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Anti-inflammatory interventions for the treatment and prevention of depression among older adults: a systematic review and meta-analysis

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Recent evidence from clinical and animal studies with anti-inflammatory agents in depression is conflicting. One possible reason is the heterogeneity of baseline inflammation levels. Since older adults are generally associated with chronic low-grade inflammation and depression is one of the most common mental disorders in this population, this meta-analysis aimed to evaluate the therapeutic and preventative effects of anti-inflammatory interventions for depression among older adults. PubMed, Cochrane Library, Embase, and PsycINFO were searched for randomized controlled trials (RCTs) up to November 18, 2024. The primary outcomes were mean change scores of depression scores and incidences of depression after treatment. Pooled standard mean differences (SMDs) and odds ratios (ORs) including 95% confidence intervals (95% CI) were calculated. Of 3116 screened articles, 31 RCTs met the inclusion criteria, with 25 studies investigating efficacy and 7 studies investigating the incidence following anti-inflammatory treatment. Anti-inflammatory interventions were statistically significantly more effective than placebo in reducing depressive scores for older adults with depression (SMD = −0.57, 95% CI = −0.98 to −0.15, p = 0.008). Sub-group analyses supported the use of omega-3 fatty acids (SMD = −0.14, 95% CI = −0.27 to −0.02, p = 0.03) and botanical drug or dietary intervention (SMD = −0.86, 95% CI = −1.58 to −0.13, p = 0.02) among older participants. While limited by substantial heterogeneity among included studies, these results reveal the moderate beneficial effects of anti-inflammatory interventions for the treatment and prevention of depression among older adults. Future high-quality RCTs are warranted to determine which anti-inflammatory interventions are most preferential for older patients with depression.

INTRODUCTION

Depression is a common mental disorder that severely affects health-related quality of life and even results in death by suicide in extreme cases. In older adults, the prevalence of depression is estimated to be about 10–20% and rises with age [1–4]. With the aging of the world's population, depression in older adults will bring an ever-greater disease burden, making it a leading public health concern [5].

When treating a depressive episode, both antidepressants and psychological therapeutic strategies are recommended for the remission of depressive symptoms [6]. In clinical practice, pharmacotherapy is used more frequently than non-pharmacological therapy due to inadequate resources [7]. However, the current antidepressants are unsatisfactory because of their significant adverse effects, lower response, and moderate efficacy, which take weeks to produce a measurable benefit [8]. Even after several sequential treatments with different conventional antidepressants, about one-third of the patients still fail to respond [9]. For geriatric patients with major depressive disorder

(MDD), the benefits of traditional antidepressants can be more limited. A meta-analysis revealed that the response rates of antidepressants were 53.9% in younger adult patients, but significantly decreased to 45.2 and 42.2% in older adult patients aged ≥ 55 years old and ≥ 65 years old, respectively [10]. Given that the response rates of placebo reached up to 39.2% in these older patients [10], the efficacy of antidepressants leaves much to be desired. Similarly, another meta-analysis found that second-generation antidepressants seem effective for older MDD patients but the magnitude of the effect is small, and the response rates are numerically lower than those reported for adult MDD patients [11]. Mechanistically, some pioneer studies have discussed that brain-based structural and functional mechanisms [12], including white matter integrity and hyperintensity [13–15], may disturb the treatment of late-life depression.

Despite the pathogenesis mechanism of depression being elusive, recent clinical and pre-clinical evidence converges to inflammation and immune dysfunction [16–19]. Inhibition of inflammation targets sheds light on the discovery of novel

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therapies for patients suffering from depression [20–22]. However, results from studies with anti-inflammatory drugs in depression are conflicting. Taking TNF-α antagonist infliximab, for instance, Lee et al. found a significant reduction in anhedonia after infliximab treatment compared to placebo [23]; McIntyre et al. claimed that infliximab failed to alleviate depressive symptoms compared to placebo [24]. A possible reason for the failure of trials of anti-inflammatory drugs in depression is the heterogeneity of this disease [25]. With the deepening understanding of the role of inflammatory mechanisms in depression, exploring the subgroups of depression patients who may benefit from anti-inflammatory treatment can maximize the treatment effects of anti-inflammatory agents.

