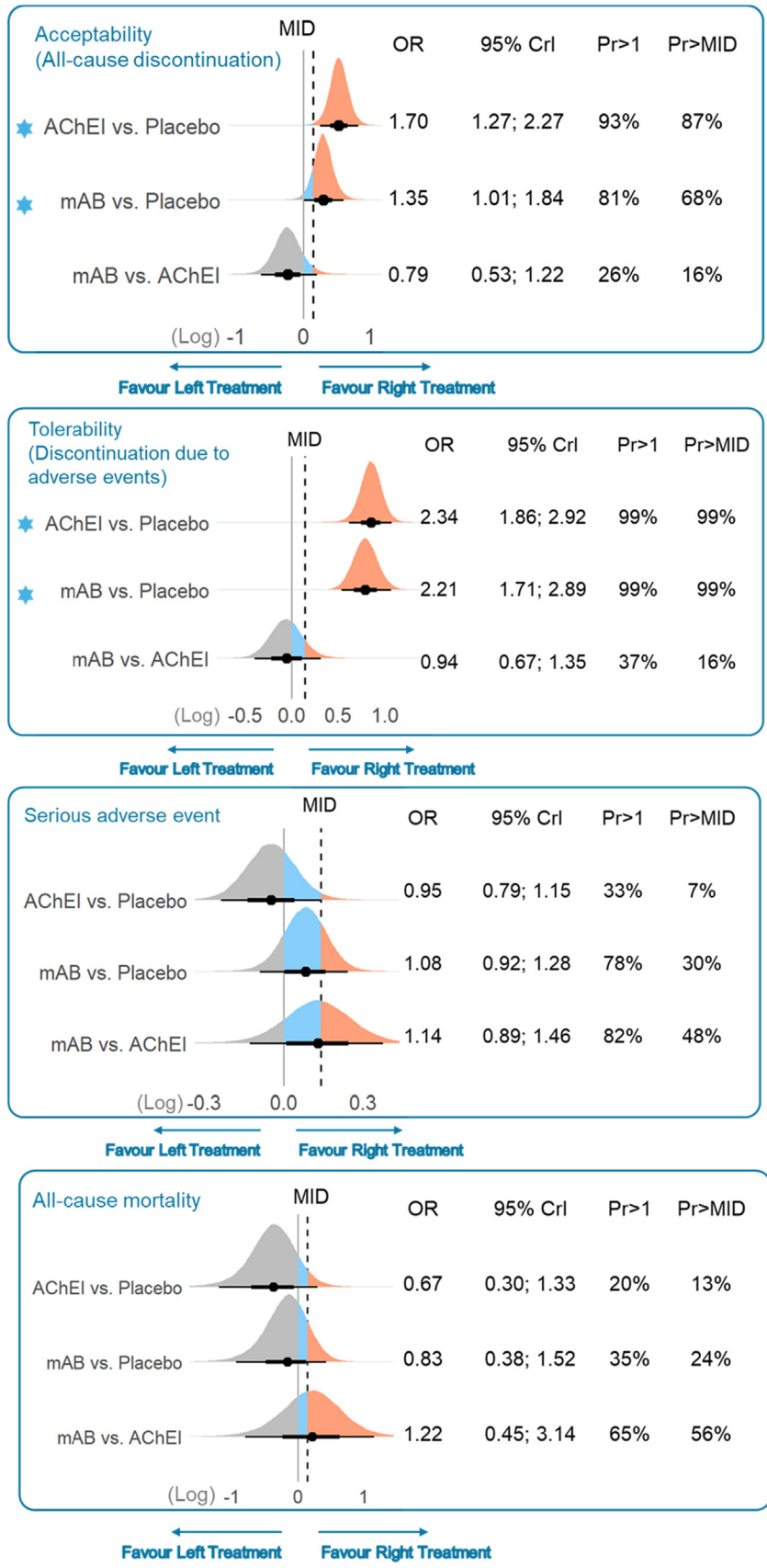
points (95 % CrI: -0.61 to -0.22) on CDR-SOB (Fig. 1). In contrast, the 95 % credible intervals for AChEIs included zero in all cognitive measures. Importantly, mABs were associated with a mean difference of -0.30 points (95 % CrI: -0.60 to -0.001) compared to AChEIs on CDR-SOB (Fig. 1). The mean differences for all pairwise comparisons among mABs, AChEIs, and placebo were below the predefined MID thresholds across all cognitive measurements.

