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Association between apolipoprotein E ε4 status and the risk of Alzheimer's disease: a meta-analysis

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Abstract

Background The apolipoprotein E ε4 (APOE ε4) status has a controversial role in predicting Alzheimer's disease (AD) factors. This meta-analysis assessed AD event risk in patients with APOE ε4 status.

Materials and methods The relevant English-language articles were identified by searching the Cochrane Library, EMBASE, and PubMed databases. The prognostic significance of APOE ε4 status in AD patients was examined on the basis of pooled hazard ratios (HRs).

Results A total of 22 studies published after 1987, including 571,800 patients, were included. Consequently, APOE ε4 status was a risk factor for disease-free survival (DFS, HR = 2.033; 95% confidence interval [CI] = 1.589–2.602; *P* = 0.000; I 2 = 93.1%) in patients with AD. Additionally, subgroup analysis suggested that the ROC curve was the main risk factor among patients with AD.

Conclusions AD patients with different events are managed via different methods; however, the present meta-analysis suggests an increased risk of AD events in patients with different APOE ε4 statuses.

Keywords APOE ε4 status, Alzheimer's disease, Prognosis, Meta-analysis

Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disease that affects people over the age of 65 and commonly results in progressive self-care ability loss, gradual memory loss, behavioral cognitive dysfunction, and neuropsychiatric abnormalities. This greatly affects quality of life in patients with AD [1, 2]. Owing to the increasing aging of the global population, an increasing number of patients with AD are being diagnosed annually, with AD becoming a primary public health challenge, resulting in tremendous burdens on patients, their families, and society.

Neurodegenerative alterations, which ultimately lead to dementia owing to AD, occur about 20 years before the appearance of clinical symptoms [3]. Currently, AD-related dementia cannot be cured; therefore, research

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should focus on AD in the prodromal and preclinical stages [4]. About two-thirds of patients with dementia are diagnosed with AD, with the characteristic features of neurofibrillary tau tangles and amyloid-β plaque deposition in neurons, glial inflammatory activation, decreased synaptic activity, and neuronal loss [5]. These cerebral pathological alterations occur owing to lifestyle and genetic factors [6]. An extended prodromal stage occurs in patients with AD, as evidenced by amyloid-β deposition initiating 15 years before dementia symptom occurrence in some people [7]. Therefore, disease risk must be accurately predicted in individuals for successful prevention and treatment of this disease.

Apolipoprotein E (apoE), a 34-kDa glycoprotein, is generated by brain astrocytes [8] and primarily by hepatocytes (> 90%) in the periphery [9]. Different morphologies of the APOE gene are present in humans, with three primary variants, namely, ε2, ε3, and ε4 [9], and the ε3 variant is significantly more common than the other two variants [10]. This may be due to the protective variant (rs10423769) distributed on chromosome 19 [11]. In recent studies, ε4 ancestry (European in comparison with African local genetic ancestry) has been demonstrated to affect APOE ε4 levels within the brain; in addition, such genetic heterogeneity may be related to the different ε4-induced risks of AD among populations of diverse races/ethnicities [12]. Thus, an increased risk of AD is related to low apoE expression in plasma [13]; moreover, the APOE ε4 genotype may be associated with increased risk through its relationship with low apoE expression in plasma [14, 15]. Nonetheless, the APOE ε4 status associated with prospective AD risk is still ambiguous. The status of the APOE ε4 gene accounts for the prospective risk of AD in certain studies [16–18]; however, such a relationship has not been reported in other studies, such as that by Elin Dybjer et al. (2023) [19]. Consequently, this study focused on evaluating the relationship between APOE ε4 status and AD risk.

Materials and methods

Registration

This study was reported following the guidelines of preferred reporting items of the systematic review and meta-analysis [20]. Owing to the retrospective nature of the study, ethical approval or patient consent was not needed.

Study screening process and eligibility criteria

Search strategy

The keywords ("APOE" OR "Apolipoprotein E") AND ("Alzheimer") were used to comprehensively search the PubMed, Cochrane Library, and Embase databases (2001–2023). The databases were searched repeatedly until no new relevant articles were obtained. To identify more qualified studies, the references of eligible articles were examined. Finally, two researchers evaluated these articles in line with our eligibility criteria.