Aging is a complex process affected by environmental, genetic, and epigenetic factors and is commonly associated with chronic low-grade inflammation [26]. The low-grade chronic inflammatory status, also termed as inflammaging, has been identified as one of the hallmarks of aging [27]. Inflammaging is a sterile systemic inflammation with self-reactivity in the absence of overt infection [28]. There is compelling evidence showing a reciprocal link between inflammation and depression in older patients, with a possible inflammatory subtype of depression driven by elevated inflammation [29, 30]. Intriguingly, for those depressed patients with increased baseline inflammation, anti-inflammatory interventions are more likely to improve the response rates [31, 32]. Inhibiting the brain inflammaging appears to be a promising strategy for treating late life depression [33]. Preliminary findings suggest that the anti-inflammatory interventions are associated with a lower risk of depressive symptoms [34]. Therefore, Anti-inflammatory treatments are warranted to be further studied in older adults [29, 35].

A few published systematic reviews and meta-analyses have suggested the anti-depressant role of anti-inflammatory interventions in affective disorders [36–38]. However, the meta-analysis from Kappelmann et al. [36] focuses on anti-cytokine treatment, but other excluded anti-inflammatory agents may have superior effects. Another meta-analysis from Husain et al. [38] includes patients with major depressive disorder and bipolar disorder, which introduces heterogeneity for the comparisons without subgroup analysis. Moreover, these meta-analyses only assess the efficacy [36] and safety [37–40] of the interventions in participants, most of whom were adults. No meta-analysis has yet evaluated the preventive effects of anti-inflammatory regimens for depression, and no meta-analysis has examined the evidence among the elder subjects. Importantly, these meta-analyses summarize the data published before 2017 [36–40], while there have been vital research updates from RCTs in this field in the last several years. Therefore, there is an urgent need for a comprehensive examination of the evidence regarding the potential benefits of anti-inflammatory interventions in older adults.

The primary aims of this meta-analysis were to investigate the anti-depressant effects and preventive effects of anti-inflammatory interventions in older participants with or without depressive symptoms. The findings of this study will provide critical insights into the prevention and management of depression in the elderly population.

MATERIALS AND METHODS
Search strategy
The present systematic review and meta-analysis is conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines from Cochrane Handbook [41]. The study protocol was pre-registered online with PROSPERO (no. CRD42023388262). Comprehensive literature searches were performed independently in four electronic databases, including EMBASE, PubMed, Cochrane, PsycINFO, from the date of database inception until November 18, 2024, with indexing terms and text

words. Keywords included (depression or depress*) AND (aged or aging or elder* or geriatri* or geronto* or senior*) AND (anti-inflammatory* or NSAID or COX-2 or "cytokine inhibito*" or glucocorticoid or statin* or minocycline or Omega-3). We tried to retrieve all articles using any agents of proved anti-inflammatory properties, including nonsteroidal anti-inflammatory drugs (NSAIDs), antibiotics, cytokine inhibitors, antibodies, steroids and other anti-inflammatory hormones (melatonin and estrogen), statins, glitazones, polyunsaturated fatty acids, modafinil, and anti-inflammatory botanical and dietary interventions. Details of the search strategies and results are provided in Supplementary Table 1. We also searched the reference lists of relevant systematic reviews and meta-analyses. No language restrictions were applied.