In the analysis of individual medications, lecanemab was associated with a mean difference of -2.27 points (95 % CrI: -4.56 to -0.08) compared to galantamine on ADAS-Cog (efig. 20). For CDR-SOB (efig. 21), both donanemab and lecanemab were associated with mean differences of -0.59 points (95 % CrI: -0.96 to -0.18) and -0.43 points (95 % CrI: -0.81 to -0.05), respectively, compared to placebo. For MMSE (efig. 22), the 95 % credible intervals included zero for all comparisons be-

tween individual mABs, AChEIs, and placebo. While several comparisons showed credible intervals excluding zero, only the comparison between lecanemab and galantamine on ADAS-Cog exceeded the predetermined MID thresholds.

### 3.4. Safety outcomes

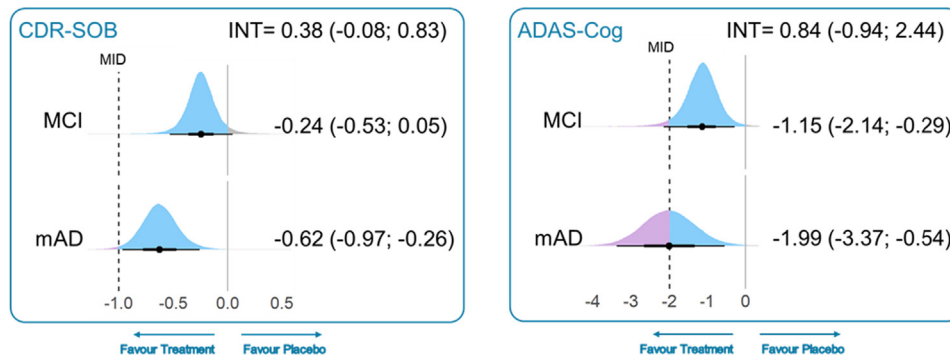
Compared to placebo (Fig. 2), AChEIs (OR 1.70; 95 % CrI 1.27 to 2.27) and mABs (OR 1.35; 95 % CrI 1.01 to 1.84) were associated with increased odds of all-cause discontinuation. Similarly, both AChEIs (OR 2.34; 95 % CrI 1.84 to 2.92) and mABs (OR 2.21; 95 % CrI 1.71 to 2.89) were associated with increased odds of discontinuation due to adverse events compared to placebo. For all four safety outcomes, the odds ratios comparing mABs with AChEIs had 95 % credible intervals including one.



**Fig. 2.** Comparisons between mABs and AChEIs on adverse events

Abbreviations: AChEI = acetylcholinesterase inhibitor; CrI = credible interval; mAB = anti-amyloid monoclonal antibody; MID = minimally important difference; OR = odds ratio; Pr = posterior probability.

(A) MCI vs Mild AD

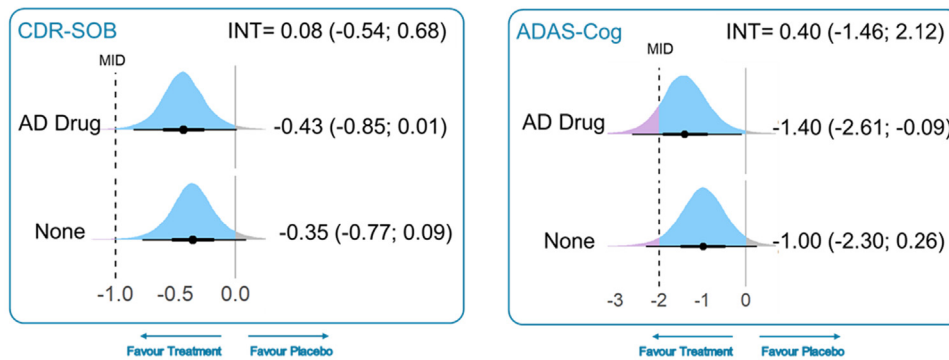


**Fig. 3.** Subgroup analysis of mABs on cognitive function

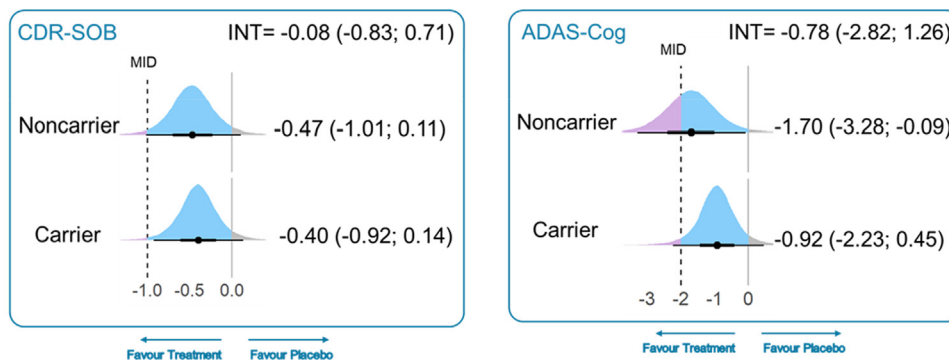
Abbreviations: AChEI = acetylcholinesterase inhibitor; AD = Alzheimer's disease; ADAS-Cog = Alzheimer's Disease Assessment Scale-Cognitive Subscale 14-item; CDR-SOB = Clinical Dementia Rating Scale Sum of Boxes; INT = interaction effect; mAB = anti-amyloid monoclonal antibody; MCI = mild cognitive impairment; MID = minimally important difference

\* Values are presented as means with 95 % credible intervals.