Study screening

First, keywords were used to retrieve relevant articles, and their titles and abstracts were assessed to eliminate irrelevant articles. Second, the remaining articles were assessed using the eligibility criteria. The studies included (a) patients pathologically diagnosed with AD and (b) available or calculable hazard ratios (HRs) and corresponding 95% confidence intervals (CIs). The studies excluded were letters, meeting summaries, commentary articles, posters, and those with unavailable results and outcomes.

Data collection

Two researchers (ZR and HG) collected the data. Any discrepancy between them was settled by discussion or the opinion of a third researcher. The data extracted were as follows: first author, publication year, study design, study population origin, case number, follow-up period, and cutoff generation approach. The present meta-analysis primarily explored APOE ε4 gene risk among AD patients.

Data processing and statistical analysis

This study aimed to examine the association of APOE ε4 gene status with AD. HRs and 95% CIs were used on the basis of a previously described method [21]. The multivariable HRs and 95% CIs or relevant univariable HRs (in the absence of multivariable HRs) were collected from the included articles. Parmar et al.'s method [22] was applied to estimate HRs when univariable and multivariable HRs were unavailable. The relevant variance was determined using Kaplan-Meier analysis, and Engauge Digitizer (version 9.4) was used for visualization. HRs < 1 and > 1 indicated good and dismal patient prognoses, respectively. Statistical heterogeneity was measured via the I^2 statistic and chi-square test. Prominent heterogeneity was represented by $I^2 > 50\%$ and $P < 0.05$, and a random or fixed effects model was applied. Statistical analysis was completed using RevMan version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration) and STATA version 12.0 (STATA Corp., College Station, TX). STATA version 12.0 was adopted to assess bias by Egger's and Begg's tests. $P < 0.05$ indicated a significant difference.

Results

Study screening results

A total of 448, 1124, and 0 articles were identified using the PubMed, Embase, and Cochrane Library databases, respectively. Next, meeting summaries and duplicates

were removed to obtain 91 eligible articles. Thereafter, 69 articles were excluded owing to their undesirable study design ($n = 31$), case reports ($n = 14$), irrelevance to AD ($n = 13$), and lack of credible data ($n = 11$). Finally, 22 eligible articles involving 571,800 cases published between 2001 and 2023 were included in the meta-analysis [16–19, 23–39] (Fig. 1).

Study characteristics

These articles were published between 1987 and 2017. Of these, seven studies were retrospective, whereas 15 were prospective. The sample size ranged from 75 to 495.942. Five studies were conducted in Asia (three in China, one in Japan, and three in Korea), four in Sweden, two in Germany, one in the UK, one in Australia, one in Spain, and five in the USA. Moreover, patients were followed up for 18 months to 23 years. Detailed information about each study, such as the study period, follow-up duration, age, and case number, was collected (Table 1).

Study quality evaluation

This study evaluated study quality using CRITICAL APPRAISAL OF PROGNOSTIC STUDIES (https://www.cebm.net/wpcontent/uploads/2018/11/Prognosis.pdf; Fig. 2). After each article was assessed cautiously, most high-quality articles were retrospective. There were two studies with a high risk and another two with an unclear risk of bias owing to their non-blinded or non-randomized study design. Moreover, since some information was lost, the above three studies had five unclear or three high-bias risks regarding objective measurement and outcome criteria. Another article showed a high bias risk owing to prognostic factors (measurement of the

