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Real-World Incidence of Amyloid-Related Imaging Abnormalities Associated with Lecanemab: A Systematic Review and Meta-Analysis

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Abstract

Background Amyloid-related imaging abnormalities (ARIA), including ARIA-edema or effusion (E) and ARIA-hemorrhage (H), are the most common and important treatment-related adverse event of anti-amyloid-β immunotherapy. Real-world populations and clinical management may differ from randomized controlled trials. This study estimated the real-world incidence of ARIA in lecanemab-treated patients and to compare it by geographic region, MRI protocol, and APOE ε4 carrier status.

Methods PubMed and Embase were searched for studies published through April 28, 2026. Real-world lecanemab studies in mild cognitive impairment due to Alzheimer disease or Alzheimer dementia reporting ARIA-E or H were included. The pooled incidences of ARIA and subgroup analyses by geographic region, MRI sequence, MRI magnet strength, and APOE ε4 status were calculated with a random-effects model; pooled ORs by APOE ε4 carrier status were also calculated.

Results Twenty-one real-world studies were identified, analyzing data from 4,818 patients. Pooled incidence was 14.5% (95%CI: 11.8–17.7) for any ARIA, 5.5% (95%CI, 3.9–7.7) for ARIA-E, 11.5% (95%CI, 9.0–14.4) for ARIA-H. Symptomatic ARIA and severe ARIA occurred in 2.1% (95%CI, 1.4–3.2) and 1.3% (95%CI, 0.8–2.0), respectively, and isolated ARIA-H in 8.5% (95%CI, 6.5–11.0). The incidence of any ARIA varied by geographic region, the highest in the United States (21.6%) and lowest in Asia (12.9%) (P=.003). Incidence of ARIA-E differed by MRI field strength (P<.001), whereas incidence of ARIA-H did not differ by MRI sequence (P=.09). APOE ε4 homozygotes had higher odds of ARIA-E than heterozygotes (OR,3.1; 95%CI, 1.7–5.7) and noncarriers (OR,3.3; 95%CI, 1.7–6.4)

(both *P*<.001), and higher odds of ARIA-H than noncarriers (OR,2.4; 95% CI, 1.1–4.9; *P*=.02) but not heterozygotes (OR,1.9; 95% CI, 0.96–3.6; *P*=.07).

Conclusion The real-world incidences of ARIA-E (5.5%) and H (11.5%) were lower than those in the Clarity AD trial (12.6% and 17.3%) and pooled phase 3 trials (9.5% and 17.8%). In real-world settings, incidence varied by geographic region (lowest in Asian cohorts), and MRI protocol, and the risk of ARIA-E increased with APOE ε4 gene dose, supporting standardized MRI surveillance and APOE ε4–informed risk stratification for the safe real-world use of lecanemab.

Keywords:

Lecanemab; Alzheimer's Disease; Real-world experience; Safety; Amyloid-related imaging abnormalities

Introduction

Anti-amyloid monoclonal antibodies have emerged as disease-modifying therapies for Alzheimer's disease (AD), representing a major shift from conventional treatments [1]. Among these, lecanemab significantly reduced amyloid burden and slowed cognitive and functional decline in the Phase 3 Clarity AD trial, leading to full FDA approval in 2023 [2]. Despite its clinical benefits, anti-amyloid therapies are closely associated with amyloid-related imaging abnormalities (ARIA), which have become the most common and important treatment-related adverse event; in the Phase 3 Clarity AD trial, ARIA-edema or effusion (E) and ARIA-hemorrhage (H) occurred in a substantial proportion of lecanemab-treated patients [2-4]. Although many cases are asymptomatic and detected only through routine MRI, ARIA can manifest as headaches, confusion, visual disturbances, or focal neurological deficits. Furthermore, severe or recurrent ARIA episodes frequently lead to treatment interruption or permanent discontinuation, highlighting its clinical significance [3].

Since the introduction of lecanemab into routine clinical practice, multiple real-world studies have evaluated its efficacy and safety [5, 6]. Because real-world studies include broader patient populations and reflect routine clinical management, the incidence and clinical characteristics of ARIA may differ from those observed in randomized controlled trials [7]. Although several systematic reviews have summarized the overall efficacy and safety of lecanemab, relatively few have specifically focused on ARIA in real-world settings [8]. Furthermore, earlier evidence was derived predominantly from Western cohorts because only limited real-world data from Asian countries were available [8]. Recently, however, multiple real-world studies from Asian institutions have been published, providing a substantially expanded evidence base. Whether ARIA incidence varies according to geographic region or imaging protocols in routine clinical practice remains uncertain.

Therefore, we performed a systematic review and meta-analysis to evaluate the incidence of ARIA in patients with mild cognitive impairment (MCI) due to AD or AD dementia treated with lecanemab in clinical practice. Additionally, we assessed the incidence of ARIA according to geographic region, APOE ε4 status, and MRI protocol to provide a comprehensive understanding of ARIA during real-world lecanemab treatment.

Methods

This systematic review and meta-analysis were conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [9-11].

Literature search

A systematic literature search of PubMed and Embase databases was performed to identify published real-world studies of ARIA in patients treated with lecanemab. The search was conducted using the following search terms: ((amyloid-related imaging abnormalities) OR (ARIA)) AND (lecanemab). We included articles published up to April 28, 2026.

Eligibility criteria

The inclusion criteria were as follows: (1) real-world studies of lecanemab used in patients with MCI due to AD or AD dementia; and (2) studies providing sufficient data to evaluate adverse events, specifically the incidence of ARIA-E or ARIA-H. The exclusion criteria were as follows: (1) conference abstracts, review articles, letters, editorials, comments, notes, short surveys, or book chapters; (2) studies not conducted in real-world settings; (3) studies with overlapping patient cohorts; (4) summaries of other studies; and (5) studies investigating anti-amyloid immunotherapies other than lecanemab, such as aducanumab or donanemab.

Data Extraction

The number of patients who developed ARIA-E and ARIA-H among those treated with lecanemab was collected from eligible studies. Information on APOE ε4 carrier status (including noncarriers and homozygous or heterozygous APOE ε4 carriers), AD severity, study regions (Asia, Europe, or the United States), MRI evaluation protocols (sequence type and magnetic field strength), ARIA characteristics (symptomatic ARIA, isolated ARIA-H, ARIA-H subtypes, concurrent ARIA-E and ARIA-H, recurrent ARIA, and ARIA severity), and treatment discontinuation due to ARIA was also extracted.

Two reviewers (S.Y.J. and M.J.P.) performed data extraction using a standardized form, and a third reviewer (C.H.S.) verified the collected data; any disagreements were resolved through consensus.

Quality assessment of the included studies

The quality assessment of the studies included was independently assessed by two reviewers (S.Y.J. and M.J.P.), with any disagreements resolved through discussion. Assessment was performed using a modified Newcastle-Ottawa Scale (NOS), which evaluates three domains: selection, comparability, and outcome. Because most of the included real-world studies were single-arm cohort studies, the three control-related items within the selection and comparability domains were omitted, resulting in maximum scores of 9 for comparative and 6 for single-arm cohorts. Study quality was categorized as high (7–9 for comparative studies; 5–6 for single-arm cohorts), moderate (4–6; 3–4), or low (0–3; 0–2), respectively.

