

Efficacy and safety of focused ultrasound-mediated blood-brain barrier opening in Alzheimer's disease: A systematic review and meta-analysis

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Abstract

Background: Alzheimer's disease (AD) manifests as an insidiously progressive neurodegenerative pathology, wherein the current therapeutic armamentarium remains constrained to symptomatic management, highlighting an urgent need for innovative therapies.

Objective: This meta-analysis systematically conducts an assessment of the safety and efficacy of focused ultrasound (FUS)-mediated reversible blood-brain barrier opening (BBBO) in AD, while further exploring its potential associations with cognitive function and amyloid- β (A β) deposition in patients.

Methods: PubMed, Embase, CNKI, Cochrane Library, and Web of Science were searched in this study. The study protocol has been registered with PROSPERO (registration number, CRD42024585286). ROBINS-I tool was used to assess the risk of bias, followed by further data analysis.

Results: Fifty-seven AD patients from eight distinct clinical studies were systematically incorporated into the meta-analytical framework. The time span was from 2018 to 2023. After FUS-mediated BBBO, the analysis demonstrated significant outcomes of FUS for both safety (OR: 0.88; 95% CI: 0.75–0.98, $p < 0.01$) and efficacy (OR: 0.91; 95% CI: 0.61–1.00, $p < 0.01$). There was no deterioration of cognitive function after surgery, and the observed adverse events were minor and temporary in nature.

Conclusions: This meta-analysis underscores the potential of FUS as a non-invasive, safe, and effective method for enhancing BBB permeability in AD patients, offering a promising avenue for targeted drug delivery and disease modification. Future multicenter studies with larger sample sizes and standardized methodologies are warranted to confirm these results and explore the integration of FUS with existing and emerging AD therapies.

Keywords

Alzheimer's disease, blood-brain barrier, efficacy, focused ultrasound, meta-analysis, safety

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Introduction

Alzheimer's disease (AD) is a progressively debilitating neurological syndrome, with aging and genetic predisposition recognized as significant risk factors.¹ The condition is primarily characterized by gradually worsening cognitive abilities and memory impairment.² Despite extensive research, there is still no curative treatment available. Current therapeutic options offer only symptomatic relief without halting or reversing disease progression.¹ The blood-brain barrier (BBB) is a key hurdle in effectively delivering drugs to the brain, making it a major challenge in treating AD. Safely and effectively opening the BBB to

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enable targeted drug transport remains a critical area of investigation.^{3,4}

The emergence of focused ultrasound-mediated blood-brain barrier opening (FUS-BBBO) technology has brought new hope to solve this problem. Focused ultrasound (FUS) is a non-invasive neurosurgical technique commonly used for imaging and diagnosis. It mainly increases the permeability of the BBB through thermal, mechanical and cavitation effects on cells and tissues. The synergistic combination of intravascular microbubbles (MBs) with transcranial FUS enables more efficient BBB disruption, which can not only promote a greater opening of the BBB but also reduce the sound power required to affect the BBB permeability, making it safer and achieving a greater degree of effective drug delivery.^{5,6} This non-invasive method improves the efficiency of drug delivery to the brain without harming the surrounding tissue, thereby opening up new prospects for AD treatment. The feasibility of employing FUS-BBBO for therapeutic agent delivery has been investigated across preclinical models and clinical research settings, and its safety and effectiveness have been partially validated.⁷

As research on FUS-BBBO advances, its potential effects on cognitive function and amyloid- β (A β) have increasingly become a central focus of investigation. Preclinical evidence suggests that FUS-BBBO may exert beneficial effects on cognitive function when ultrasound parameters are precisely adjusted.^{8,9} Furthermore, studies in mouse models have demonstrated that FUS-BBBO enhances A β clearance.^{10,11} However, the effects of FUS-BBBO on human cognitive function and A β remain inconclusive.

The safety and efficacy of FUS-BBBO, as well as its potential to enhance cognitive performance and reduce A β levels in AD cases, still require further elucidation. Consequently, a comprehensive analysis of existing literature was performed to assess both safety and effectiveness profiles of FUS-BBBO and to explore the feasibility of its potential therapeutic value.

Methods

This systematic review and meta-analysis was registered (CRD42024585286) in PROSPERO. This study follows the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.

Study selection

We screened the literature published in PubMed, Embase, CNKI, Cochrane Library, and Web of Science dated 2015–2024. Inclusion criteria for studies are as follows: (1) The study must be a clinical trial. (2) Eligible participants must

fulfill current international diagnostic standards for AD, as described by either: the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) Working Group criteria,¹² National Institute on Aging-Alzheimer's Association (NIA-AA) Working Group criteria¹³ or Diagnostic and Statistical Manual of Mental Disorders (DSM) series criteria.^{14,15} Studies that did not explicitly specify diagnostic criteria were still included if AD diagnosis was confirmed through clinician assessment and neuroimaging findings. (3) Sample size $n \geq 5$. (4) For the computation of effect size metrics—specifically odds ratios (OR) and weighted mean differences (WMD)—studies were required to provide complete datasets meeting predetermined quantitative thresholds.

The study applied rigorous methodological filters, eliminating: (1) secondary literature (reviews, editorials, letters); (2) preliminary research (conference abstracts, unpublished data); (3) limited evidence sources (case reports); (4) pre-clinical investigations (animal/cellular studies); (5) incomplete datasets.

Information source and search strategy

Two independent researchers conducted a literature search, beginning with a review of abstracts and titles against the inclusion criteria. They utilized EndNote to delete irrelevant data, retaining only the most recent or comprehensive studies in cases of overlap. After further assessment of the full-text papers, a third expert was consulted to resolve any disagreements. To ensure consensus, a group analysis and data extraction were performed on the selected studies, following a process akin to a PRISMA flowchart.

Each study's essential characteristics were meticulously documented, including the investigator's name, study design, publication date, sample demographics, AD severity, follow-up duration, effectiveness indicators, and post-operative adverse events.

Quality assessment

ROBINS-I assesses the risk of bias by the comparative effectiveness of treatments in studies that do not utilize randomization to allocate units to control groups.¹⁶ Introduce seven areas of prejudice. The first two sections, which include confounding and the selection of research participants, address the concerns to be compared before the intervention begins (the “baseline”). The final aspect is the categorization of interventions themselves. The next four topics address post-intervention issues: bias owing to deviation from the planned intervention, incomplete data records, outcome assessment, and selective reporting of results.