Selection criteria
Two independent investigators (H. Gong and W.-J. Su) selected the studies for inclusion. After removing the duplicates, they screened the title/abstract and identified a waitlist of potentially relevant studies for further full-text review. The divergences were resolved by reaching a consensus. Only prospective RCTs, including cross-over randomized trials, were selected when they met all the following inclusion criteria: (1) included older adults aged 55 years or older; (2) reported the depression-related score or incidence; (3) administered monotherapy or combination therapy with anti-inflammatory intervention; (4) included a placebo or active control group. Exclusion criteria included: (1) studies published only as abstracts or reporting insufficient data; (2) enrolled fewer than 20 participants; (3) included patients with bipolar depressive disorder; (4) for multiple studies with overlapping data, only the one with the most information or the largest sample size was selected.
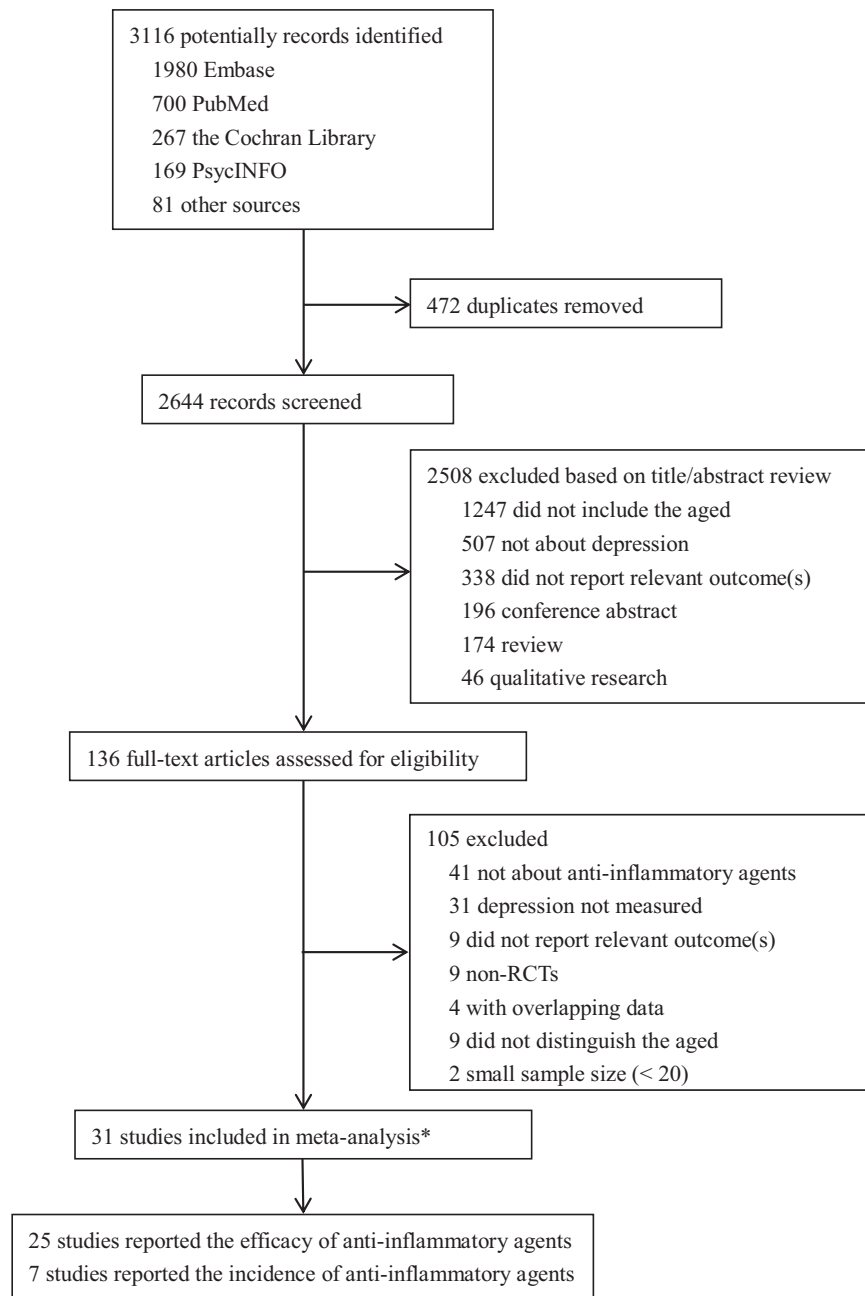
Data extraction
Two investigators (H. Gong and W.-J. Su) extracted the data independently from included RCTs according to a predefined data extraction form. The following information from each trial was obtained: (1) the first author's surname and publication date of literature; (2) the country where the trial was conducted; (3) the number, age, and sex of the participants (N, age, % women); (4) diseases and comorbidity conditions; (5) intervention and control conditions; (6) treatment duration; and (7) methods for evaluating depression severity. The extracted data were assessed by another author, and the divergence between the two investigators was resolved by discussion with another author.

Quality assessment
The study risk of bias was assessed using the Risk of Bias Tool of the Cochrane Handbook (version 5.1.0. 2011). Briefly, the quality assessment of included RCTs was performed on seven domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases. Studies were high quality if five or more domains were assessed as having a low risk of bias, and all other items were evaluated as having a low or unknown risk of bias. Studies were classified as low quality if one or more domains were rated as having a high risk of bias. The remaining studies were considered of unclear quality if they met neither the criteria for high risk nor low risk. Divergence was resolved by discussion with a third investigator (S.-L. Deng).