Statistical Methods

The primary outcome was the pooled proportion of patients who developed ARIA-E or ARIA-H during real-world use of lecanemab in patients with MCI due to AD or AD dementia. The secondary outcomes included the proportion of patients with (1) isolated ARIA-H, (2) concurrent ARIA-E and ARIA-H, (3) symptomatic ARIA, (4) severe ARIA, and (5) treatment discontinuation due to ARIA.

Subgroup analyses were performed according to study region (Asia, Europe, and the United States), MRI sequence, MRI field strength, and APOE ε4 carrier status. The subgroup classification of each study is provided in **Supplementary Table S1**; the single study from Israel was grouped with Europe. Pooled incidences of ARIA-E and ARIA-H were calculated using a random-effects model with logit-transformed proportions, and between-study variance was estimated using the restricted maximum-likelihood method [12]. To explore potential sources of heterogeneity, meta-regression was specifically applied to evaluate differences across study regions. For analyses based on APOE ε4 carrier status, pooled ORs with 95% CIs were calculated using a random-effects model. For the regional meta-regression analysis, regression coefficients were exponentiated and reported as ORs with 95% CIs. A sensitivity analysis was additionally performed by excluding studies that employed a dose-titration regimen to assess its potential influence on the pooled ARIA incidence and regional differences.

Statistical heterogeneity was evaluated using the Higgins inconsistency index (I^2) and Cochran's Q test, with I^2 values greater than 50% indicating substantial heterogeneity [13]. Publication bias was evaluated using funnel plot asymmetry and Egger's test, with a p-value of < 0.1 suggesting significant bias [14]. All statistical analyses were conducted using the "meta" package in R version 4.6.0 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Literature Search

The systematic search of PubMed and Embase identified 320 articles. After removing 79 duplicates, 212 studies that did not meet the inclusion criteria were excluded based on the title and abstract. The full texts of the remaining 29 studies were assessed, and 9 studies were excluded because they were review articles (n = 1), were based on spontaneous adverse-event reporting databases, lacked sufficient data to assess ARIA (n = 3), or had cohorts that overlapped with other studies included in our meta-analysis (n = 1). In addition, one eligible real-world study on ARIA was manually identified and included. Finally, 21 real-world studies were included in the meta-analysis (**Figure 1**) [15-35]. A total of 4,818 patients with available data on ARIA were analyzed.

Characteristics of Included Studies

Table 1 summarizes the characteristics of the 21 included studies, which were published between 2025 and 2026. The studies were conducted across six countries, including China (n = 8), the United States (n = 6), Japan (n = 4), and Italy, Israel, and Korea (n = 1, each). Most cohorts included patients with MCI due to AD or mild AD dementia. The mean patient age ranged from 62.5 to 75.3 years, and the proportion of apolipoprotein E (APOE) ε4 carriers ranged from 43.1% to 84.0%. When compared by region, the proportions of APOE ε4 carriers and homozygotes were higher in the United States than in Asian cohorts (carriers, 70.1% [459/655] vs 55.4% [2,232/4,030]; homozygotes, 16.9% [111/655] vs 11.2%

[450/4,030]) (P <.001). Additional characteristics of each study, including the MRI protocol and lecanemab regimen, are summarized in **Supplementary Table S1**. For ARIA-H assessment, SWI alone was used in nine studies, GRE alone in two, both SWI and GRE in three, and either SWI or GRE in two, while five studies did not report the sequence. MRI field strength was reported in 13 studies (3T, n = 7; 1.5T, n = 2; 3T or 1.5T, n = 3; 3T and 7T, n = 1).

With respect to the lecanemab administration regimen, all 21 studies administered the manufacturer-recommended dose of 10 mg/kg body weight every two weeks, of which two studies employed a dose-titration protocol before reaching the full dose **(Supplementary Table S1)** [25, 35].

Quality Assessment

The quality assessment of the 21 included studies is summarized in **Figure 2**. All studies were rated as high methodological quality on the modified NOS. Each of the 19 single-arm cohorts attained the maximum of 6 stars, whereas the two comparative cohort studies received 7 and 9 of a possible 9 stars [23, 24]. The two unmet items were the selection of the non-exposed cohort and the adequacy of follow-up. No study was rated as moderate or low quality.

Pooled Incidence of Any ARIA, ARIA-E, and ARIA-H

The overall pooled incidence of any ARIA was 14.5% (95% confidence interval [CI]:

11.8–17.7%) based on a random-effects model, with substantial heterogeneity (I^2 = 86%) (**Table 2**). The overall pooled incidence of ARIA-E was 5.5% (95% CI: 3.9–7.7%; I^2 = 83%). The pooled incidence of symptomatic ARIA was 2.1% (95% CI: 1.4–3.2%; I^2 = 13%), and that of severe ARIA was 1.3% (95% CI: 0.8–2.0%; I^2 = 0%). The overall pooled incidence of ARIA-H was 11.5% (95% CI: 9.0–14.4%; I^2 = 86%). The pooled incidence of isolated ARIA-H was 8.5% (95% CI: 6.5–11.0%; I^2 = 79%) (**Table 2**). Study-level incidences of each ARIA outcome are provided in **Supplementary Table S2**.

Subgroup Analysis According to Geographic Region

The pooled incidence of ARIA varied across geographic regions (**Table 2, Supplementary Table S2).** The incidence of any ARIA was highest in the USA (21.6%; 95% CI: 17.9–25.8%; I^2 = 0%), followed by Europe (18.0%; 95% CI: 11.5–27.1%; I^2 = 0%) and Asia (12.9%; 95% CI: 10.1–16.2%; I^2 = 82%), with a significant difference among regions (P = .003). A similar statistically significant (P < .001) pattern was observed for ARIA-E, which was higher in the USA (11.5%; 95% CI: 8.4–15.5%; I^2 = 23%) than in Asia (4.2%; 95% CI: 2.9–6.0%; I^2 = 63%) and Europe (3.7%; 95% CI: 1.3–10.0%; I^2 = 0%) (**Figure 3**). The incidence of ARIA-H was 14.8% (95% CI: 9.0–23.4%; I^2 = 0%) in Europe, 14.1% (95% CI: 9.8–19.9%; I^2 = 58%) in the USA, and 10.0% (95% CI: 7.3–13.6%; I^2 = 87%) in Asia, although the difference among regions was not significant (test for subgroup differences, P = .249) (**Figure 4**). Symptomatic ARIA was most frequent in the USA (3.7%; 95% CI: 2.2–6.2%), with a significant difference among regions (P = .028), whereas isolated ARIA-H (most frequent in the USA at 9.0%; 95% CI: 5.8–13.6%) did not differ significantly across regions (P = .919).

Severe ARIA was uncommon across all regions (≤1.7%).