Statistical analysis

Certain data in this meta-analysis were collected and statistically analyzed using Stata software (version 15.1). Discontinuous variables were summarized as standardized mean differences (SMD) with corresponding 95% confidence intervals (CI). Heterogeneity was quantified through the chi-square test and I^2 statistics. There was statistical heterogeneity ($I^2 > 50\%$ and $p < 0.05$), suggesting that applying a random effects model is feasible. The study also conducted sensitivity and subgroup analyses to identify potential sources of heterogeneity. To evaluate publication bias, funnel plots were used along with Egger's test, setting the significance threshold at $p < 0.05$.¹⁷ Additionally, the trim-and-fill method was applied to examine the potential impact of publication bias.¹⁸ For additional analyses, the remaining portion of the data was processed using Review Manager (RevMan) software (version 5.3 for Windows). Continuous variables were compared using WMD, and binary variables were analyzed using OR, with both reported alongside 95% confidence intervals. Heterogeneity was again assessed through chi-square tests, with I^2 values quantifying its degree. Statistical significance thresholds for heterogeneity were established as a chi-square p -value < 0.05 or $I^2 > 50\%$.

Results

Search strategy and screening

After the initial search, we identified 390 potential studies. After addressing duplicates, 217 studies remained. We then applied our predefined inclusion and exclusion criteria to screen the abstracts. Following a full-text review and reference check of 14 publications, we included 8 studies in our meta-analysis (Figure 1).^{19–26} These studies encompassed a total of 57 participants with AD.

Baseline characteristics

The eight trials included 57 AD patients who underwent FUS-BBBO surgery. Among these patients, 24 were male. Notably, while the studies were conducted across various countries, 30 participants were from the United States (Table 1).

Risk of bias assessment

The ROBINS-I evaluation's findings revealed that 2 studies (25.0%) had a low risk of bias,^{20,26} 2 studies (25.0%) exhibited significant bias,^{21,25} and the remaining studies (50.0%) demonstrated a moderate risk of bias (Figure 2).^{19,22–24} It is mainly reflected in the bias caused by missing data and the selective reporting bias of results. Three studies exhibited patient loss to follow-up and varying degrees of missing

data due to non-surgery-related illnesses,^{19,21,23} procedural complications, or COVID-19 pandemic impacts, potentially introducing missing data bias. In the studies by Lipsman et al., Park et al., and Rezai et al.,^{19,22,24,25} outcomes were not subjected to repeated measurements and analyses. Furthermore, Rezai et al.'s study provided only abbreviated reports on BBB patency, adverse events, and cognitive outcomes.²⁵ These limitations may contribute to selective reporting bias in outcome interpretation.

As the quantitative overall score derived from the ROBINS-I checklist has not yet been correlated with qualitative categories, the indicators suggested by de Oliveira et al. are employed.²⁷ A study with a score greater than 80.0% is considered 'high quality' (HQ), a score between 70% and 80.0% is 'good quality' (GQ), a score ranging from 50.0% to 69.9% is 'medium quality' (MQ), and a score of less than 50.0% is considered 'low quality' (LQ). Based on this, 2 studies were classified as good quality (GQ),^{20,26} 4 studies were assessed as moderate quality (MQ),^{19,22–24} and 2 studies were rated as low quality (LQ).^{21,25} Because the studies were non-randomized controlled trials, there is no high quality in this classification (Supplemental Table 1).

Efficacy evaluation

A total of 8 studies (including 57 patients) provided data on FUS-BBBO.^{19–26} Owing to the lack of a control group and insufficient detailed data, a single-arm meta-analysis was performed. Transient BBBO detected by magnetic resonance imaging (MRI) was used as the primary outcome to evaluate FUS-BBBO effectiveness. The analysis demonstrated statistically significant efficacy of FUS-BBBO (OR: 0.91; 95% CI: 0.61–1.00, $P < 0.01$), yet significant heterogeneity was noted among studies ($I^2 = 83.84\%$, $p < 0.01$) (Figure 3).

The asymmetry observed in the funnel plot (Supplemental Figure 1) underwent assessment for publication bias using Egger's test, which showed no statistically meaningful bias ($p = 0.773$) (Supplemental Figure 2A). However, the statistical power of Egger's test may have been limited by the small sample size of the studies analyzed. ($n < 10$).²⁸ To comprehensively evaluate potential publication bias, we further applied the trim-and-fill method. This analysis demonstrated that the relative effectiveness of FUS-BBBO increased to 2.175 ($p < 0.001$) after incorporating two hypothetical studies (Supplemental Figure 2B). These findings suggest the possible existence of publication bias in the current research. However, this bias did not significantly affect the validity of our primary conclusions.

Security assessment

Eight studies that included 57 patients in total provided information on adverse events that occurred during and