(B) With AD medications vs Without AD medications



(C) Noncarrier of ApoE4 vs Carrier of ApoE4



In the analysis of individual medications (efig. 23 to efig. 26). donepezil and lecanemab were associated with increased odds of all-cause discontinuation, and aducanumab, donanemab, donepezil, galantamine, and lecanemab were associated increased odds of discontinuation due to adverse event.

3.5. Subgroup analyses of mABs on cognitive outcomes

We examined potential effect modifiers by incorporating interaction terms between treatment (mABs versus placebo) and three clinical conditions in our models (Fig. 3): (A) disease stage (MCI versus mild AD); (B) medication status (with versus without concomitant AD medications); and (C) genetic profile (ApoE4 carriers versus non-carriers). The 95 % credible intervals of all interaction effects included zero, suggesting that the treatment effects of mABs compared to placebo were not modified by these clinical conditions (Fig. 3).

3.6. Individual mABs on ARIA-E and AIRA-H

Compared to placebo, aducanumab (OR 5.00; 95 % CrI 2.72 to 8.25) and donanemab (OR 3.22; 95 % CrI 1.88 to 6.49) reached the MID threshold on ARIA-H (Fig. 4). Notable, lecanemab was associated with a lower risk of ARIA-H than aducanumab (OR 0.36; 95 % CrI 0.15 to 0.82). On ARIR-E, aducanumab (OR 15.49; 95 % CrI 2.53 to 53.52) and donanemab (OR 11.59; 95 % CrI 1.36 to 48.42) reached the MID threshold when compared to placebo.

3.7. Genotypes on ARIA-E and AIRA-H

Compared to ApoE4 non-carriers (Fig. 5), the ApoE4 carriers were not associated with increased odds of ARIA-E (OR 1.97; 95 % CrI 0.54 to 6.96), although they had an 89 % posterior probability of ARIA-E and an 84 % posterior probability of reaching the MID threshold. Com-

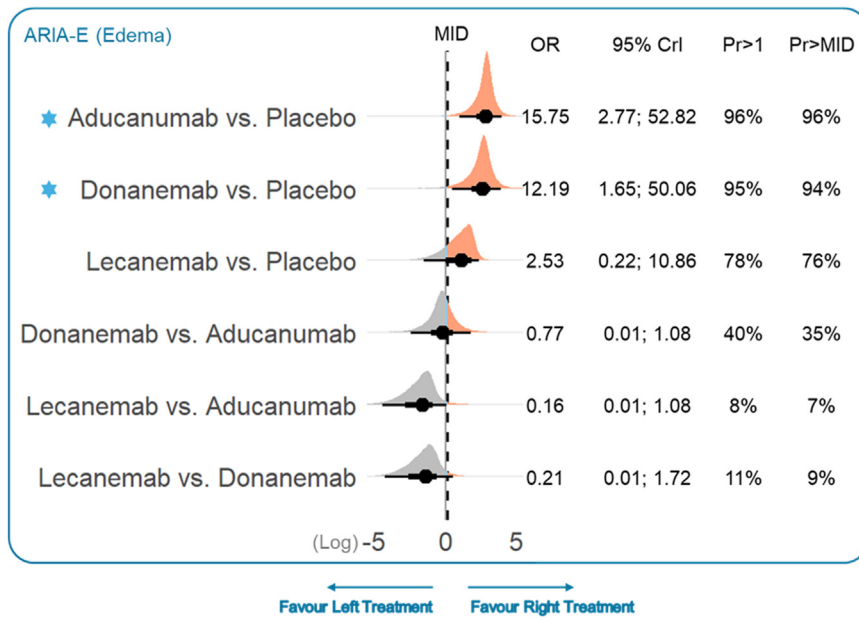
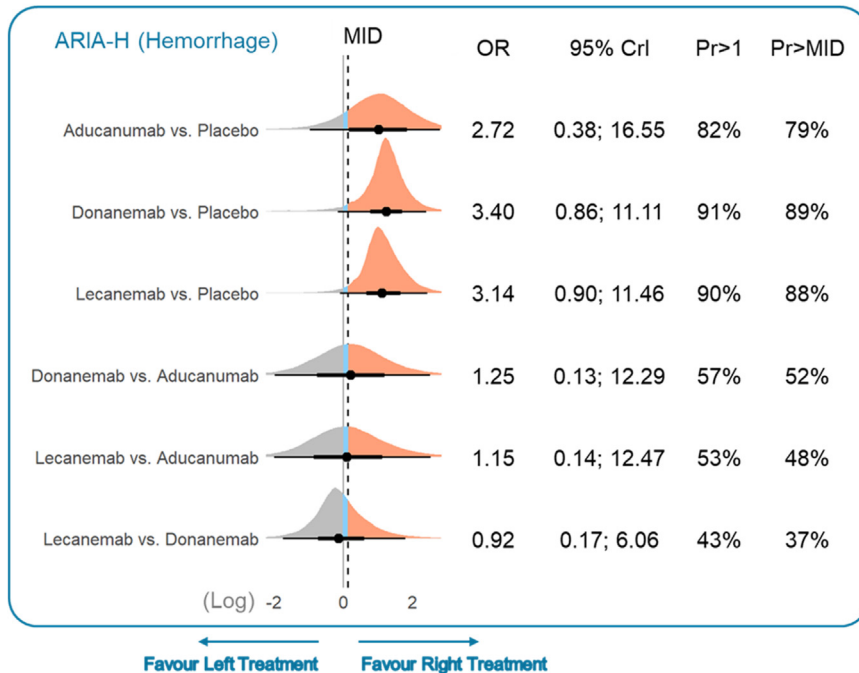