In a sensitivity analysis excluding the two studies that employed a dose-titration regimen,[25, 35] the pooled incidence of any ARIA was 14.3% (95% CI: 11.5–17.7%; I^2 = 87%) and that of ARIA-E was 5.4% (95% CI: 3.7–7.8%; I^2 = 84%). Any ARIA was highest in the USA (21.9%) and lowest in Asia (12.4%; P = .001), and ARIA-E was higher in the USA (11.7%) than in Asia (4.0%; P < .001).

Subgroup Analysis According to MRI Field Strength and Sequence

In subgroup analyses according to MRI magnet strength, the pooled incidence of any ARIA was 21.3% (95% CI: 16.2–27.5%; I^2 = 0%) at 1.5T, 15.5% (95% CI: 12.0–19.9%; I^2 = 45%) at 3T, 16.9% (95% CI: 9.0–27.7%) for 3T or 1.5T, and 6.9% (95% CI: 2.3–15.5%) for combined 7T and 3T; however, the difference among magnet strength subgroups was not significant (P = .049) (**Table 2**). The corresponding pooled incidences of ARIA-E were 14.7% (95% CI: 10.4–20.3%; I^2 = 0%) at 1.5T, 4.3% (95% CI: 2.9–6.2%; I^2 = 0%) at 3T, 7.0% (95% CI: 4.3–11.2%; I^2 = 2%) for combined 3T and 1.5T, and 0.0% (95% CI: 0.0–5.0%) for combined 7T and 3T, with a significant difference among subgroups (P < .001).

In subgroup analyses according to MRI sequence, the pooled incidence of ARIA-H was 17.3% (95% CI: 13.4–21.9%; I^2 = 0%) for combined GRE and SWI, 13.6% (95% CI: 8.3–21.7%; I^2 = 0%) for GRE, 11.8% (95% CI: 3.8–31.4%; I^2 = 88%) for GRE or SWI, and 10.7% (95% CI: 8.1–14.1%; I^2 = 54%) for SWI, although the difference among sequence subgroups was not significant (P = 0.09) (**Figure 5**). The pooled incidence of isolated ARIA-H was 12.6% (95% CI: 7.5–20.5%; I^2 = 0%) for GRE, 9.6% (95% CI: 5.3–16.8%; I^2 = 44%)

for combined GRE and SWI, 9.0% (95% CI: 6.2–12.9%; I^2 = 56%) for SWI, and 5.0% (95% CI: 0.3–45.9%; I^2 = 86%) for GRE or SWI, although this difference was not significant (*P* = .71).

Pooled Incidences and Odds Ratios of ARIA According to APOE ε4 Carrier Status

ARIA incidence according to APOE ε4 genotype is summarized in **Table 3**. The pooled incidence of ARIA-E was 17.6% (95% CI: 9.9–29.4%; I^2 = 28%) in homozygotes, 6.9% (95% CI: 4.0–11.5%; I^2 = 40%) in heterozygotes, and 7.7% (95% CI: 5.3–10.9%; I^2 = 0%) in noncarriers. The pooled incidence of ARIA-H was 19.9% (11.4–32.4%; I^2 = 43%) in homozygotes, 12.2% (95% CI: 9.7–15.3%; I^2 = 0%) in heterozygotes, and 11.1% (7.9–15.4%; I^2 = 24%) in noncarriers.

In the pooled OR analysis, APOE ε4 homozygotes had significantly higher odds of ARIA-E than heterozygotes (OR: 3.1; 95% CI: 1.7–5.7; $P < 0.001$) and noncarriers (OR: 3.3; 95% CI: 1.7–6.4; $P < 0.001$) (Table 4). For ARIA-H, homozygotes had significantly higher odds than noncarriers (OR: 2.4; 95% CI: 1.1–4.9; P = .02), whereas the difference from heterozygotes was not significant (OR: 1.9; 95% CI: 1.0–3.6; P = .07).

Discussion

In this systematic review and meta-analysis of 21 real-world studies comprising 4,818 patients treated with lecanemab, the pooled incidence of any ARIA was 14.5%, with ARIA-E occurring in 5.5% and ARIA-H in 11.5% of patients. Symptomatic and severe ARIA were

2.1% and 1.3%, respectively. In the subgroup analysis, the incidence of ARIA varied by geographic region, highest in the United States and lowest in Asia. The incidence of ARIA differed according to MRI field strength. The risk of ARIA-E increased with APOE ε4 gene dose, whereas the odds of ARIA-H were higher in homozygotes than in noncarriers but did not show a consistent gene-dose relationship. After review of the literature, this is the first meta-analysis to focus specifically on real-world ARIA associated with lecanemab and to incorporate the recently expanded evidence base from Asian cohorts.

The real-world incidences of ARIA-E (5.5%) and ARIA-H (11.5%) were substantially lower than those reported in the Clarity AD trial (ARIA-E, 12.6%; ARIA-H, 17.3%) and in pooled analyses of phase 3 randomized trials of lecanemab (ARIA-E, 9.5%; ARIA-H, 17.8%) [2, 36]. This discrepancy is more likely methodological than biological. ARIA detection in routine practice may be less standardized and complete compared to the centralized expert review used in the trial, potentially leaving subtle or asymptomatic lesions unrecognized in real-world cohorts. Rather than indicating a genuinely lower biological risk of ARIA, the lower real-world incidence may reflect differences in patient selection and the imaging surveillance, underscoring that trial-derived incidence figures should be interpreted with caution when counseling patients in clinical practice.

In our subgroup analysis according to geographic region, the incidence of ARIA was highest in the United States (any ARIA, 21.6%; ARIA-E, 11.5%) and lowest in Asia (any ARIA, 12.9%; ARIA-E, 4.2%). A similar pattern was observed for symptomatic and severe ARIA, both of which were less frequent in Asian than in other cohorts. A comparable regional trend was previously noted in the Asian subgroup analysis of the Clarity AD trial [37]. The reasons for the lower ARIA incidence in Asia remain incompletely understood. One

plausible contributor is the lower frequency of the APOE ε4 allele in Asian compared to in Western populations. Consistent with this, both the proportion of APOE ε4 carriers (55.4% vs 70.1%) and, in particular, that of homozygotes (11.2% vs 16.9%) were lower in Asian than in the United States cohorts, respectively. Given the strong gene-dose relationship observed in our analysis, this lower ε4 burden may partly account for the lower ARIA-E incidence in Asian cohorts. In addition, the amyloid-promoting effect of APOE ε4 itself may also be attenuated in Asian populations [38], although its association with overall Alzheimer disease risk appears stronger in East Asian populations [39]. A further hypothesis relates to baseline amyloid burden, which tends to be lower in Asian than in Western populations, as a higher baseline amyloid load has been proposed to increase ARIA risk [40]. Consistent with this, a higher baseline occipital amyloid burden was associated with increased ARIA-E risk in donanemab-treated participants [41]. In the Clarity AD trial of lecanemab, however, ARIA-E incidence did not show a clear dose-response relationship across baseline amyloid-PET centiloid tertiles, rendering this explanation less certain for lecanemab [42]. Furthermore, dose titration may also influence ARIA incidence; in our dataset, two studies reported a dose-titration regimen, but ARIA incidence remained lower in Asian cohorts (any ARIA, 12.4%; ARIA-E, 4.0%) than in the USA cohorts (any ARIA, 21.9%; ARIA-E, 11.7%) after their exclusion [25, 35]. Overall, ARIA risk is likely influenced by additional confounding factors; in our data, region was confounded with MRI protocol and cohort size. Therefore, these regional differences warrant further study with controlled imaging protocols and adjustment for such confounders.