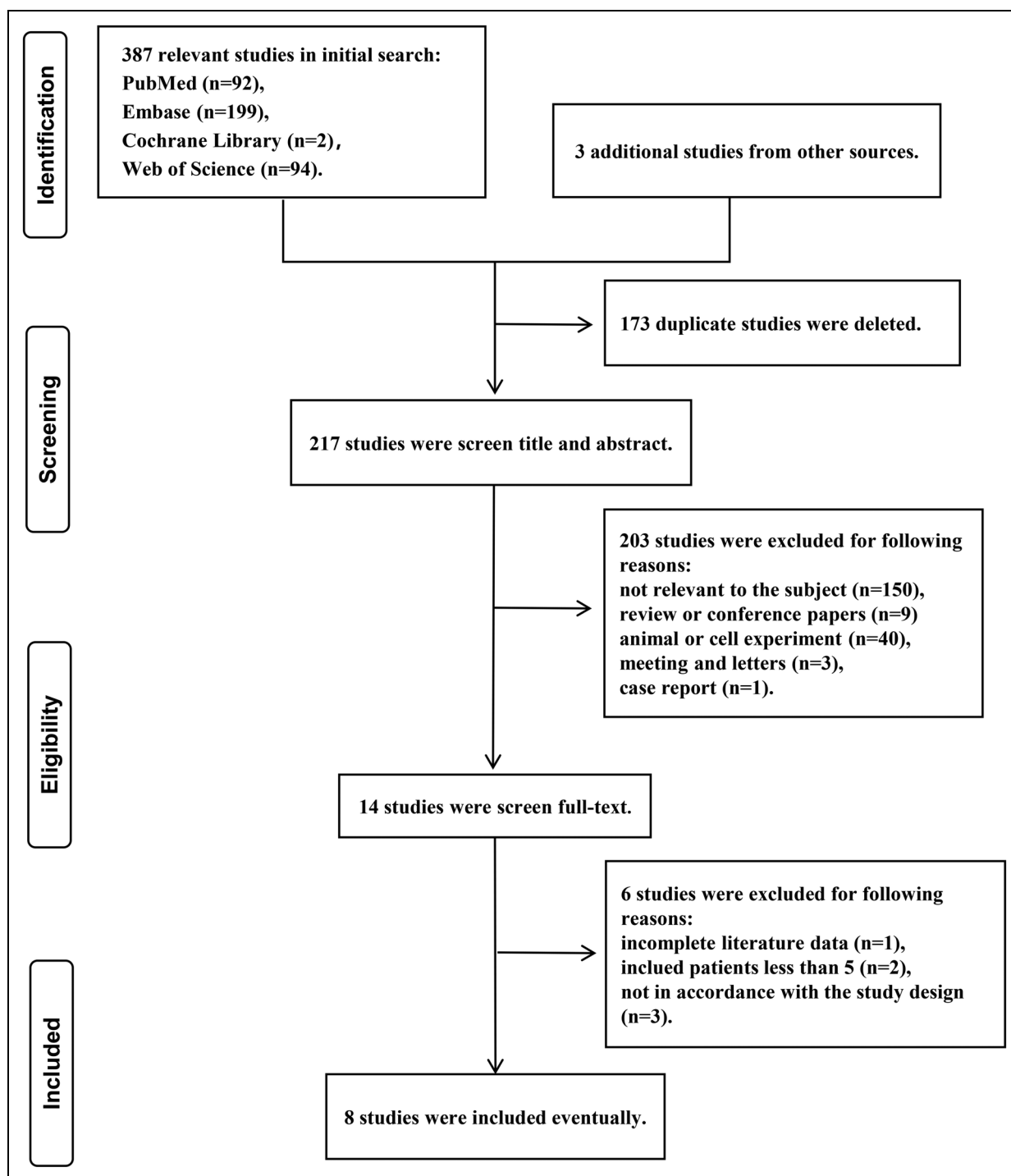


Figure 1. PRISMA Flow Diagram shows the search and inclusion process of the meta-analysis.

following FUS-BBBO surgery.^{19–26} Given the absence of serious adverse events across included studies and considering the lack of control groups or incomplete data in some investigations, we conducted a single-arm meta-analysis of safety outcomes. The safety profile was defined as the occurrence of minor adverse events during and after FUS-BBBO procedures, including edema, headache,

microhemorrhage, erythema, mild cognitive impairment, etc. The results demonstrated that the procedure's safety was statistically significant (OR=0.88; 95% CI: 0.75–0.98, $p<0.01$). Meanwhile, a statistically small heterogeneity was observed among the trials. ($I^2=21.22\%$, $p=0.26$) (Figure 4). Funnel plot analysis demonstrated a symmetrical distribution of included studies, with no

Table 1. Baseline characteristics.

Study	Nation	Study design	Severity of AD	Mean age, y	Sample size, sex ratio (M: F)	Intervention	Follow-up period	Target area
Lipsman et al., 2018 ¹⁹	Canada	an open-label, prospective, proof-of-concept, phase I trial	mild-to-moderate AD	66.2 ± 6.6	5 (3:2)	MRgFUS-mediated BBBO was performed twice, with a one-month interval between procedures	3 months	The right frontal lobe, the superior frontal gyrus white matter of the dorsolateral prefrontal cortex (DLPFC)
Mehta et al., 2023 ²⁰	United States	a prospective trial	mild AD	65.3 ± 7.1	8 (5:3)	Underwent three successive targeted BBBO procedures at 2-week intervals using a 220 kHz FUS transducer in combination with systemically administered microbubbles	44 weeks after study enrollment; 36 weeks after completion of FUS treatment	Non-dominant (right) hippocampus and EC (subject 1); frontal and parietal lobes in addition to the medial temporal lobes (subjects 2–8); volumes in bilateral frontal and/or parietal lobes (some patients)
Bae et al., 2024 ²¹	United States	Phase I clinical study.	mild AD	69.7 ± 7.2	6 (2:4)	Underwent a single session of microbubble-mediated NgFUS to induce transient BBBO	approximately 3 months	PET amyloid-positive region of the right frontal lobe
Park et al., 2021 ²²	Korea	an open-label, prospective study	AD patients with a K-MMSE score of ≤ 23	70.6 ± 13.5	5 (1:4)	FUS-mediated BBBO, targeting the bilateral frontal lobe regions over 20 cm ³ , was performed twice at three-month intervals.	3 months	Bilateral frontal lobes, mainly the prefrontal area
Meng et al., 2023 ²³	Canada	a single-arm, open-label study	mild-to-moderate AD	70.2 ± 7.2	9 (4:5)	Three biweekly MRgFUS procedures targeting the bilateral precuneus, bilateral ACC and unilateral/bilateral hippocampi	6 months	Bilateral precuneus, bilateral ACC and unilateral/bilateral hippocampi
Rezaei et al., 2022 ²⁴	United States	an open-label trial	mild AD	66.4 ± 7.5	10 (3:7)	Underwent MRI-guided FUS sonication to open the BBB in β-amyloid positive regions of the hippocampus, EC, frontal lobe, and parietal lobe	On days 7, 8, 180 and 365 after the last FUS treatment	Hippocampus, EC, frontal and parietal lobes
	United States	an ongoing	mild AD	66.7 ± 7.1	6 (1:5)	Underwent MR-guided, lobe	Within 1 month	

(continued)

Table 1. Continued.

Study	Nation	Study design	Severity of AD	Mean age, y	Sample size, sex ratio (M: F)	Intervention	Follow-up period	Target area
Rezaei et al., 2020 ²⁵		multicenter phase II trial				low-intensity FUS treatment at 220 kHz (ExAblate Neuro Type 2; INSIGHTEC) directed to the hippocampus/EC with simultaneous injection of i.v. microbubbles (Definity)	after tFUS surgery (approximately 20 and 26 days, respectively)	The right or left hippocampus/EC
Jeong et al., 2022 ²⁶	Korea	a prospective trial	suspected AD	78.1 ± 2.9	8 (1:7)	Low-intensity tFUS was applied to the right hippocampus and microbubbles were injected intravenously	15 months	The right hippocampus

K-MMSE: Korean Mini-Mental State Examination; FUS: focused ultrasound; MRgFUS: magnetic resonance-guided focused ultrasound; NgFUS: neuronavigation-guided focused ultrasound; tFUS: low-intensity transcranial focused ultrasound; BBB: blood-brain barrier; BBBO: blood-brain barrier opening; MR: magnetic resonance; MRI: magnetic resonance imaging; ACC: anterior cingulate cortex; EC: entorhinal cortex; Targeting region: anatomical region of FUS action.

statistically significant publication bias detected (Supplemental Figure 3).