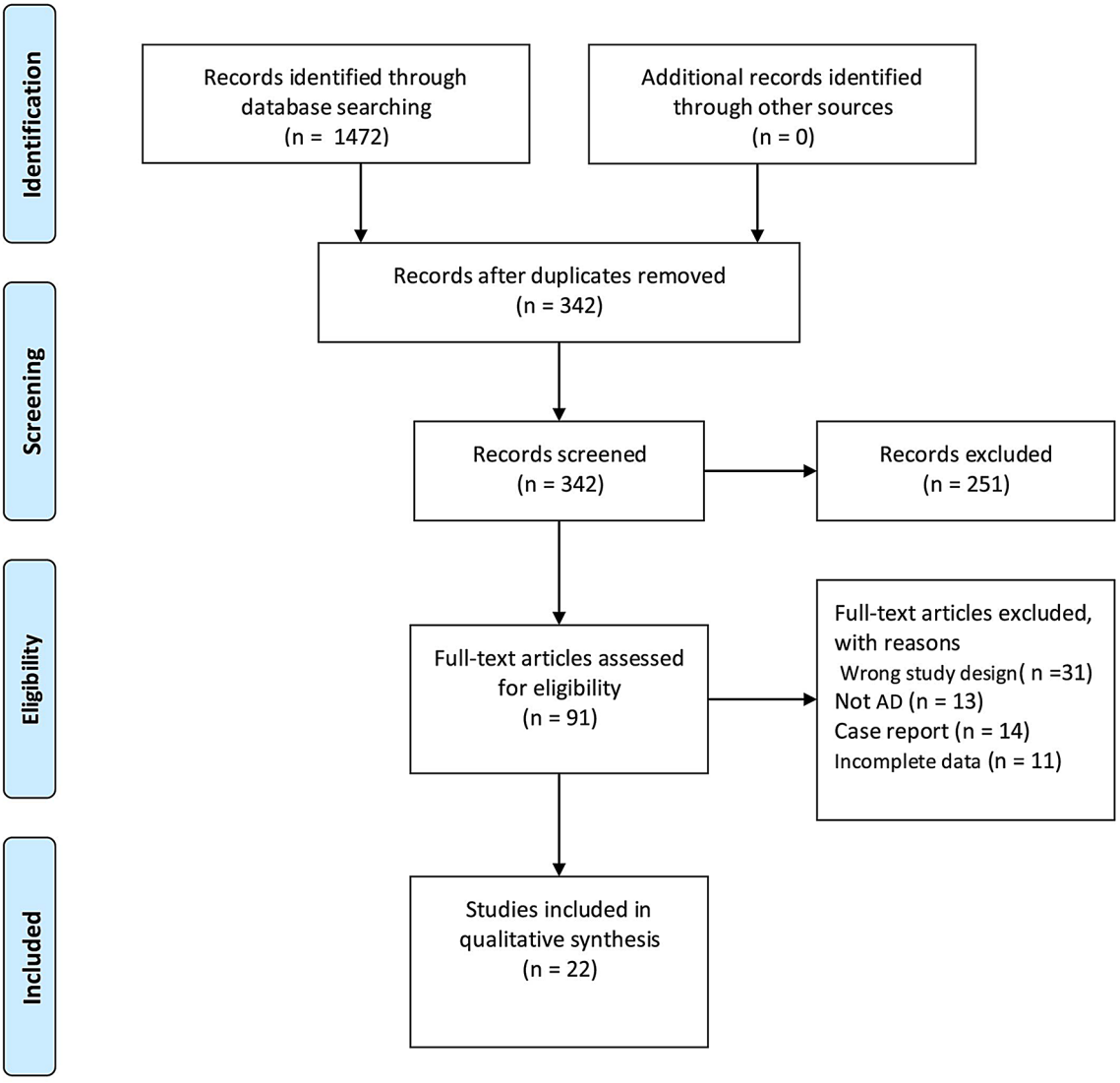

Fig. 1 Flow diagram of the study selection process

Table 1 Enrolled study features

Study	Year	Year of sample collection	Country	Study design	Sample size	Follow up period (years; median, IQR)	Cutoff generating approach
Elin Dybjer et al.	2023	1991–1994	Sweden	P	30 446	20–23 years.	others
IL Han Choo et al.	2022	2017.4-2021.1	Korea	R	75	24months	ROC
ChenjieXu et al.	2022	2006–2010	China	P	495,942	11 years	others
Samia et al.	2021	1995–1998	Germany	R	2,880	14.9 ± 4.0 years	others
Fernanda et al.	2021	2016/2017	Sweden	P	4425	25 years	others
Chinedu T et al.	2019	2016	UK	R	91	120 months	others
Rosalindeet al.	2019	2015	Australia	P	2978	3.9 ± 2.2 years	others
Sungmin Jun et al.	2019	2003	Korea	P	340	36 months.	others
Marcos Dolado et al.	2018	-	Spain	P	135	40 months	ROC
Dong-GyuPark et al.	2018	2005.12– 013.11	Korea	R	2,470	45.3 ± 13.0 months	others
Weili Xu et al.	2017	1987–1989	Sweden	P	1,173	9years	others
Shanna L. Burke et al.	2016	-	USA	R	12,083	3458days	others
Britta Haenisch et al.	2014	2003	Germany	R	3,327	18 months	others
Wei-Li Xu et al.	2012	1987–1989	China	P	1,700	9 years	others
Michael et al.	2012	1995	World Wide Epidemiology,	R	3078	15years	-
Tomoyuki Ohara et al.	2011	1988	Japan	P	534	17years	ROC
Pei-Ning Wang et al.	2010	2000–2008	Taiwan	P	1167	42.5 ± 18.5 months	others
Christiane Reitz et al.	2010	1999–2007	USA	P	2190	4.0years	others
Ge Li et al.	2010	1994–1996	USA	P	2581	6.1 years	others
Patricio et al.	2006	1992	USA	P	1410	8.1 years	others
Oskar Hansson et al.	2006	1998.6-2001.7	Sweden	P	180	5·2 years	others
A. Borenstein et al.	2001	1992–1994	USA	P	3,045	3.8 years	others