Fig. 4. Comparisons between individual mABs on ARIA-E and ARIA-H

Abbreviations: ARIA-E = Amyloid-related imaging abnormalities-edema; ARIA-H = Amyloid-related imaging abnormalities-hemorrhage; CrI = credible interval; mAB = anti-amyloid monoclonal antibody; MID = minimally important difference; OR = odds ratio; Pr = posterior probability.



pared to ApoE4 non-carriers, the ApoE4 carriers were not associated with a higher risk of ARIA-H (OR 1.77; 95 % CrI 0.01 to 50.91), although they had an 80 % posterior probability of ARIA-H and a 78 % posterior probability of reaching the MID threshold. A dose-response relationship was observed when considering heterozygotes and homozygotes. Compared to non-carriers, heterozygotes had a higher risk of ARIA-E (OR 2.08; 95 % CrI 0.98–5.10) with a 95 % posterior probability of reaching the MID threshold. Homozygotes demonstrated an even higher risk (OR 5.53; 95 % CrI 2.48–13.07) and a 99 % probability of reaching the MID threshold.

3.8. The overall profile of each active treatment and placebo across the nine outcomes

Fig. 6 summarized the overall profile on cognitive and safety outcomes among three mABs, three AChEIs, and placebo using SUCRA. The higher SUCRA values indicated greater benefits for the outcome.

Donanemab and lecanemab seemed to have slightly better efficacy on cognitive function. Lecanemab showed relatively lower risk of ARIA-E among mABs, and aducanumab revealed better acceptability across all active treatments. The three AChEIs showed limited efficacy on cognitive outcomes.

3.9. Transitivity assumption and publication bias

The assessments of transitivity assumption are showed in efig. 27 to efig. 34. The results of the statistical tests (Egger, Begg, and Thompson-Sharp tests) for funnel plot asymmetry, along with visual inspection of the funnel plots, did not indicate publication bias (efig. 35 to efig. 37).

3.10. Sensitivity analyses

Sensitivity analysis on ADAS-Cog (efig. 38) revealed robust treatment effects across different model specifications. While point estimates