Cognitive assessment results and $a\beta$ changes

We summarized the Mini-Mental State Examination (MMSE) score data of four articles^{19,21,22,24} and no statistically significant changes from baseline (MD: -0.58 ; 95% CI: -1.95 – 0.79 , $p=0.40$). Similarly, an analysis of the Alzheimer's Disease Assessment Scale-Cognitive Subscale 14 (ADAS-cog14) score data from two studies^{19,24} found that the change relative to the baseline was not statistically significant (MD: -0.48 ; 95% CI: -3.56 – 2.61 , $p=0.76$). This indicates that FUS-BBBO did not lead to cognitive changes (Figure 5). The remaining four studies were excluded from the statistical analysis of cognitive function due to insufficient relevant data or the presence of missing datasets.^{20,23,25,26}

Three studies conducted by Park et al., Meng et al., and Rezaei et al. involved a total of 23 participants who received amyloid positron emission tomography (PET) imaging using the ^{18}F -florbetaben tracer. The findings demonstrated a decrease in aberrant $A\beta$ accumulation in the brains of AD patients post-surgery.^{22–24} In the work of Lipsman et al., ^{18}F -florbetaben amyloid PET scan was performed on 5 participants, and it was reported that the operation did not significantly affect the aberrant accumulation of $A\beta$ in the brain.¹⁹

Adverse events

Four of the 57 participants had edema. The occurrence of edema was not statistically significant (event rate (ER): 0.04; 95% CI: 0.00–0.13, $p=0.07$), and no significant statistical heterogeneity was identified ($I^2=0.00\%$, $p=0.66$) (Supplemental Figure 4). Additionally, research conducted by Lipsman et al. indicated that one of the five patients experienced a temporary rise in the neuropsychiatric inventory questionnaire (NPI-Q) score, and two suffered microbleeds.¹⁹ In the study of Bae et al., one of the six participants had mild skin erythema, superficial cerebral hemorrhage, and MRI abnormalities.²¹ In the study of Meng et al., one of the nine participants had headaches and two had mild cognitive confusion.²³ The above adverse events subsided during the follow-up period or were resolved after correction. No serious adverse events occurred in 8 studies.

Subgroup analysis and sensitivity analysis

In order to explore possible factors contributing to heterogeneity, we performed subgroup analyses based on study quality scores in our meta-analysis. The results demonstrated a statistically significant effect across all subgroups, high-quality studies ($I^2=0.0\%$, $p=0.001$), moderate-quality studies ($I^2=0.0\%$, $p<0.001$), and low-quality

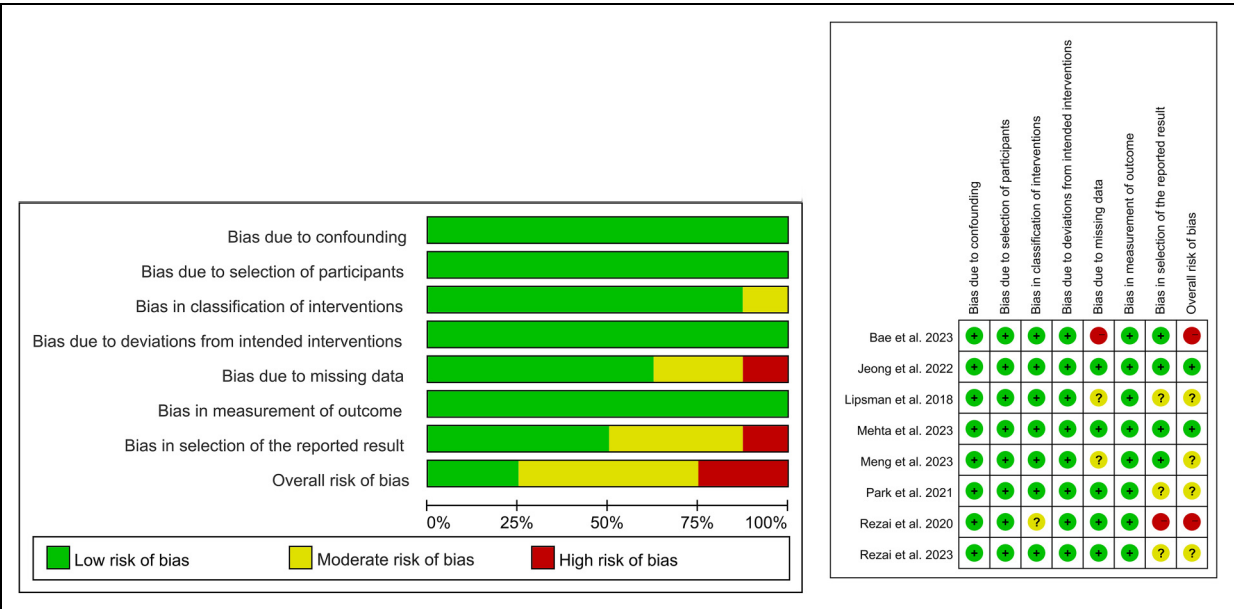


Figure 2. Collective data for risk of bias of all included studies, according to each domain. Green, red, and yellow indicated low, high, and moderate risk of bias, respectively. Comprehensive analysis showed that two studies (25.0%) had low risk of bias, two studies (25.0%) had high risk of bias, and four studies (50.0%) had moderate risk of bias.