P = prospective, R = retrospective, ROC = receiver operating characteristic

follow-up period). Most of these included articles were well-designed and reported adverse reactions objectively.

Primary outcome: DFS

Twenty-two studies reported the risk of AD with APOE ε4 status. The studies by Elin Dybjer et al., Chenjie Xu et al., Weili Xu et al., Shanna L. Burke et al., Wei-Li Xu et al., Tomoyuki Ohara et al., Pei-Ning Wang et al., and Christiane Reitz et al. were regarded as independent works since two datasets associated AD with APOE ε4 status were used. A fixed-effects model was used to analyze significance (HR = 1.840; 95% CI = 1.739–1.940; $P = 0.000$; $I^2 = 93.1\%$). Between-study heterogeneity was analyzed, and significant results were obtained via a random effects model (HR = 2.033; 95% CI = 1.589–2.602) (Fig. 3A). A sensitivity analysis was conducted to predict the influence of each study on pooled HRs. Consequently, the results did not significantly change when one article was eliminated (Supplementary Fig. 1A), suggesting that the results were stable. Furthermore, publication bias was not detected in the funnel plots (Fig. 3B). Egger's test and Begg's test revealed the absence of prominent publication bias ($P = 0.338$, $P = 0.392$) (Supplementary Fig. 1B). Subgroup analyses stratified by region, study design, and cutoff method were conducted (Table 2). The region-stratified subgroup analysis revealed 11 Asian articles with an HR of 2.18 (95% CI: 1.47–3.22; $P = 0.000$; $I^2 = 92.7\%$), 12 European studies presented significant associations (HR = 1.94; 95% CI = 1.33–2.83; $P = 0.000$; $I^2 = 90.9\%$), and seven USA articles presented obvious connections (HR = 2.00; 95% CI = 1.40–2.88, $P = 0.000$; $I^2 = 75.4\%$). All the cases were classified into two subgroups based on the study design: for the 22 prospective studies, the HR was 2.02 (95% CI = 1.46–2.78, $I^2 = 94.3\%$), whereas the HR was 2.13 (95% CI = 1.54–2.93, $I^2 = 83.1\%$) for eight retrospective studies. According to the ROC curve, in four studies that adopted the cutoff method, the HR was 3.07 (95% CI: 2.26–4.16; $P = 0.661$; $I^2 = 0.0\%$), whereas 26 articles that adopted the cutoff method had an HR of 1.95 (95% CI: 1.49–2.54; $P = 0.000$; $I^2 = 93.9\%$).

Discussion

The relationship between neurodegenerative diseases and APOE ε4 gene status has been widely investigated. A potentially increased risk of AD has been demonstrated [40, 41]. AD demonstrates an extended prodromal stage, which is evidenced by the deposition of amyloid-β, which is initiated 15 years before dementia symptoms occur in some individuals [7, 42]. Therefore, disease risk must be accurately predicted to successfully prevent and treat AD, which is beneficial for patients once APOE ε4 status contributes to AD risk prediction. To the best of our