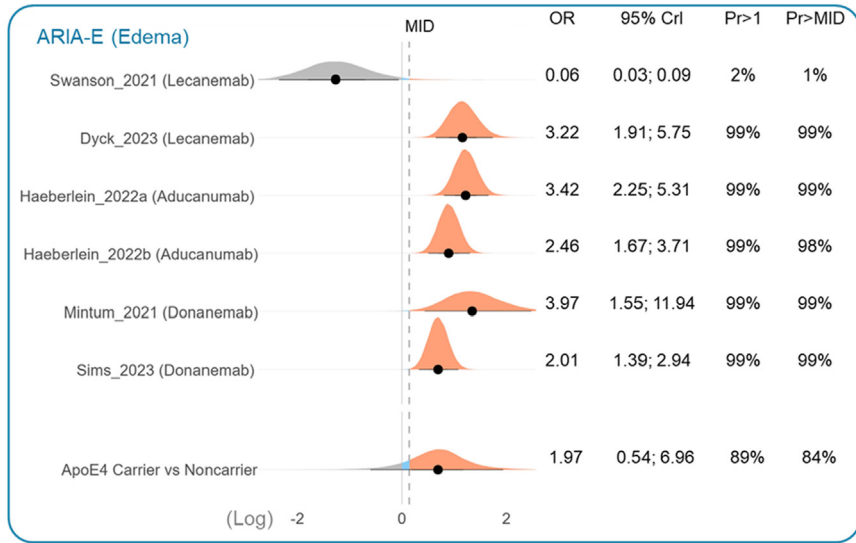
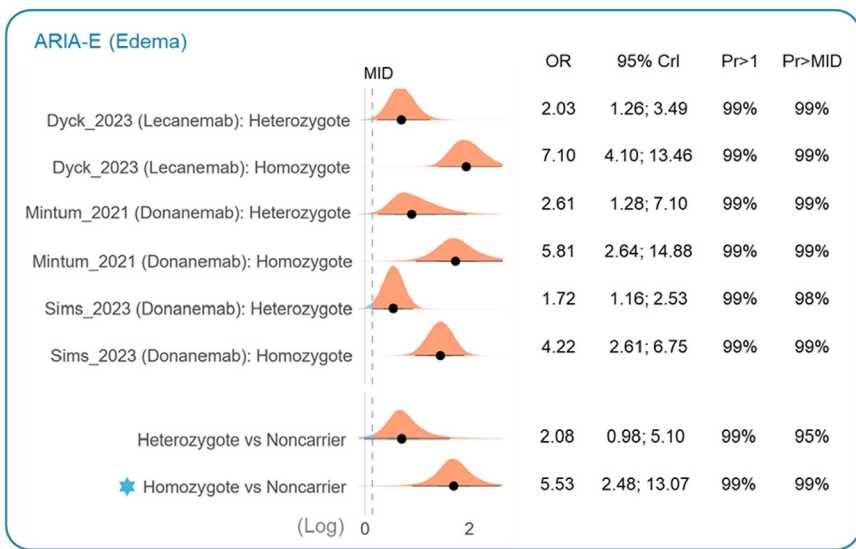
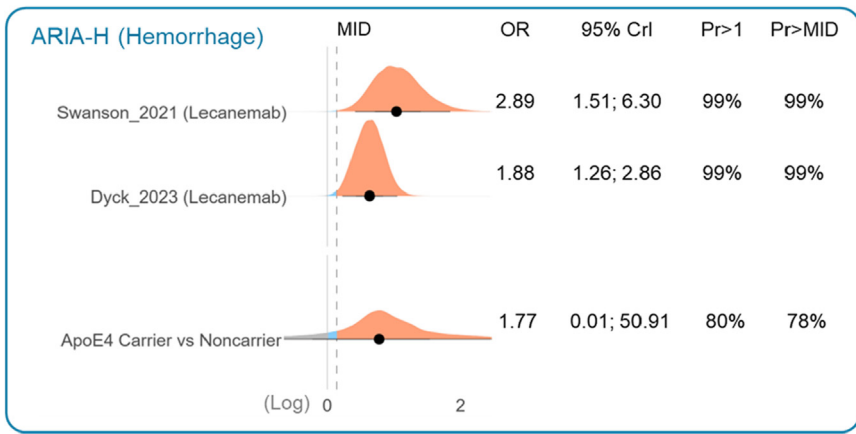
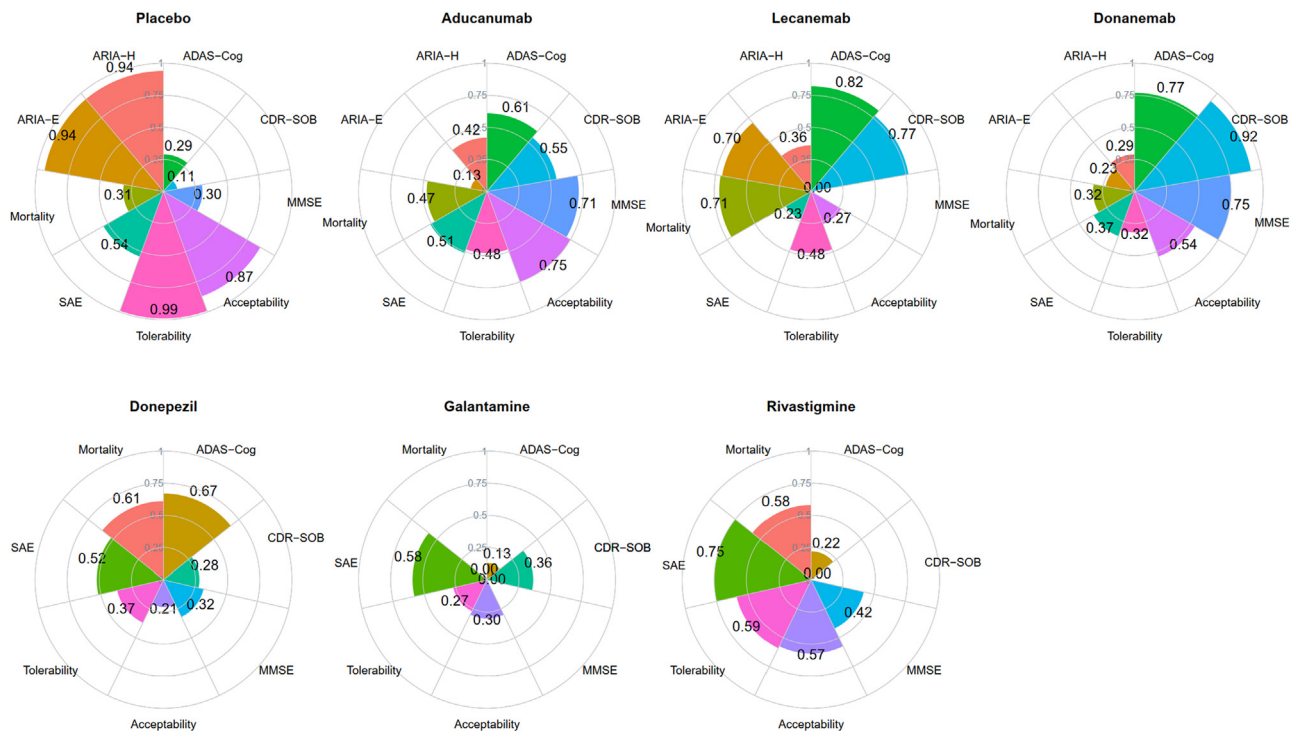