Although the pooled incidence of ARIA-H varied numerically across imaging protocols, the difference was not statistically significant. Given the greater intrinsic sensitivity of SWI

over GRE for microhemorrhage and superficial siderosis, SWI-containing protocols would be expected to yield a higher incidence than GRE alone [43, 44]. Contrary to this expectation, SWI alone showed a lower incidence than GRE alone (10.7% vs. 13.6%), whereas the combined GRE and SWI protocol showed the highest incidence (17.3%). This pattern likely reflects between-study differences rather than a genuine sequence-sensitivity effect, as studies that specified and combined multiple susceptibility-based sequences may also have applied more detailed and systematic image review, thereby detecting more ARIA-H. In the subgroup analysis by field strength, the higher pooled incidence of ARIA-E at 1.5T than at 3T (14.7% vs. 4.3%) similarly runs counter to the expectation that higher field strength improves lesion conspicuity and is most likely confounded by the small number and regional distribution of 1.5T cohorts rather than reflecting a true field-strength effect. An additional, 1.5T scanners are often more readily available for urgent or emergency imaging than 3T scanners, symptomatic patients may be more likely to undergo immediate 1.5T imaging, whereas 3T is more commonly used for scheduled, routine surveillance MRI in asymptomatic patients. This referral pattern could enrich the 1.5T subgroup with symptomatic patients who inherently have a higher probability of ARIA, rather than reflecting a true difference in diagnostic sensitivity between field strengths. These subgroup findings, however, are limited by the small number of contributing studies and warrant cautious interpretation. Taken together, these findings indicate that the apparent incidence of ARIA is partly protocol-dependent, underscoring the need for standardized, sensitive MRI protocols to ensure consistent detection and valid cross-study comparison in the era of anti-amyloid therapy [45, 46].

Consistent with randomized trials, the risk of ARIA-E increased with APOE ε4 gene dose, with homozygotes showing about three-fold higher odds than heterozygotes (OR, 3.1) and

noncarriers (OR, 3.3). This association was weaker than in phase 3 trials, which reported an OR of approximately 5.6 for homozygotes versus noncarriers, possibly because homozygous patients are excluded or treated more cautiously in practice [36]. The APOE ε4 allele promotes cerebral amyloid angiopathy and blood–brain barrier disruption, predisposing to edema and microhemorrhage during amyloid clearance [47]. These findings support pretreatment APOE genotyping and risk counseling, in line with the European Medicines Agency's recommendation to exclude APOE ε4 homozygotes [48]. The association between APOE ε4 and ARIA-H was weaker, reaching significance only for homozygotes versus noncarriers (OR, 2.4), suggesting that hemorrhagic ARIA may also depend on additional factors such as older age or pre-existing small vessel disease. Given the predominance of asymptomatic, isolated ARIA-H and the low incidence of symptomatic (2.1%) and severe (1.3%) ARIA, integrating APOE genotype, baseline microhemorrhage burden, and standardized surveillance MRI into a structured monitoring pathway may optimize the benefit–risk balance of lecanemab in real-world practice.

Limitations

Our study has several limitations. First, substantial statistical heterogeneity was observed for most pooled estimates (I^2 up to 88%), reflecting differences in patient populations, follow-up duration, MRI protocols, and ARIA ascertainment across studies. Second, several subgroups, particularly the European and Korean cohorts, were represented by only one or a small number of studies. Region, MRI field strength, pulse sequence, and the clinical indication for imaging were mutually confounded, limiting causal interpretation of the subgroup differences. Third, the included studies varied in the frequency and timing of

surveillance MRI, which directly affects ARIA detection, particularly for transient ARIA-E and asymptomatic ARIA-H. Fourth, our analyses were based on cohort-level rather than individual patient data, precluding adjustment for confounders and a more granular evaluation of risk factors and severity. Fifth, differences in treatment eligibility criteria across regions could not be accounted for in our analysis. The United States and Asian cohorts generally did not restrict enrollment based on APOE ε4 homozygosity, whereas the European cohorts, consistent with the European Medicines Agency's recommendation, excluded APOE ε4 homozygotes. This difference in inclusion criteria may partly account for the lower ARIA-E incidence observed in Europe, rather than a true regional difference in biological risk. Finally, the relatively short interval since lecanemab's approval means that long-term and cumulative ARIA risk could not be fully captured.

Conclusions

In conclusion, this real-world meta-analysis showed a pooled incidence of any ARIA of 14.5%, with ARIA-E and ARIA-H occurring in 5.5% and 11.5% of lecanemab-treated patients, respectively, which was lower than the incidences reported in the Clarity AD trial. Our study showed that ARIA incidence varied by geographic region (lowest in Asian cohorts) and by MRI field strength, and the risk of ARIA-E increased with APOE ε4 gene dose. These findings highlight the importance of standardizing MRI surveillance protocols and employing APOE-informed risk stratification for the safe real-world clinical use of lecanemab.

List of abbreviations

AD, Alzheimer's disease

APOE, Apolipoprotein E

ARIA, Amyloid-related imaging abnormalities

ARIA-E, Amyloid-related imaging abnormalities-edema or effusion

ARIA-H, Amyloid-related imaging abnormalities-hemorrhage

CI, confidence intervals

GRE, gradient-recalled echo

SWI, susceptibility-weighted imaging

MCI, Mild cognitive impairment

OR, odds ratio

Declarations

Ethics approval and consent to participate

Not applicable. This study is a systematic review and meta-analysis of previously published, de-identified, aggregate-level data extracted from publicly available articles; no new patient data were collected and no individual participants were enrolled by the authors. Ethical approval and participant consent, where required, were obtained by the investigators of the original studies included in this meta-analysis.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analysed during this study are included in this published article and its supplementary tables (Tables 1–4). The full data-extraction spreadsheet compiled from the included studies is available from the corresponding author on reasonable request.

Competing interests

R.Y.H. has served as a consultant for Servier, Telix, and Merit-CRO, and on the scientific advisory board for Vysioneer. J.M.R. has served as a consultant for TMA Precision Medicine

and Wellumio. C.H.S. has served as a medical consultant for Neurophet. All other authors declare that they have no competing interests.

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Authors' contributions

S.Y.J. and C.H.S. conceived and designed the study. S.Y.J. performed the literature search. S.Y.J. and M.J.P. performed study selection and data extraction, and C.H.S. verified the extracted data and adjudicated disagreements. S.Y.J. performed the statistical analysis. S.Y.J. drafted the manuscript. H.J., J.S.L., S.G., S.F., J.N.F., M.L., R.Y.H., and J.M.R. contributed to data interpretation and critically revised the manuscript for important intellectual content. C.H.S. supervised the study and is the guarantor. All authors read and approved the final manuscript.