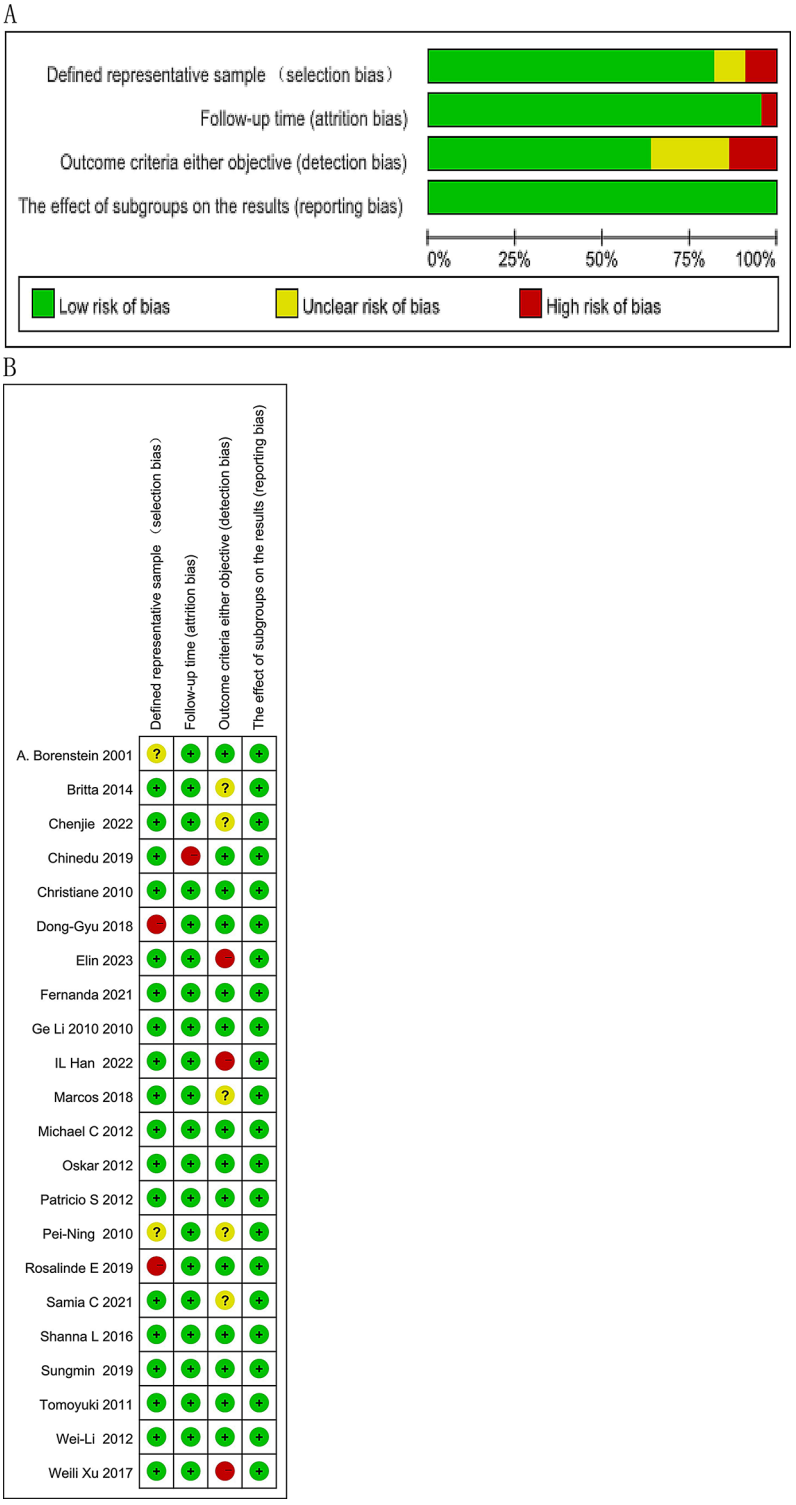

Fig. 2 **A** graph exhibiting bias risk judgments on bias risk items through reviewers displaying percentages among all included studies. **B** Risk of bias summarization: The risk of biased item judgment by reviewers for all the included studies

knowledge, this meta-analysis is the first to illustrate the importance of APOE ε4 status for AD prediction. This meta-analysis included 22 qualified articles with a total of 131,987 articles that mentioned the association between APOE ε4 and AD. According to the pooled analysis, although AD might be influenced by various factors, the HR of AD development with respect to APOE ε4 status was significantly increased (HR = 2.033;