Fig. 5. The association between different genotypes and ARIA-E and ARIA-H

Abbreviations: ARIA-E = Amyloid-related imaging abnormalities-edema; ARIA-H = Amyloid-related imaging abnormalities-hemorrhage; CrI = credible interval; mAB = anti-amyloid monoclonal antibody; MID = minimally important difference; OR = odds ratio; Pr = posterior probability.





**Fig. 6.** Summary of spie plots for the overall profile of each active treatment and placebo across the nine outcomes

Abbreviations: ADAS-Cog = Alzheimer's Disease Assessment Scale-Cognitive Subscale 14-item; ARIA-E = Amyloid-related imaging abnormalities-edema; ARIA-H = Amyloid-related imaging abnormalities-hemorrhage; CDR-SOB = Clinical Dementia Rating Scale Sum of Boxes; MMSE = Mini-Mental Status Examination; SAE = serious adverse event

\* Values are presented as surface under the cumulative ranking (SUCRA), with higher SUCRA values indicating more beneficial outcomes.

remained stable (ranging from  $-1.38$  to  $-1.46$  points) when incorporating covariates either individually or simultaneously, the wider CrI in the full model of five covariates ( $-4.02$  to  $1.05$ ) suggested these covariates contributed primarily to model uncertainty rather than meaningful effect modification. This pattern of stable estimates with increased uncertainty in full models was consistent across sensitivity analyses for both CDR-SOB and MMSE outcomes (efig. 39–40).

#### 4. Discussion

Our comprehensive analysis of treatments for prodromal to mild AD revealed several key findings with important clinical implications. In this patient population, AChEIs showed credible intervals including zero when compared with placebo for cognitive outcomes. However, mABs were associated with greater efficacy in slowing cognitive decline compared to both placebo and AChEIs, though these improvements did not exceed the MID threshold. The safety profile analysis suggested comparable results between mABs and AChEIs in terms of acceptability, tolerability, serious adverse events, and all-cause mortality. The cognitive benefits of mABs showed no evidence of differential effects across disease stages (MCI versus mild AD), medication use status, or ApoE4 carrier status. However, an important safety consideration emerged regarding APOE4 homozygotes, who were associated with a 5.53-fold increased odds ARIA-E compared to non-carriers. Although mABs showed promising cognitive benefits compared to both placebo and AChEIs, the effect sizes remained below the MID thresholds. Moreover, the safety signals, particularly ARIA concerns in APOE4 homozygotes, warrant careful consideration in clinical practice. These findings suggest that treatment decisions should carefully weigh modest cognitive benefits against potential safety concerns, particularly in APOE4 homozygotes.