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Not applicable.

Reference

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Tables

Table 1. Study and patient characteristics within the selected studies.

Study (publication year)	Country	Institution, inclusion period	Inclusion period	Patient characteristics				
				ARIA-assessed, n	AD severity	Mean age	F:M	APOE-4 carrier (%)[hetero/homo]
Agosta F, et al. (2026)[15]	Italy	IRCCS San Raffaele Scientific Institute	Sep. 2024 – Oct. 2025	9	MCI, mild	67.8	6:3	78.0 [78.0/0.0]
Bregman N, et al. (2025)[16]	Israel	Tel Aviv Medical Center	Nov. 2023 – Jan. 2025	86	MCI, mild	72.0	53:33	53.0 [53.0/0.0]
Chen S, et al. (2025)[17]	China	West China Hospital, Sichuan University	N/A	68	MCI–severe	68.7	50:18	61.8 [50.0/11.8]
Curd BC, et al. (2026)[18]	USA	University of Utah	Apr. 2023 – Jul. 2025	70	MCI, mild	72.5	31:39	70.0 [51.0/19.0]
Iwata A, et al. (2026)[19]	Japan	Multicenter (nationwide)	Dec. 2023 – Jul. 2025	2672	MCI, mild	74.3	1752:920	55.1 [44.1/11.0]
Kang W, et al. (2025)[20]	China	Ruijin Hospital (Hainan Branch), Shanghai Jiao Tong University	Nov. 2023 – ongoing	64	MCI, mild	68.0 (median)	32:32	67.2 [62.5/4.7]
Leng L, et al. (2026)[21]	China	Multicenter (8 sites, Zhejiang)	Sep. 2024 – Mar. 2025	176	MCI, mild–moderate	67.9	135:55	61.4 [48.9/12.5]
Li LL, et al. (2025)[22]	China	Huashan Hospital, Fudan University	Jun. 2024 – May 2025	321	MCI, mild–moderate	68.1	217:104	56.5 [44.0/12.5]
Liao W, et al. (2026)[23]	China	Multicenter (21 sites; lead: Second Affiliated Hospital of Guangzhou Medical University)	Jun. 2024 – NA	261	MCI, mild–moderate	69.7	154:107	47.9 [40.2/7.7]
Mao C, et al. (2026)[24]	China	Peking Union Medical College Hospital	Jul. 2024 – Jul. 2025	42	MCI, mild	66.4	18:11	62.0 [37.9/24.1]
Mervosh N, et al. (2025)[25]	USA	Park Avenue Neurology	Jan. 2021 – Dec. 2023	19	MCI, mild	72.0	13:6	84.0 [42.0/42.0]
Noguchi-Shinohara M, et al. (2025)[26]	Japan	Kanazawa University Hospital	Jan. 2024 – Oct. 2025	71	MCI, mild	72.7	68:32	68.0 [52.0/16.0]

O'Donnell AJ, et al. (2025)[27]	USA	Multicenter (4 VHA centers, unspecified)	Oct. 2023 – Jul. 2024	32	MCI, mild	75.3	0:32	50.0 [50.0/0.0]
Otani K, et al. (2026)[28]	Japan	Kakogawa Central City Hospital	May 2024 – Jan. 2026	38	MCI, mild	NA	NA	NA
Paczynski M, et al. (2025)[29]	USA	Washington University Memory Diagnostic Center	Aug. 2023 – Dec. 2024	194	MCI, very mild–mild	74.4	117:117	60.8 [52.6/8.2]
Rosenbloom M, et al. (2025)[30]	USA	UW Medicine Memory and Brain Wellness Center	Feb. 2023 – Dec. 2024	165	MCI, mild	72.0	110:55	70.0 [58.0/12.0]
Shang J, et al. (2025)[31]	China	Second Affiliated Hospital of Zhejiang University	Jun. 2024 – Aug. 2025	58	MCI, mild	65.5	51:25	64.5 [44.7/19.7]
Shields LBE, et al. (2026)[32]	USA	Norton Neuroscience Institute Memory Center	Aug. 2023 – Aug. 2025	175	MCI, mild	73.0	127:60	82.1 [51.3/30.8]
Shimasaki R, et al. (2026)[33]	Japan	Tokyo Metropolitan Institute for Geriatrics and Gerontology	Dec. 2023 – Nov. 2025	120	MCI, mild	74.2	89:31	49.2 [34.0/15.0]
Zhang W, et al. (2026)[34]	China	Xiangya & Second Xiangya Hospitals, Central South University	Jun. 2024 – Jul. 2025	72	MCI	62.5	48:24	43.1 [38.9/4.2]
Jang H, et al. (2026)[35]	Korea	Asan Medical Center	Dec. 2024 – Oct. 2025	105	MCI	71.3	46:66	58.0 [48.0/10.0]

Note. AD, Alzheimer's disease; MCI, mild cognitive impairment

Table 2. Results of subgroup analysis of ARIA incidence stratified by geographic region

Study name	Any ARIA	ARIA-E	ARIA-H	Symptomatic ARIA	Isolated ARIA-H	Severe ARIA
Overall incidence (%) [95% CI]	14.5 [11.8–17.7], I^2=86%	5.5 [3.9–7.7], I^2=83%	11.5 [9.0–14.4], I^2=86%	2.1 [1.4–3.2], I^2=13%	8.5 [6.5–11.0], I^2=79%	1.3 [0.8–2.0], I^2=0%
Subgroup analysis						
Asia	12.9 [10.1–16.2], I^2=82%	4.2 [2.9–6.0], I^2=63%	10.0 [7.3–13.6], I^2=87%	1.5 [0.9–2.3], I^2=0%	8.3 [5.8–11.6], I^2=84%	0.9 [0.5–1.7], I^2=0%
Europe	18.0 [11.5–27.1], I^2=0%	3.7 [1.3–10.0], I^2=0%	14.8 [9.0–23.4], I^2=0%	1.9 [0.4–8.8], I^2=0%		1.7 [0.2–12.9], I^2=16%
USA	21.6 [17.9–25.8], I^2=0%	11.5 [8.4–15.5], I^2=23%	14.1 [9.8–19.9], I^2=58%	3.7 [2.2–6.2], I^2=24%	9.0 [5.8–13.6], I^2=53%	1.7 [0.9–3.0], I^2=0%
GRE and SWI			17.3 [13.4–21.9], I^2=0%		9.6 [5.3–16.8], I^2=44%	
GRE or SWI			11.8 [3.8–31.4], I^2=88%		5.0 [0.3–45.9], I^2=86%	
SWI			10.7 [8.1–14.1], I^2=54%		9.0 [6.2–12.9], I^2=56%	
GRE			13.6 [8.3–21.7], I^2=0%		12.6 [7.5–20.5], I^2=0%	
1.5T	21.3 [16.2–27.5], I^2=0%	14.7 [10.4–20.3], I^2=0%				
3T	15.5 [12.0–19.9], I^2=45%	4.3 [2.9–6.2], I^2=0%				
3T or 1.5T	16.9 [9.0–27.7]	7.0 [4.3–11.2], I^2=2%				
7T and 3T	6.9 [2.3–15.5]	0.0 [0.0–5.0]				