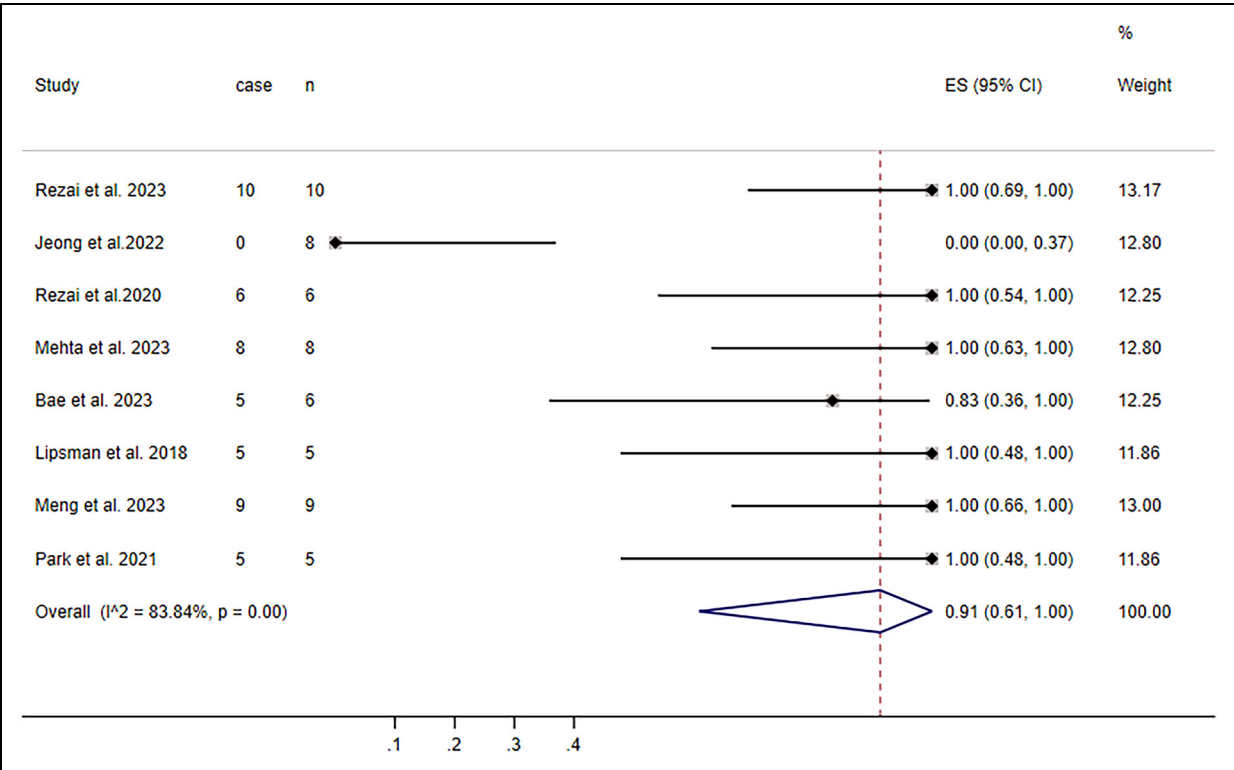


Figure 3. Forest plot: the efficacy of focused ultrasound-mediated blood-brain barrier opening in Alzheimer's disease. The plot shows the significant correlation between focused ultrasound surgery and the imaging changes of blood-brain barrier opening in patients with Alzheimer's disease after the operation.

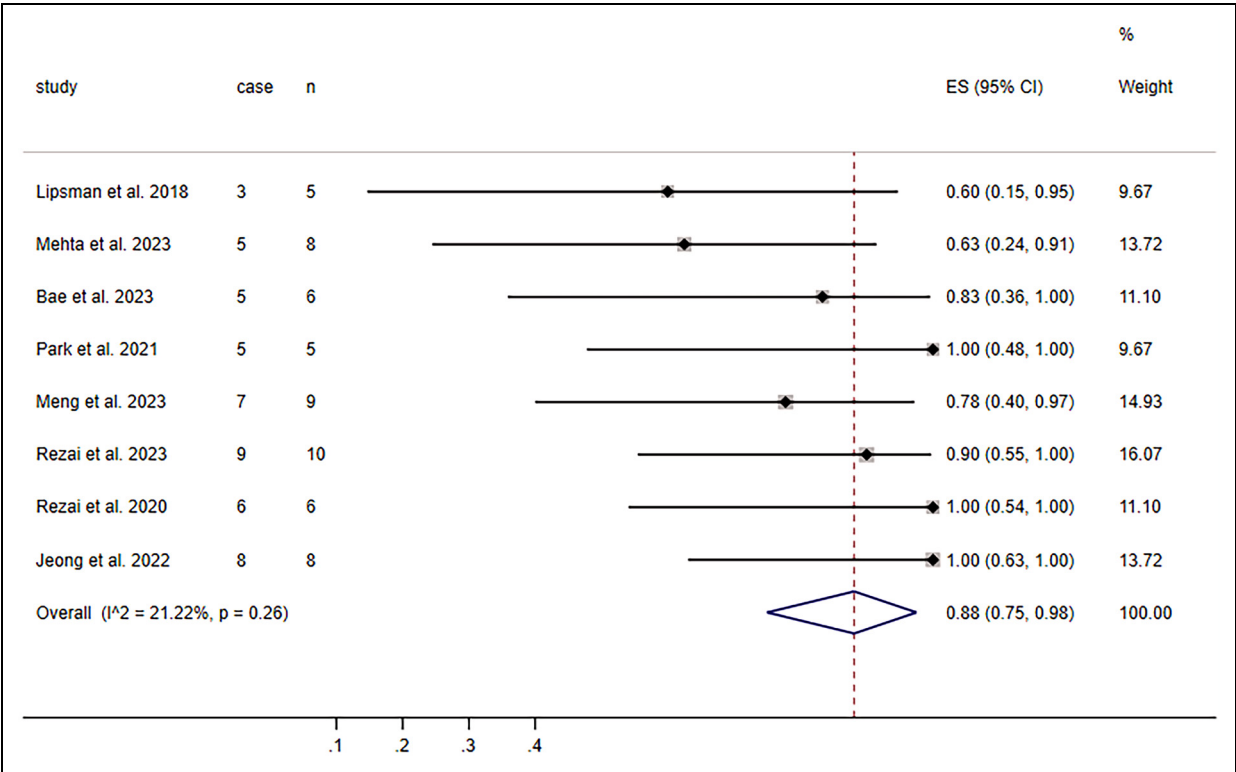


Figure 4. Forest plot: the security of focused ultrasound-mediated brain-blood barrier opening in Alzheimer's disease. The plot shows that focused ultrasound surgery is not related to the postoperative adverse reactions of patients with Alzheimer's disease.