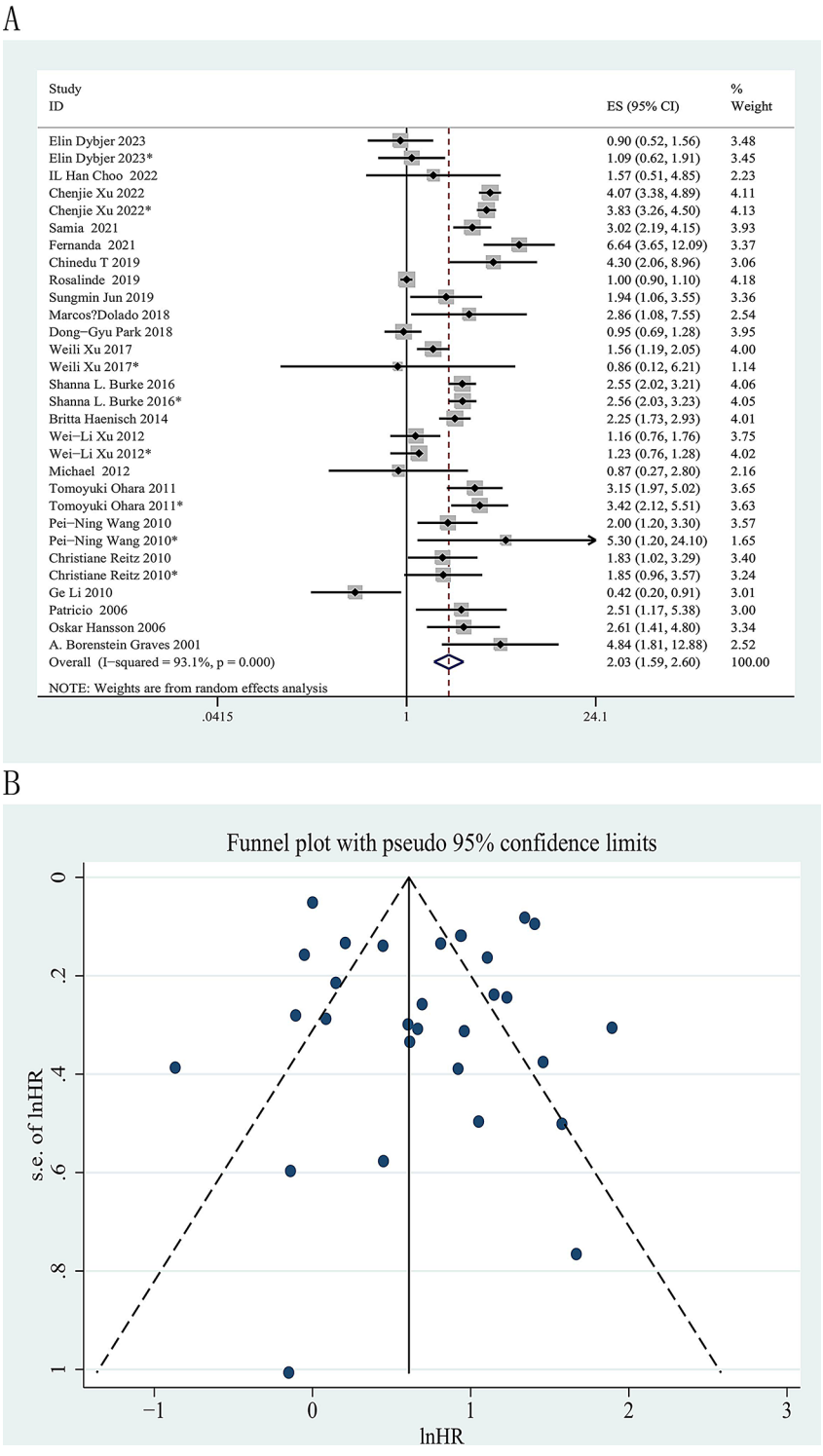

Fig. 3 Forest plots showing hazard ratios (HRs) of disease-free survival (DFS) **(A)** and funnel plots on DFS **(B)**. Heterogeneity was detected via the chi-square test, where $P < 0.05$ indicated distinct heterogeneity between studies. Horizontal lines = 95% confidence intervals (CIs). (Fixed: fixed-effects model; horizontal lines = 95% CI. Rhombuses = estimates with corresponding 95% CIs. Squares = individual study point estimates). DFS = disease-free survival, and OS = overall survival