Over the past 20 years, AChEIs have provided therapeutic benefits through symptom relief by increasing acetylcholine levels, but without

addressing the underlying amyloid pathology [2]. In contrast, mABs directly target amyloid deposits and show possibly slight clinical benefits. Notably, patients selection criteria differed between these trials: AChEI trials relied solely on clinical symptoms, while mAB trials required confirmation of AD pathology through amyloid- $\beta$  PET imaging or cerebrospinal fluid (CSF) A $\beta$ 1–42. This biomarker-based patient selection in mAB trials suggests more precise targeting of the underlying amyloid- $\beta$  pathophysiology, which might contribute to the observed treatment effects.

The relationship between ApoE4 status and mABs' efficacy and safety profiles warrant attention. Evidence suggests that ApoE4 carriers tend to have a higher amyloid burden [40], while non-carriers may develop AD with less amyloid buildup or through other mechanisms [40]. Our analysis revealed a dose-response relationship between ApoE4 genotypes and ARIA-E risk, with the highest risk in homozygous carriers, followed by heterozygous carriers, and then non-carriers. This pattern is consistent with previous findings that ApoE4 genotype was associated with a dose-dependent increase in amyloid- $\beta$  plaque accumulation in the brain tissue [40,41]. The mechanism underlying ARIA-E may involve mAB-induced clearance of amyloid- $\beta$  plaques via perivascular and vascular pathways, potentially leading to temporary increases in cerebral amyloid angiopathy and vascular permeability, resulting in protein-rich fluid extravasation [42]. While this mechanism explains the increased ARIA-E risk in ApoE4 homozygotes who typically have higher amyloid burden, the greater amyloid clearance did not translate to enhanced treatment effects in this population.

Among the three mABs, donanemab showed the best possible cognitive benefits but higher ARIA risks, lecanemab demonstrated balanced efficacy-safety profile with some possible cognitive effects (less than donanemab) and moderate ARIA risks, while aducanumab had relatively modest performance but better acceptability. A previous meta-analysis [17] reported that donanemab ranked first among mABs in  $\beta$ -amyloid

clearance, as measured by PET-Standardized Uptake Value ratios, and aducanumab ranked second. Consistently, in our study, we found that aducanumab and donanemab were associated with a higher risk of ARIA-E and ARIA-H. However, aducanumab did not show greater efficacy in slowing cognitive decline despite its strong amyloid- $\beta$  clearance effect. On the other hand, lecanemab specifically targets  $A\beta$  protofibrils, smaller aggregates implicated in earlier disease stages. Lecanemab demonstrated better cognitive outcomes, lower risk of ARIA-E, but poorer acceptability and tolerability. Importantly, while ARIA emerged as a distinct safety concern specific to mAB therapy, other safety outcomes including mortality and serious adverse events showed comparable profiles across all treatments, suggesting these novel therapies don't introduce additional major safety concerns beyond ARIA.

#### 4.1. Major concerns regarding mAB studies

First, mAB trials are often subject to cohort bias. Previous studies have shown that amyloid-PET positivity indicates only about a 50 % risk of developing AD later in life [43–45], and it is also observed that amyloid positivity tends to decrease with age in patients with probable AD [46]. Whether amyloid positivity is a reliable hallmark of AD still remains questionable [43]. However, to date, mAB trials have exclusively enrolled amyloid-positive patients, which may in turn limit the generalizability of their findings. Second, mAB trials failed to control for changes in other treatments over time, particularly the concurrent use of AChEIs or Memantine (or both). In these trials, approximately 50 % to 60 % of participants were simultaneously using AD medications. However, whether these medications were adjusted throughout the long study period remains unclear. More importantly, there is currently a lack of head-to-head comparisons between mABs and standard practice (AChEIs or Memantine), or at least, AChEI or memantine should be administered to 100 % of participants in both the mAb arm and the control arm. Otherwise, failing to compare the mAb with the most proven effective intervention may constitute a violation of research ethics as outlined in the Declaration of Helsinki [47]. Third, to date, all published mAB trials have failed to demonstrate clinically meaningful effects (i.e., not achieving MID thresholds in cognitive scale scores at the study endpoint). Additionally, the treatment groups usually experienced two to three-times higher dropout rates compared to the control groups. The estimated efficacy of mAB was based on a highly selected and substantially reduced sample. This substantial attrition raises concerns about the long-term risk-benefit ratio of mAB therapy in real-world settings. Fourth, the clinical efficacy of mAB was lower in individuals with the APOE4 genotype, which is a well-known risk factor for AD-related amyloid beta pathophysiology. The paradoxical finding is difficult to reconcile with the hypothesis that amyloid beta is a causal factor of the disease [48–50]. Fourth, the occurrence of ARIA-related poses a risk to blinding integrity in mAB studies. This may introduce bias into efficacy assessment, because most mAB trials use unusual or self-constructed cognitive/functional scales as primary outcomes. Additionally, the long-term consequences of ARIAs remain unknown. Several deaths in the mAB arms have been considered ARIA-related [51,52]; however, the determination of whether these deaths are therapy-related currently judged by the sponsoring pharmaceutical companies [53]. Sixth, brain volume loss (both whole brain and hippocampus) occurs across all mAb trials, and its long-term impact remains unclear. However, amyloid accumulation does not cause brain swelling, so it is unlikely that amyloid clearance would lead to brain atrophy [54]. Autopsy studies have shown that the total volume of amyloid deposition accounts for less than 1 % of the neocortex, and in patients with early Alzheimer's disease, amyloid occupies virtually no space in the cerebral cortex [55–57]. Therefore, brain atrophy may be a warning sign of neuronal damage. Despite the known potential risks of ARIA and brain volume loss, as well as the unknown long-term effects identified in earlier phase I-II studies, continuing with subsequent trials could potentially violate research ethics of the Declaration of Helsinki [47].