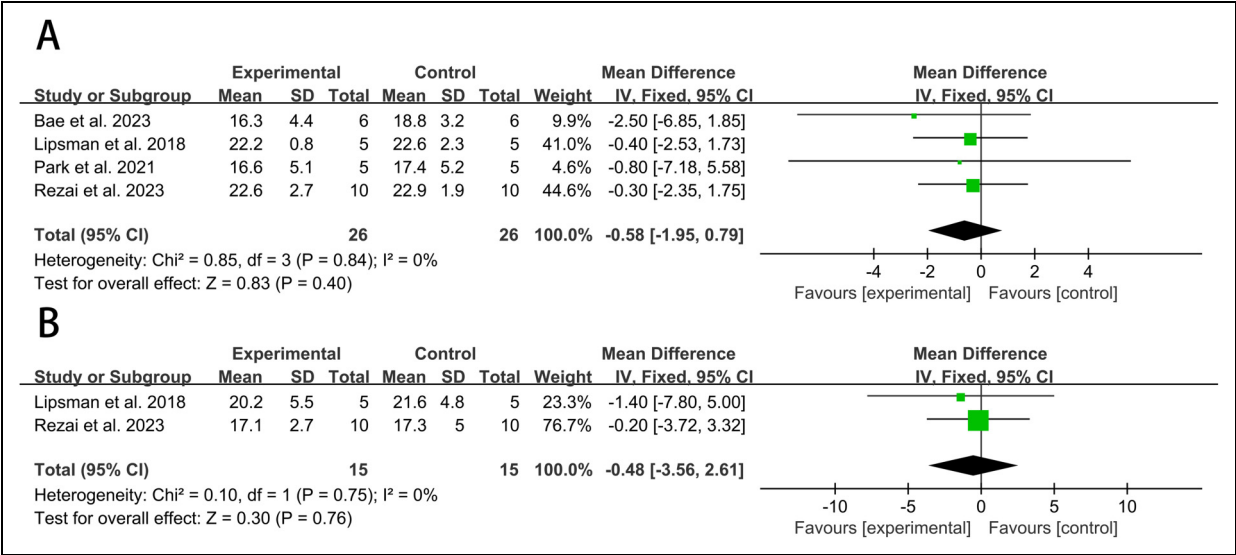


Figure 5. Forest plot: comparison of (A) MMSE and (B) ADAS-cog14 scores before and after blood-brain barrier opening surgery in patients with Alzheimer's disease. The figure shows that the relative baseline is not statistically significant, which indicates that focused ultrasound-mediated blood-brain barrier opening technology does not lead to deterioration of cognitive function. MMSE: Mini-Mental State Examination; ADAS-cog: Alzheimer's Disease Assessment Scale-Cognitive Subscale.

studies ($I^2 = 76.5\%$, $p = 0.039$) (Figure 6A). To confirm the stability and reliability of our findings, the sensitivity analyses using the leave-one-out method were performed to assess both the efficacy and safety outcomes of FUS-BBBO (Figure 6B, Supplemental Figure 5). Specifically, we systematically excluded individual

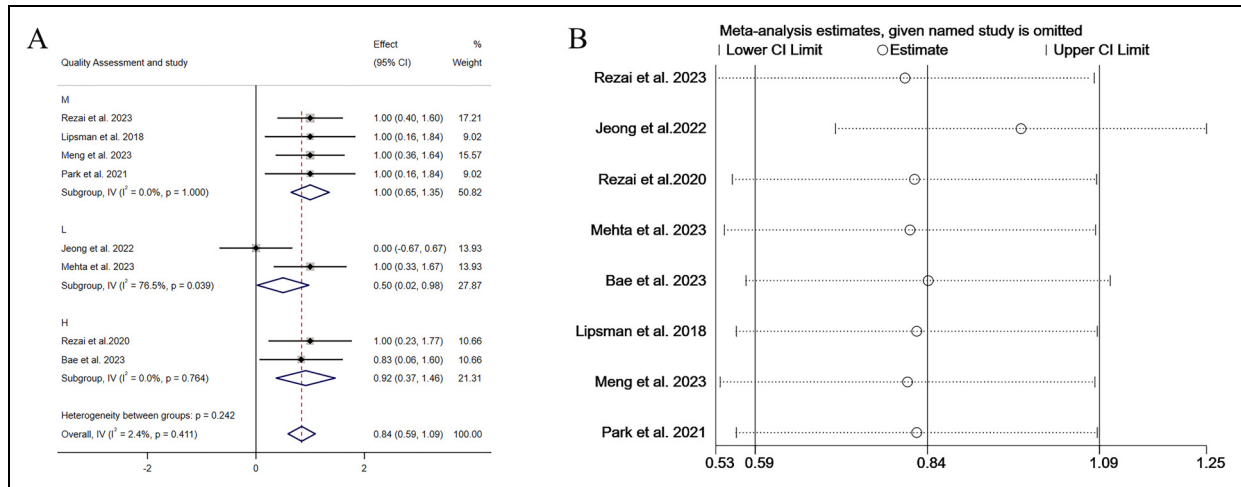


Figure 6. Figures of subgroup analysis and sensitivity analysis. (A) A plot of the subgroup analysis was stratified by study quality scores. (B) The sensitivity analysis plot (Leave-One-Out approach) investigates heterogeneity and assesses the influence of individual studies on pooled results. The limited variability observed demonstrates the robustness of the overall analysis.

studies and re-evaluated the pooled effect size. The results showed that the overall effect direction remained consistent without reversal following the exclusion of any single study, indicating minimal variation in effect magnitude across different analytical scenarios and demonstrating concordant contributions of individual studies to the final conclusions.

Discussion

This meta-analysis establishes that FUS is a safe and effective non-invasive technique for opening the BBB in individuals suffering from mild to moderate AD. Expanding on a prior systematic review that explored FUS in AD treatment across animal and human models,²⁹ our study incorporates six additional papers and conducts a meta-analysis and heterogeneity analysis to reinforce these findings. The analysis of pooled data from included studies (57 subjects) demonstrated that FUS effectively mediated BBBO with post-procedure closure within 24 h. The observed intraoperative and postoperative adverse events (such as edema and headache) occurred at low rates, with no statistical significance observed. These findings collectively suggest a favorable safety profile for FUS-BBBO. Stata 15.1 analysis revealed significant heterogeneity in the efficacy of this study, potentially attributable to variations in FUS parameters, with the greatest divergence observed in a study employing low-intensity transcranial-focused ultrasound (tFUS).²⁶ Cognitive outcomes (MMSE and ADAS-Cog scores) in 26 AD patients showed no significant changes (without deterioration) before and after the procedure, diverging somewhat from preclinical findings. Meanwhile, A β deposition in BBB-opened regions on PET remains controversial, necessitating further investigation and more comprehensive data.