Table 3. Results of subgroup analysis of ARIA incidence according to APOE ε4 carrier status

Study name	ARIA-E			ARIA-H		
	Homozygote	**Heterozygote**	**Noncarrier**	**Homozygote**	**Heterozygote**	**Noncarrier**
Overall incidence (%) [95% CI]	17.6 [9.9–29.4], I^2=28	6.9 [4.0–11.5], I^2=40	7.7 [5.3–10.9], I^2=0	19.9 [11.4–32.4], I^2=43	12.2 [9.7–15.3], I^2=0	11.1 [7.9–15.4], I^2=24
Agosta F, et al.[15]	—	0.0 [0.0–41.0]	0.0 [0.0–84.2]	—	—	—
Curd BC, et al.[18]	—	—	—	46.2 [19.2–74.9]	11.1 [3.1–26.1]	19.0 [5.4–41.9]
Jang H, et al.[35]	27.3 [6.0–61.0]	2.0 [0.0–10.4]	4.7 [0.6–15.8]	18.2 [2.3–51.8]	17.6 [8.4–30.9]	7.0 [1.5–19.1]
Kang W, et al.[20]	0.0 [0.0–70.8]	—	—	0.0 [0.0–70.8]	—	—
Li LL, et al.[22]	7.9 [1.7–21.4]	4.1 [1.5–8.6]	5.9 [2.4–11.7]	10.5 [2.9–24.8]	10.1 [5.8–16.2]	12.6 [7.2–19.9]
Mervosh N, et al.[25]	0.0 [0.0–36.9]	12.5 [0.3–52.7]	0.0 [0.0–70.8]	12.5 [0.3–52.7]	0.0 [0.0–36.9]	0.0 [0.0–70.8]
Noguchi-Shinohara M, et al.[26]	8.3 [0.2–38.5]	0.0 [0.0–9.3]	4.8 [0.1–23.8]	16.7 [2.1–48.4]	18.4 [7.7–34.3]	0.0 [0.0–16.1]
O'Donnell AJ, et al.[27]	—	6.2 [0.2–30.2]	12.5 [1.6–38.3]	—	6.2 [0.2–30.2]	25.0 [7.3–52.4]
Paczynski M, et al.[29]	37.5 [15.2–64.6]	14.7 [8.5–23.1]	10.8 [4.8–20.2]	6.2 [0.2–30.2]	8.8 [4.1–16.1]	4.1 [0.8–11.4]
Shang J, et al.[31]	6.7 [0.2–31.9]	5.9 [0.7–19.7]	3.7 [0.1–19.0]	6.7 [0.2–31.9]	11.8 [3.3–27.5]	14.8 [4.2–33.7]
Shields LBE, et al.[32]	28.0 [12.1–49.4]	10.5 [5.2–18.5]	9.1 [3.0–20.0]	40.0 [21.1–61.3]	14.7 [8.3–23.5]	10.9 [4.1–22.2]
Zhang W, et al.[34]	0.0 [0.0–70.8]	0.0 [0.0–12.3]	0.0 [0.0–8.6]	33.3 [0.8–90.6]	7.1 [0.9–23.5]	4.9 [0.6–16.5]

Table 4. Pooled odds ratio for ARIA-E and ARIA-H according to APOE4 ε4 status

	ARIA-E		ARIA-H	
Subgroups	**OR [95% CI]**	**P value**	**OR [95% CI]**	**P value**
APOE ε4-heterozygote	REF		REF	
APOE ε4-homozygote	3.1 [1.7–5.7]	$P < 0.001$	1.9 [0.96–3.6]	$P = .07$
APOE ε4-noncarrier	REF		REF	
APOE ε4-homozygote	3.3 [1.7–6.4]	$P < 0.001$	2.4 [1.1–4.9]	$P = .02$