Outcome measures
The primary outcome of this meta-analysis focused on the efficacy and prevention of depression among older adults. To measure the efficacy of anti-inflammatory agents, we summarized the overall mean change in depressive symptom scores from baseline to the end of the trial for patients diagnosed with depression before enrollment. To clarify the preventive effect, we considered the proportion of participants who met the

3116 potentially records identified
  1980 Embase
  700 PubMed
  267 the Cochran Library
  169 PsycINFO
  81 other sources

→ 472 duplicates removed

2644 records screened

→ 2508 excluded based on title/abstract review
  1247 did not include the aged
  507 not about depression
  338 did not report relevant outcome(s)
  196 conference abstract
  174 review
  46 qualitative research

136 full-text articles assessed for eligibility

→ 105 excluded
  41 not about anti-inflammatory agents
  31 depression not measured
  9 did not report relevant outcome(s)
  9 non-RCTs
  4 with overlapping data
  9 did not distinguish the aged
  2 small sample size (< 20)

31 studies included in meta-analysis*

25 studies reported the efficacy of anti-inflammatory agents
7 studies reported the incidence of anti-inflammatory agents

Fig. 1 PRISMA flow chart of study selection. Of the 3116 relevant studies, 472 were excluded due to duplication, 2508 were excluded because their titles and abstracts did not meet the criteria, and 105 studies were excluded following full-text screening. 31 RCTs were finally included. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses. *One article reported both the score changes of depressive symptoms and the numbers of patients with severe depressive symptoms after treatment, thus this study was included in the meta-analyses of the treatment and prevention of depression.

diagnostic criteria for depression at the endpoint. To determine the severity of depressive symptoms, we extracted the score data from several reported rating scales, including the Geriatric Depression Scale (GDS), Center for Epidemiological Studies Depression (CES-D), Hamilton Depression Rating Scale (HDRS), Beck Depression Inventory (BDI), Self-Rating Depression Scale (SDS), Patient Health Questionnaire (PHQ), and Montgomery-Asberg Depression Rating Scale (MADRS). When more than one standardized rating scale was adopted in a single included trial, we selected the data using a predefined hierarchy based on the utilizing frequency and consistency across all included studies. Besides, secondary outcomes included mental health quality (measured by the Quality-of-Life Short Form, SF), response rate

(provided in the original trials), all-cause discontinuation, and adverse effects (not presented due to the limited original data obtained).

Data synthesis and analysis
Where applicable, data from comparable trials were pooled in a statistical analysis using the RevMan software (version 5.4, Cochrane Collaboration, Oxford, United Kingdom). Meta-analyses were conducted when data were available from two or more trials for each comparison. A trial with two or more intervention groups was split into two comparisons with the same number of participants in their control groups. Studies without the necessary data were not included in the corresponding quantitative analysis.

Table 1. Characteristics of 31 included studies.