Risk of bias

By referencing existing AD studies that applied the ROBINS-I tool for quality assessment,^{30,31} we found that although such single-arm trial-based research may carry elevated bias risks, their conclusions still retain substantial academic value and high credibility. In the current systematic review, our predefined search strategy did not identify any eligible randomized controlled trials (RCTs) or before-after studies that met the inclusion criteria. Among the eight included single-arm studies, two showed a serious risk of bias owing to incomplete outcome data and potential selective reporting. Given these outcomes, subsequent research endeavors should prioritize strict compliance with the methodological framework prescribed by the Cochrane Handbook, ensuring no deviation from evidence synthesis protocols. For example, in non-randomized controlled trials (non-RCTs), detailed information on controlling confounders and handling missing data should be provided. Furthermore, given the methodological limitations identified in the current evidence base, we emphasize the current evidence base necessitates more rigorous study designs to substantiate existing observations and elevate the quality of available evidence to meet contemporary research standards. Notably, RCTs remain the gold standard for evaluating therapeutic interventions. The establishment of FUS-BBBO's clinical reliability in AD management necessitates multicenter RCT designs, particularly for definitive safety confirmation and intervention outcome verification.

Safety and efficacy

In this study, we utilized Stata 15.1 to analyze both the safety and efficacy of FUS-BBBO. Patwardhan et al. have suggested potential adverse effects associated with

FUS-BBBO procedures, including microhemorrhages, major hemorrhage from vascular rupture, ischemia due to vasoconstriction, cerebral edema or inflammation caused by protein extravasation, and direct cellular death resulting from thermal or mechanical damage.³² However, in our observational cohort of 57 subjects, only minor and transient adverse events were documented, with no instances of severe clinical complications or tissue injury. In this study, by defining the absence of minor adverse events as safety indicators, the statistical analysis demonstrated statistically significant results with no observable publication bias. These findings therefore suggest that the surgical procedure has a favorable safety profile.

Post-FUS treatment, contrast-enhanced T1-weighted MRI consistently showed significant enhancement in the targeted regions across all cases. Over time, this high signal intensity gradually decreased, and the parenchyma of the ultrasound area was re-enhanced with subsequent FUS sessions, demonstrating the transient nature of BBBO. Additionally, low-intensity black spots, indicative of FUS-BBBO, were observed in T2*-weighted/GRE images, fading gradually over successive scans. While some spots disappeared before the next BBB opening, others persisted in high-energy ultrasonic areas.³³ This study interpreted MRI-documented BBB permeability alterations as evidence of reversible BBBO.

Statistical analysis revealed significant efficacy ($I^2 = 83.84\%$, $p < 0.01$) with substantial heterogeneity across studies, which initially suggested possible potential publication bias. Subsequently, we employed Egger's test and the trim-and-fill method for bias assessment. No significant publication bias was detected by Egger's test ($p = 0.773$) (Supplemental Figure 2A), while trim-and-fill adjustment incorporating two hypothetical studies elevated the relative effectiveness of FUS-BBBO to 2.175 ($p < 0.001$) (Supplemental Figure 2B). Collectively, these results indicate that while potential publication bias may exist, it does not substantially compromise the conclusions regarding the efficacy of FUS-BBBO in AD applications.

At the same time, given the critical influence of technical parameters (e.g., transducer frequency, acoustic pressure amplitude, sonication duration) on the extent of BBBO,³⁴ we speculate that changes in relevant images were not observed in Jeong et al.'s study, which may be due to the use of lower ultrasound power, resulting in abnormal cavitation of microbubbles.²⁶ Considering the above research process and results, we can conclude that reversible FUS-BBBO in AD is effective when the technical parameters are fully guaranteed.

Heterogeneity analysis

In this study, the analysis demonstrated statistically significant efficacy ($I^2 = 83.84\%$, $p < 0.01$) and safety ($I^2 = 21.22\%$, $p < 0.01$) of FUS-BBBO technology in AD.

Although substantial heterogeneity was observed in the effectiveness analysis, sensitivity and subgroup analyses confirmed the stability of our results, strengthening the credibility of the outcomes. It is worth noting that even though the 95% confidence interval for the pooled effect size of sensitivity (0.59 to 1.09) crosses 1, this does not imply that our results are insignificant. This statistical phenomenon may be attributed to the limited sample size, high data dispersion, methodological constraints, and statistical power issues.^{35,36} Collectively, the safety and efficacy of FUS-BBBO in AD, as demonstrated in this study, remain credible and reliable.

Subgroup analysis further identified multiple sources of heterogeneity in the study. Notably, low-quality studies exhibited moderate heterogeneity ($I^2 = 76.5\%$, $p = 0.039$), indicating that study quality may be a contributing factor to variability. However, due to incomplete data, we were unable to further explore specific sources of heterogeneity. Additional analysis suggested that the high heterogeneity may originate from the following factors. First, both analyses relied on single-arm rate data, which exhibited extreme and non-normal distribution and lacked control groups. The inherent peculiarity of such data may contribute to elevated heterogeneity. Second, differences in FUS methodologies across the eight included studies likely increased inter-study variability—six studies used Magnetic Resonance-guided Focused Ultrasound (MRIGFUS),^{19,20,22–25} one employed Neuronavigation-guided Focused Ultrasound (NgFUS),²¹ and one utilized low-intensity transcranial focused ultrasound (tFUS).²⁶ Prior research has shown that differences in microbubble administration and acoustic pressure levels can affect variations in BBBO volume, potentially introducing additional heterogeneity.³⁷

Overall, the results of this study are valid and hold significant reference value. Although some degree of heterogeneity exists, this is common in similar studies and results from multiple contributing factors. These factors, while increasing study complexity, also reflect the diversity of real-world conditions. Future research should focus on optimizing study design, controlling variables, and further validating the application of FUS-BBBO in AD to reduce heterogeneity and enhance result generalizability.

Cognitive function

This study explored the potential cognitive benefits of FUS. While multiple preclinical studies have reported cognitive improvements following FUS treatment,^{11,38,39} our statistical analysis of clinical data revealed no significant changes in cognitive function after FUS-BBBO. Nevertheless, the absence of cognitive deterioration further supports the safety profile of this intervention.

Heterogeneity in cognitive outcomes was observed across the included studies. Bae et al., Meng et al., and

Rezai et al. reported no significant cognitive improvements following FUS-BBBO.^{21,23,24} In contrast, Park et al. documented transient neuropsychiatric symptom improvement following extensive frontal lobe BBBO,²² while Jeong et al. observed modest memory enhancement in AD patients.²⁶ We hypothesize that the transient improvements in Park et al.'s study may relate to concomitant medications (e.g., rivastigmine and donepezil) rather than FUS-BBBO alone. In addition, the duration of BBBO may also influence therapeutic outcomes. Compared to previous studies, Park et al.'s investigation employed an extended treatment protocol with a 3-month interval. Based on these observations, the study hypothesizes that the therapeutic effects of BBBO may persist for 2–4 weeks, followed by potential symptom recurrence.²² In Jeong et al.'s study, the use of tFUS failed to achieve detectable BBBO or assess A β /tau pathology changes.²⁶ Therefore, although the study reported modest improvements in memory performance, the mechanisms need to be further explored.