Note. OR, odds ratio; REF, reference group

Figures and Legends

Figure 1. Flow diagram depicting the study selection process

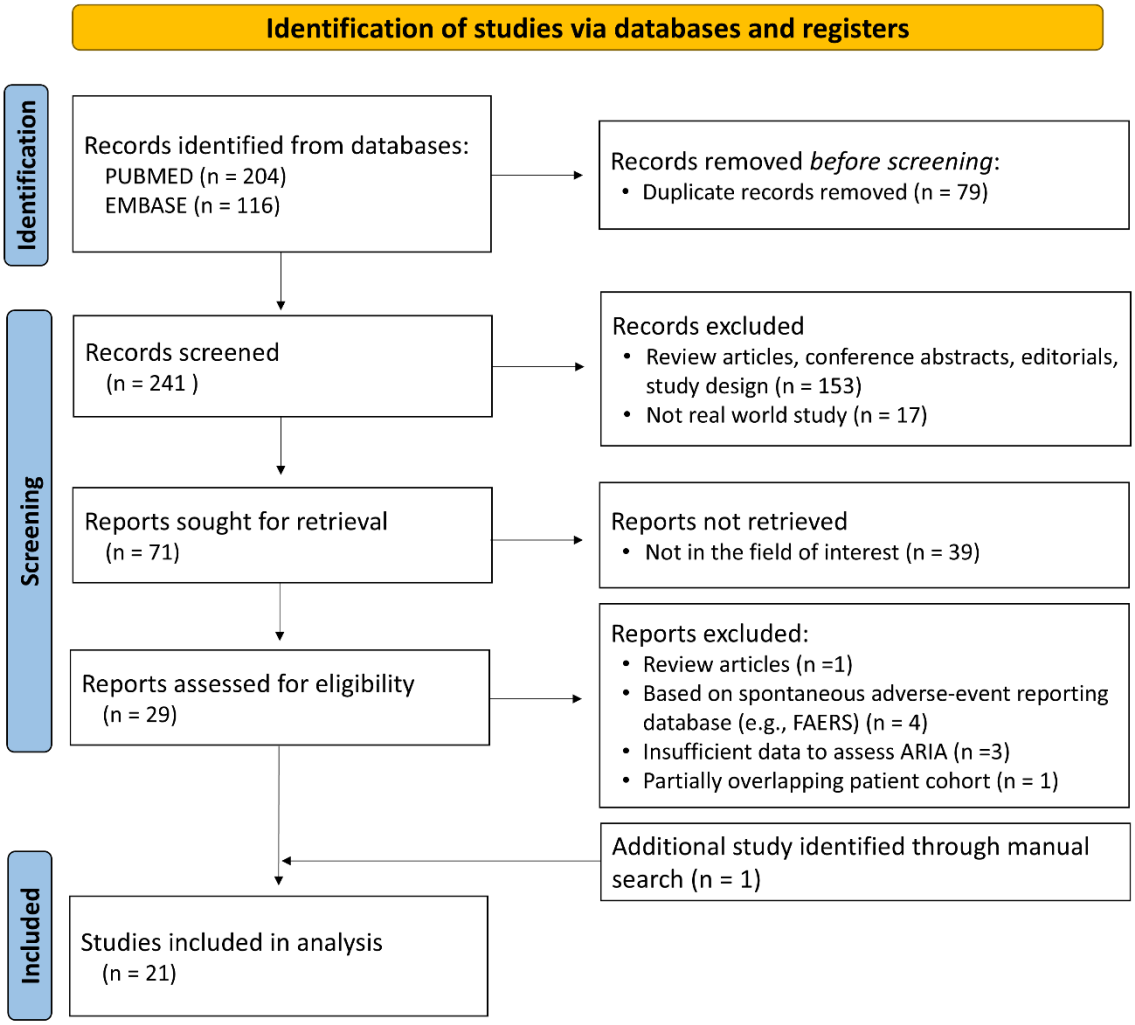


Figure 2. Quality assessment of the included studies using the Newcastle–Ottawa Scale



Methodological quality of the included studies assessed with the Newcastle–Ottawa Scale (NOS), across three domains: Selection (S1–S4), Comparability (C1–C2), and Outcome (O1–O3). Green (+), criterion met (star awarded); red (−), not met; gray, not applicable. Because most studies were single-arm, real-world cohorts, S2, C1, and C2 were not applicable and these studies were scored out of 6; comparative cohort studies were scored out of 9. "Total" shows stars awarded over the applicable maximum, and "Quality" the overall rating.

Note. NOS items: S1, representativeness of the exposed cohort; S2, selection of the non-exposed cohort; S3, ascertainment of exposure; S4, demonstration that the outcome of interest was not present at the start of the study; C1, comparability of cohorts for the most important factor; C2, comparability of cohorts for any additional factor; O1, assessment of outcome; O2, adequacy of follow-up duration

for outcomes to occur; O3, adequacy of follow-up of cohorts. Abbreviation: NOS, Newcastle–Ottawa Scale.

Figure 3. Forest plots showing the pooled incidence of ARIA-E, stratified by geographic region

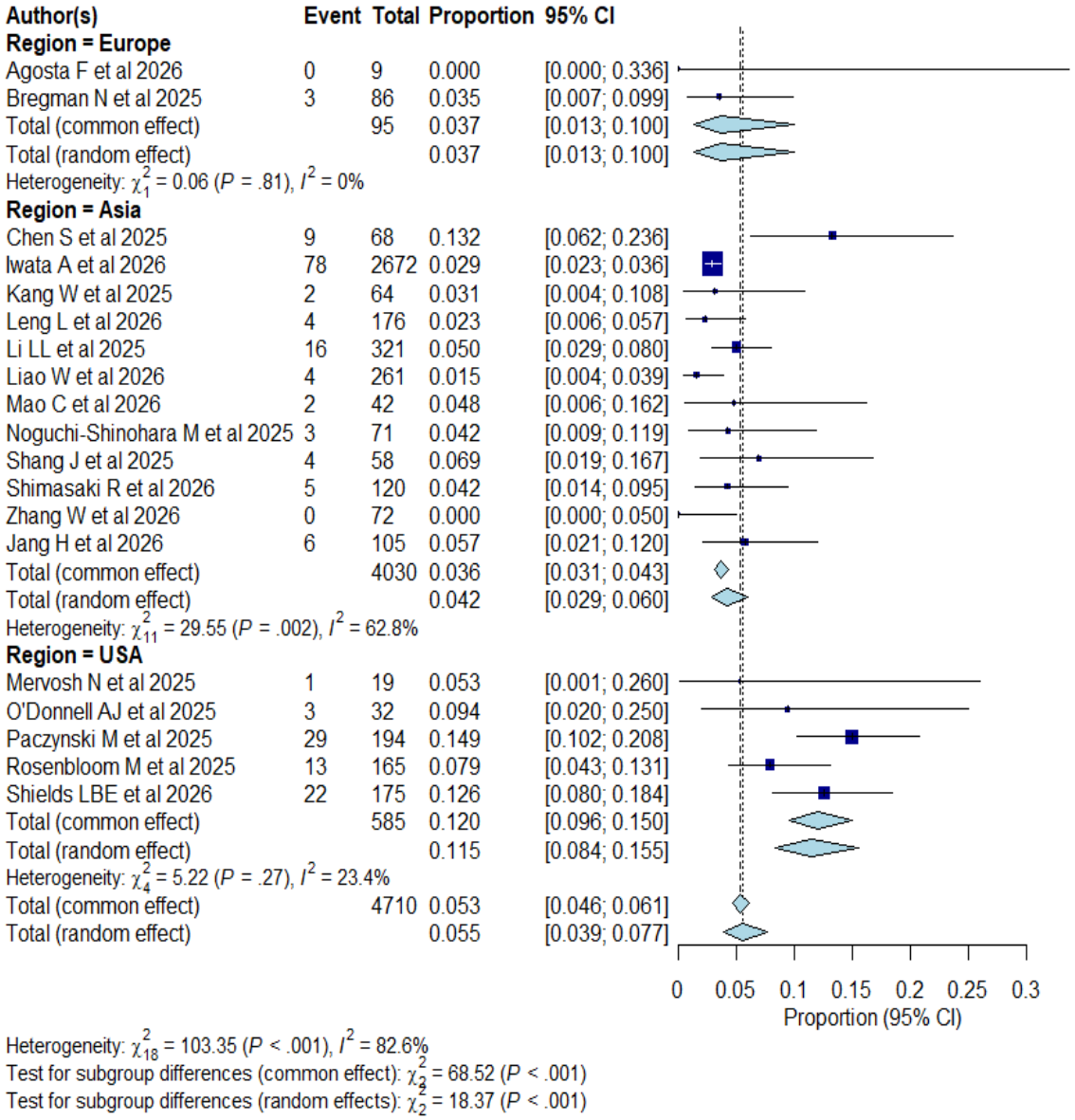


Figure 4. Forest plots showing the pooled incidence of ARIA-H, stratified by geographic region