Study (year)	Country	Participants (N, age, % women)	Diseases /Condition	Comorbidity	Interventions	Control condition	Study duration	Relevant outcomes
Osali et al. [68]	Iran	N = 22, 60–65 years old, 100%	Metabolic syndrome	NR	Nanocurcumin (80 mg/d)	Placebo	6 weeks	BDI
Vyas et al. [52]	United States	N = 720, 65.4 ± 6.5 years old, 44.4%	NR	Medical comorbidity (12.1–14.0%)	Omega-3 PUFA (1 g/d)	Placebo	2 years	DSM-IV, PHQ-9
Ogawa et al. [61]	Japan	N = 60, 65–80 years old, 50%	Healthy	NR	Flaxseed oil (3.7 g/ day) containing 2.2 g ALA	Placebo	12 weeks	GDS
Berk et al. [57]	Australia	N = 1879, ≥ 65 years old, 66.42%	Depression (CESD ≥ 8)	NR	Aspirin (100 mg/d)	Placebo	4.7 years	CES-D-10, SF-12
Ahmadpanah et al. [53]	Iran	N = 50, 65.6 ± 4.32 years old, 30%	Major depressive disorders (DSMV)	NR	Saffron (60 mg/d)	Sertraline (100 mg daily)	6 weeks	HDRS
Rondanelli et al. [63]	Italy	N = 46, 66–95 years old, 100%	Depression (DSMIV)	NR	Omega-3 PUFA (2.5 g/d)	Placebo	8 weeks	GDS, immunological parameters
Fields et al. [55]	United States	N = 449, 75.1 (70.1–90.6) years old, 46.5%	Depression (GDS > 5)	With a family history of Alzheimer-like dementia	Celecoxib (200 mg twice/d), naproxen (220 mg twice/d)	Placebo	2 years	GDS
Rondanelli et al. [64]	Italy	N = 25, 86 ± 6 years old, 80.0%	Depression (GDS > 5)	MCI	DHA (720 mg/d), tryptophan (95 mg) /d, and melatonin (5 mg/d)	Placebo	12 weeks	GDS, RAVLT, SF-36
Carlsson et al. [54]	United States	N = 35, ≥ 70 years old, 68.3%	Depression (GDS > 5)	hypercholesterolemia	Pravastatin (20 mg/d)	Placebo and tocopherol (400 IU/d)	6 months	GDS, GHP
Tajalizadekhoob et al. [65]	Iran	N = 66, ≥ 65 years old, 69.70%	Depression (GDS > 5)	None	Omega-3 PUFA (1 g/d)	Placebo	6 months	GDS, adverse events
Sharifan et al. [45]	Iran	N = 180, ≥ 55 years old, 45%	Depression (DSMIV, BDI)	Hypertension, diabetes, heart failure, stroke (11.7–50.0%)	Caspian white fish marinated with EOPF (434 g/week)	Common diet	6 months	BDI, GHQ
Tetsunaga et al. [46]	Japan	N = 70, 64 (30–84) years old, 62.86%	Depression (SDS)	Low back pain	Celecoxib (200 mg/d)	Tramadol acetaminophen (2 tablets/d)	8 weeks	SDS, NRS, PDAS, HADS, PCS
Ma et al. [47]	China	N = 55, 61 ± 11 years old, 32.73%	Depression (HADS)	Coronary artery disease	Xinkeshu (4 tablets, three times/d)	Placebo	12 weeks	HADS, PHQ-9
Chang et al. [48]	China	N = 59, 61.5 ± 9 years old, 36%	Major depressive disorders (HDRS)	Cardiovascular diseases	Omega-3 PUFA (3 g/ d)	Placebo	12 weeks	HDRS, BDI,
Okereke et al. [62]	United States	N = 10,547, 67.5 ± 7.1 years old, 49.2%	NR	NR	Omega-3 PUFA (1 g/ d) and vitamin D3 (2000 IU/d)	Placebo	5.3 years	PHQ-8