Preclinical evidence indicates FUS enhances A β clearance through glial activation and glymphatic system potentiation.¹¹ However, species-specific differences in FUS effects, attributable to variations in neuroanatomy, skull thickness, and cerebrovascular physiology between small and large animals,⁴⁰ may explain limited cognitive benefits in human studies. In AD transgenic mice, FUS improves memory via microglia-mediated A β reduction and tau clearance.^{11,39} Meng et al. observed decreased ¹⁸F-florbetaben uptake in the right parahippocampal gyrus and inferior temporal cortex after FUS-BBBO,^{23,41} aligning with animal findings.^{11,39} However, this study did not show significant improvement in cognitive function, and given the small area change in ¹⁸F-florbetaben uptake reported, it is speculated that the non-significant changes in ADAS-cog and MMSE scores may be explained by insufficient effect size.²³ In summary, FUS showed significant A β clearance and cognitive improvement in small animal models, but its effect in large animals and humans was limited, which may be limited by species differences and insufficient effect size. Further optimization of treatment parameters and a larger sample size are needed to verify its clinical potential.

Additionally, concomitant AD medications (e.g., rivastigmine, donepezil) and adjunct therapies (e.g., rosuvastatin) may confound cognitive assessments.⁴² Progressive neuronal loss, cholinergic dysfunction, and neural network degradation during AD pathogenesis likely exacerbate cognitive decline over time, potentially obscuring treatment effects and limiting study interpretability.

Amyloid- β deposition

Preclinical murine investigations have demonstrated FUS-BBBO's capacity to potentiate endogenous antibody distribution and peripheral blood-derived protein transport to specific cerebral zones, likely mediated through

upregulated opsonin-dependent A β clearance mechanisms.^{10,11} However, its regulatory effects on human cerebral A β pathology require further investigation. Current clinical data from three independent studies demonstrated relative A β reduction in BBBO-targeted areas.^{20,21,24} This finding may suggest the effectiveness of therapeutic interventions, implying a regulatory effect on pathological processes. However, it must be noted that current evidence cannot determine which dynamic process the observed A β reduction represents (i.e., whether it reflects sustained A β clearance homeostasis induced by BBBO or a relative decrease phase during A β re-accumulation). Furthermore, these findings may be confounded by limited sample sizes and concomitant pharmacological interventions. Therefore, rigorously designed large-scale longitudinal trials incorporating multimodal biomarker monitoring are essential to systematically characterize FUS-BBBO's long-term impacts on A β metabolism.

Adverse event analysis

None of the 8 included studies reported severe adverse reactions.^{19–26} Previous investigations suggest that FUS-BBBO may induce microhemorrhages, overt hemorrhage from vascular rupture, and cerebral edema due to protein extravasation.³² Beyond FUS-related complications, pharmacological agents may also contribute to adverse effects. First, event occurrence may be associated with the application and dosage of intraoperative microbubble administration. All included studies employed intravenous microbubble injection combined with FUS. Notably, Rashi et al. reported postprocedural edema in two subjects receiving higher hippocampal FUS cavitation doses.²⁰ Second, therapeutic drug regimens might influence postoperative and follow-up adverse events. In the study by Lipsman et al., rosuvastatin was administered to one patient who experienced a headache and another patient with transiently increased Neuropsychiatric Inventory Questionnaire (NPI-Q) scores,¹⁹ while the headache could potentially be attributed to rosuvastatin.⁴³ Additionally, the U.S. Food and Drug Administration (FDA) issued a statement in 2012 indicating that statins may cause non-serious and reversible cognitive side effects.⁴²

Limitations

There are some limitations in our study: (1) Our study is limited by the inclusion of heterogeneous research designs and a relatively small number of studies, as well as the absence of rigorous double-blind protocols and standardized sampling methods, which may affect the results of the study. To mitigate heterogeneity across included studies, we implemented random-effects models. (2) The studies we included were all single-arm trials, and FUS-BBBO could not be compared with sham or control

groups. Therefore, we performed a one-arm meta-analysis using a binary classification and compared it with the pre-operative baseline. However, the quality of the evidence remains constrained by the absence of controlled randomization. (3) Potential confounding from intraprocedural microbubble administration and therapeutic drug regimens could influence adverse event profiles. (4) The methodology and follow-up period used to evaluate cognitive function in the included research varied significantly, which may have an impact on the outcomes of cognitive function investigations. (5) Limited study quantity and design heterogeneity, particularly incomplete reporting of quantitative A β data, precluded comprehensive analyses of FUS-BBBO's potential A β clearance effects.

For future research, studies should be conducted with expanded sample sizes, extended follow-up durations, rigorous randomization protocols, and incorporate controlled double-blind designs. Multicenter clinical trial registration should be promoted to comprehensively evaluate long-term effectiveness and safety profiles. Furthermore, we recommend investigating combined therapeutic strategies integrating repetitive FUS-BBBO protocols with adjuvant therapies, particularly focusing on whether such interventions can ameliorate degenerative cognitive alterations in AD patients.

Conclusion

This meta-analysis indicates that FUS-BBBO demonstrates safety and efficacy in individuals with AD. The procedure did not induce cognitive deterioration, with a low incidence of adverse events. Specifically, the occurrences of edema and headache did not reach statistical significance, supporting the technical safety profile of FUS-BBBO. These results create the foundation for more extensive trials combining FUS-BBBO with promising AD therapies. However, due to the limitations inherent in the single-arm trial design, this study carries a high risk of bias. It is essential to conduct future high-quality RCTs and large-scale multicenter studies to further validate and optimize FUS-based therapeutic strategies.

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Ethical considerations

The systematic aggregation of pre-existing research data in this meta-analysis rendered ethics committee oversight unnecessary, in accordance with international standards for evidence synthesis studies.

Author contributions

Mengru Bai: Formal analysis; Writing - original draft.

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Xin Zhou: Data curation.

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Zhengyi Han: Conceptualization; Data curation; Methodology; Supervision; Writing - review & editing.

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Data availability statement

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

Supplemental material

Supplemental material for this article is available online.

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