Table 2 Subgroup analysis of DFS

Endpoint	Factor	No. of studies	Heterogeneity test (I^2, *P*)	Effect model	HR	95%CI of HR	Conclusion
DFS	region						
	Asian	11	92.7,0.000	random	2.18	1.47,3.22	significant
	Europen	12	90.9,0.000	random	1.94	1.33,2.83	significant
	USA	7	75.4, 0.000	random	2.00	1.40, 2.88	significant
	study design						
	P	22	94.3,0.000	random	2.02	1.46,2.78	significant
	R	8	83.1,0.000	random	2.13	1.54,2.93	significant
	Cutoff method						
	ROC	4	0.0,0.661	fixed	3.07	2.26,4.16	significant
	Others	26	93.9,0.000	random	1.95	1.49,2.54	significant

DFS = disease-free survival, HR = hazard ratio, CI = confidence interval, P prospective, R retrospective, ROC = receiver operating characteristic

95% CI = 1.589–2.602), regardless of the high degree of between-study heterogeneity; however, our combined analyses with a random effects model enhanced the robustness of our results.

There was obvious heterogeneity in the ability of APOE ε4 status to predict AD risk ($P = 0.000$; $I^2 = 93.1\%$). Therefore, we conducted a sensitivity analysis to predict whether one study impacted our pooled HRs; consequently, the results did not change when one study was eliminated, indicating that our results were significant. In addition, Egger's and Begg's tests and funnel plots were used to analyze potential publication bias, and obvious publication bias was not detected. Nonetheless, the relationship between APOE ε4 status and AD might be affected by certain confounders. Thus, we conducted subgroup analyses on the basis of region, study design, and cutoff method for investigating the source of heterogeneity. On the basis of region stratification and study design—stratified analysis—the groups did not show a reduction in heterogeneity. According to the cutoff method-stratified subgroup analysis, only the ROC group demonstrated statistical significance ($I^2 = 0.0\%$, $P = 0.661$), with the absence of heterogeneity. Therefore, different cutoff methods are considered sources of heterogeneity in DFS.

Although our results revealed the causes of heterogeneity from a statistical point of view, although subgroup and sensitivity analyses were performed, the sources of heterogeneity remain unclear. However, clinically, AD can be affected by many factors, such as different ages [43], diagnostic criteria are not uniform, and treatment options vary widely [44, 45]. Different lifestyles, living environments, people in different regions [46], and genetic susceptibilities [47, 48] may affect heterogeneity. In addition, the research methods of the 22 studies included in this study are not exactly the same, which may be the cause of heterogeneity. In the future, more high-quality, large-sample randomized controlled trial (RCT) studies are needed to confirm our conclusions.

Additionally, the quality of the included studies must be considered since it was a limitation of the present study. First, the included studies were evaluated using the Cochrane risk bias tool to identify high-quality studies; however, some of these studies had incomplete patient data. In addition, most of these articles were retrospective. Thus, further prospective studies integrating AD with APOE ε4 status are warranted. Second, while funnel plots and formal statistical tests suggest no publication bias, while funnel plots and formal statistical tests suggest no publication bias, this study included patients with different events who received diverse treatments owing to AD heterogeneity; from a clinical point of view, we cannot fully explain the causes of heterogeneity, which might affect event occurrence. Third, only studies published in English were included, and the majority of the included studies were from Asian, European, and U.S. populations. Other populations are not fully addressed, which may cause bias. This could be an important factor, as genetic risk factors for AD may differ across populations. Future research should aim to include more diverse populations and published studies in different languages. Fourth, published studies that used databases were included, which might have caused publication bias. In the future, more high-quality studies with large samples are needed to prove our conclusions.

Conclusion

Different methods are used to evaluate AD patients with different events; the present meta-analysis suggests an increased risk of AD events in patients with different APOE ε4 statuses. More large and high-quality studies are needed for further verification.

Abbreviations

APOE ε4	Apolipoprotein E ε4
AD	Alzheimer's disease
DFS	Disease-free survival
CI	Confidence interval
HRs	Hazard ratios
P	Prospective
R	Retrospective

ROC Receiver operating characteristic

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12868-024-00914-8.

Supplementary Material 1: Sensitivity analysis ondisease-free survival (DFS) (A) and Egger's test on DFS (B)

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Author contributions
Conceptualization- Zijun Ren, Zhenting Guan. Investigation- Zijun Ren, Zhenting Guan, Qingliang Guan. Methodology - Qingliang Guan, Hongjian Guan. Original draft- Zijun Ren, Hongjian Guan, Huiying Che. Review and editing- Zhenting Guan, Huiying Che. All authors have read and approved the final manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

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Not applicable.

Competing interests
The authors declare no competing interests.

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