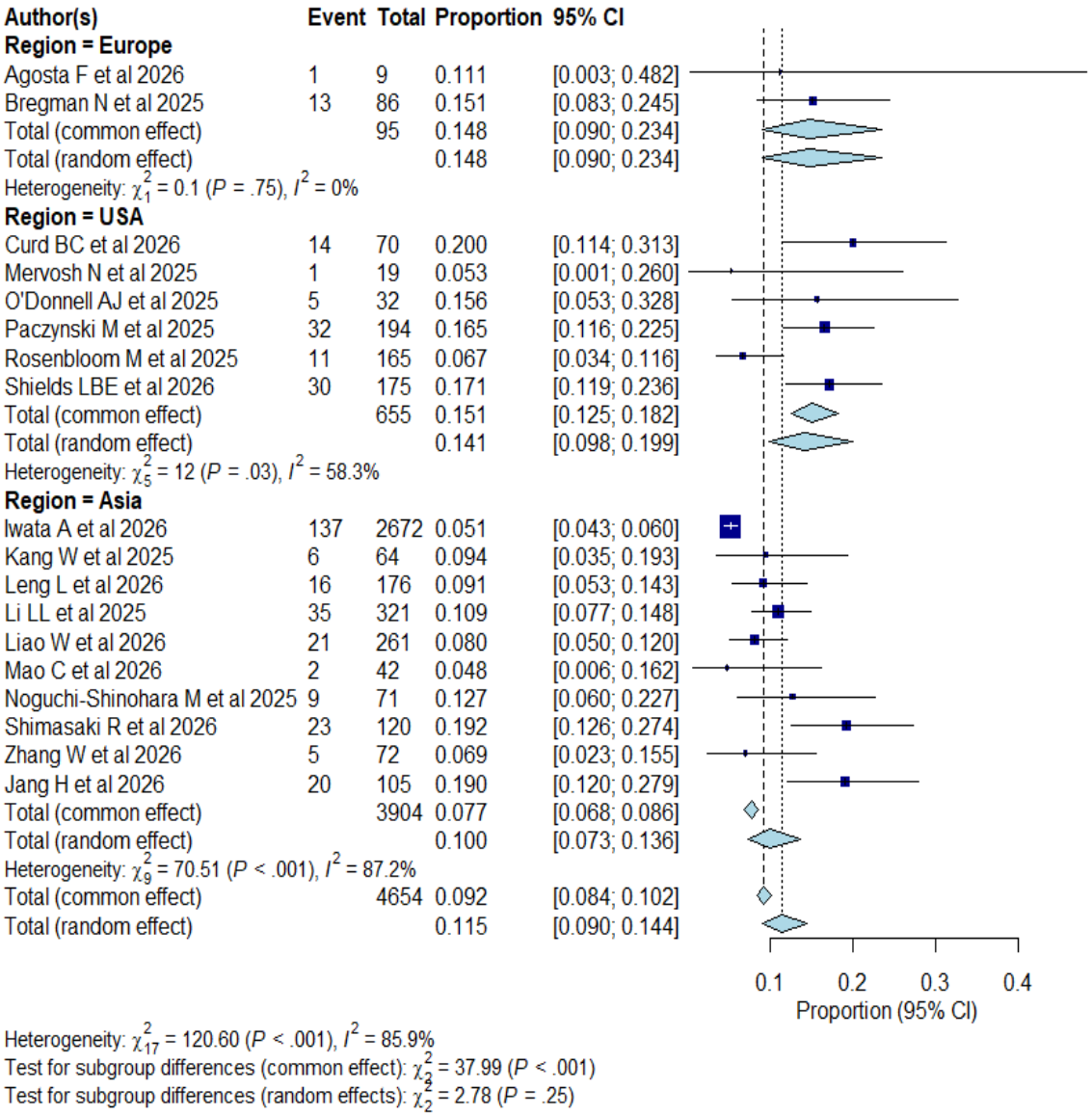
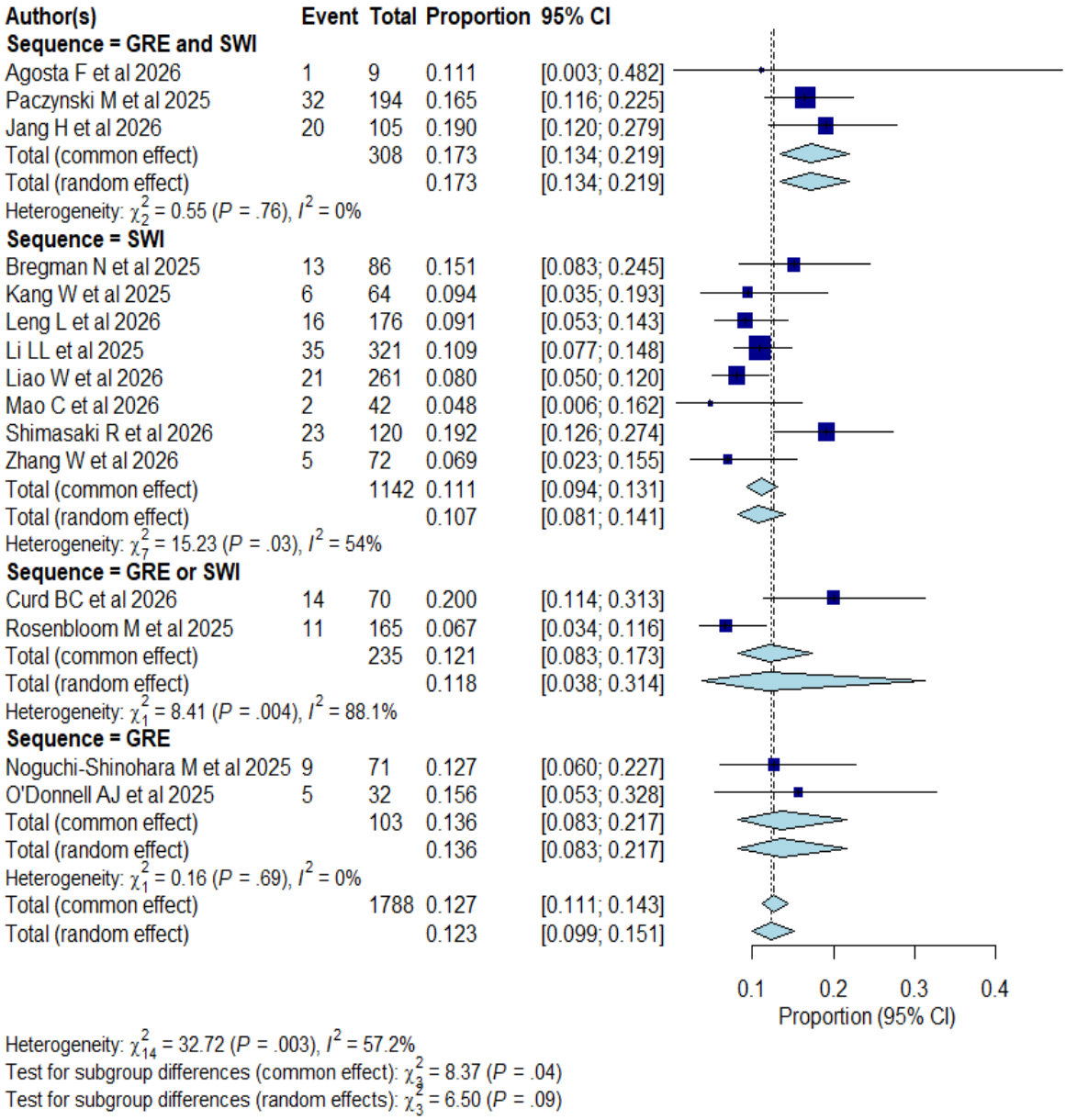


Figure 5. Forest plots showing the pooled incidence of ARIA-H, stratified by sequence



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