#### 4.2. Strengths and limitations of this study

This study has several strengths. Firstly, our study also considered MID for all outcomes. Using Bayesian network meta-analysis, we leveraged borrowing of strength to enhance estimate precision and calculated posterior probabilities for a more nuanced interpretation, alongside comprehensive uncertainty estimates from full posterior distributions. Additionally, we conducted extensive sensitivity analyses, demonstrating consistent treatment effects despite varying covariate adjustments. We also performed several subgroup analyses to examine the efficacy and safety of mAbs across different disease stages, genotypes, and concomitant medication use. Finally, we used SCURA and spie plots to illustrate the performance of different drugs across various outcomes, providing clinicians with a valuable reference for drug selection.

Nevertheless, our study has several limitations. Firstly, there are no head-to-head studies comparing mABs and AChEIs, and therefore, the comparisons between mABs and AChEIs rely on indirect comparisons. We addressed this by including studies with similar patient populations and applying Bayesian statistical methods. Secondly, most AChEI trials were published between 2000 and 2010, while the mAB trials were published after 2020. Thirdly, in the mAB trials, approximately 50 % to 60 % of participants were concurrently using AD medications, such as AChEIs or memantine. However, our subgroup analysis showed no evidence of differential treatment effects based on concomitant AD medication use. Fourthly, the treatment duration of the included studies varied, ranging from 24 weeks to 48 months. For these time-varying factors, we conducted sensitivity analyses through separate Bayesian models with each potential effect modifier, and our results remained robust across different model specifications. Finally, interpretation of safety profiles requires careful consideration. The reporting of adverse events in clinical trials lacks standardization across studies and is often conducted within the context of efficacy assessments. Moreover, our safety analyses relied on general trial reports rather than specialized safety assessments, which may limit the comprehensiveness of safety comparisons.

#### 4.3. Implications and conclusions

In patients with prodromal to mild AD, mABs were possibly associated with a slower progression of cognitive decline compared to either AChEIs or placebo; however, neither treatment benefits exceeded the MID threshold. Regarding safety outcomes, mABs showed comparable risks with AChEIs in terms of acceptability, tolerability, serious adverse events, and all-cause mortality. We found no evidence of differential treatment effects between ApoE4 carriers and non-carriers on cognitive outcomes, though ApoE4 homozygotes were associated with a 5.53-fold increased odds of developing ARIA-E. These findings offer valuable insights to guide clinical decision-making regarding first-line pharmacological treatments for patients in the early stages of AD.

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#### Ethical approval

Not required; analysis of aggregated identified clinical trial data.

#### Consent statement

Consent was unnecessary because this is an analysis of aggregated, de-identified clinical trial data.

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## Data sharing

The data that support the findings of this study are available from the corresponding author (CSL) upon reasonable request.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## CRediT authorship contribution statement

**Chih-Wei Hsu:** Writing – review & editing, Validation, Funding acquisition, Data curation, Conceptualization. **Tien-Wei Hsu:** Writing – original draft, Data curation, Conceptualization. **Yu-Chen Kao:** Writing – review & editing, Validation. **Yu-Hsuan Lin:** Writing – review & editing, Validation. **Trevor Thompson:** Writing – review & editing, Validation. **Andre F. Carvalho:** Writing – review & editing, Validation. **Brendon Stubbs:** Writing – review & editing, Validation. **Ping-Tao Tseng:** Writing – review & editing, Validation, Data curation. **Fu-Chi Yang:** Writing – review & editing, Validation. **Chia-Kuang Tsai:** Writing – review & editing, Validation. **Chia-Ling Yu:** Resources, Data curation. **Yu-Kang Tu:** Validation, Supervision, Conceptualization. **Chih-Sung Liang:** Writing – original draft, Visualization, Validation, Methodology, Formal analysis, Conceptualization.

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## Supplementary materials

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