Table 1. continued

Study (year)	Country	Participants (N, age, % women)	Diseases /Condition	Comorbidity	Interventions	Control condition	Study duration	Relevant outcomes
Berk et al. [72]	Australia	N = 7252, 75.2 ± 4.0 years old, 56.4%	NR	History of depression (24.16%)	Aspirin (100 mg/d)	Placebo	4.7 years	CES-D-10, SF-12
Tofler et al. [56]	Australia	N = 85, 66.1 ± 9.4 years old, 70.59%	Bereavement	History of hypertension, depression, anxiety et al. (9–48%)	Metoprolol (25 mg/d) and aspirin (100 mg/d)	Placebo	6 months	CES-D, STAI, CBI-17
Bourdel-Marchasson et al. [69]	France	N = 125, 70.4 ± 3.9 years old, 53.6%	None	None	Native® Argan oil (25 mL/d)	Healthy Diet	2 months	CES-D, STAI, SF-36
Maltais et al. [88]	France	N = 807, 75.3 ± 4.4 years old, 65%	Memory complaints	NR	Omega-3 PUFA (1 g/d) and lifestyle intervention	Placebo	3 years	GDS
Hashimoto et al. [60]	Japan	N = 75, 88.5 ± 0.6 years old, 86.67%	NR	NR	DHA (1720 mg/d), EPA (410 mg/d)	Placebo	12 months	SDS
Kok et al. [89]	Netherlands	N = 404, 68.4 (62.2–75.9) years old, 21.96%	NR	Preexisting medical conditions (0.2–34.6%)	Dexamethasone (1 mg/kg body weight)	Placebo	1.5 years	BDI, SF-36, SRIP
Duffy et al. [58]	Australia	N = 51, 72.2 ± 4.1 years old, 37.25%	NR	MCI diagnosis (14–16%), history of depression (4–9%)	Omega-3 PUFA (1 g/d)	Placebo	12 weeks	PHQ-9
Iyengar et al. [49]	United States	N = 1497, 61 (52–69) years old, 68%	NR	Medical conditions (0–52%), Medications (0–62%)	Ibuprofen (800 mg, 3 times/d), naproxen (500 mg, twice /d), celebrex (200 mg/d)	Placebo	6 weeks	PHQ-9
Sinn et al. [67]	Australia	N = 50, ≥ 65 years old, 32%	MCI	Diabetes (14%)	EPA (1.67 g EPA + 0.16 g DHA/d), DHA (1.55 g DHA + 0.40 g EPA/d)	Linoleic acid (2.2 g/d)	6 months	GDS, SF-36, RAVLT
Giltay et al. [44]	Netherlands	N = 2037, 69 ± 5.5 years old, 19.8%	Myocardial infarction	Diabetes (18.1–20.3%), history of stroke (5.9–7.1%)	EPA + DHA (400 mg/d)	Placebo	40 months	GDS
Jean-Pierre et al. [50]	United States	N = 616, 61(18–90) years old, 67%	Cancer patients undergoing chemotherapy	NR	Modafinil (200 mg/d)	Placebo	NR	BFI-3, ESS, CESD, POMS-DD
Rest et al. [66]	Netherlands	N = 202, 70 ± 3.4 years old, 45%	NR	NR	EPA + DHA (1800 mg/d, 400 mg/d)	Placebo	26 weeks	CESD, GDS, HADS
Freund-Levi et al. [59]	Sweden	N = 178, 74 ± 9 years old, 51.7%	Alzheimer's disease	NR	EPA (150 mg) and DHA (430 mg), 4 times/d	Placebo	6 months	MADRS, NPI
Kok et al. [70]	Netherlands	N = 202, 66.6 ± 4.8 years old, 100%	Postmenopausal women	NR	Soy protein containing genistein (52 mg/d), daidzein (41 mg/d), and glycitein (6 mg/d)	Placebo	12 months	GDS, SF-36

Table 1. continued

Study (year)	Country	Participants (N, age, % women)	Diseases /Condition	Comorbidity	Interventions	Control condition	Study duration	Relevant outcomes
Ness et al. [51]	United Kingdom	N = 452, 61.1 ± 6.7 years old, 0%	Men with angina	NR	Fish dietary	Non-fish dietary	6 months	Derogatis Stress Profile
Santanello et al. [71]	United States	N = 431, ≥ 65 years old, 71%	LDL-C ≤ 221 mg/dl, LDL-C ≥ 159 mg/dl	Coronary heart disease (17%)	Lovastatin (20 mg/d, 40 mg/d)	Placebo	12 months	CESD

NR not reported in source publication, *BDI* beck depression inventory, *PUFA* polyunsaturated fatty acids, *DSM-IV*, diagnostic and statistical manual of mental disorders-IV, *PHQ* patient health questionnaire, *SF-12/36* the quality of life short form-12/36, *ALA* alpha-linolenic acid, *GDS* global health perception, *CES-D* center for epidemiological studies depression, *SF* the quality of life short form, *HDRS* hamilton depression rating scale, *GDS* geriatric depression scale, *RAVLT* rey auditory verbal learning test, *EOPF* essential oil of perilla frutescens, *GHQ* general health questionnaire, *SDS* self-rating depression scale, *NRS* numeric rating scale, *ODI* oswestry disability index. *PDAS* pain disability assessment scale, *HADS* hospital anxiety and depression scale, *PCS* pain catastrophizing scale, *IQR* interquartile range, *STAI* spielberg state-trait anxiety and anger inventory, *CBI* core bereavement items questionnaire, *DHA* docosahexaenoic acid, *SRIP* self-rating inventory for posttraumatic stress disorder, *MCI* mild cognitive impairment, *BFI* brief fatigue inventory, *ESS* epworth sleepiness scale, *POMS-DD* profile of mood states-depression dejection, *MADRS* montgomery-asberg depression rating scale, *NPI* neuropsychiatric inventory, *LDL-C* low-density lipoprotein-cholesterol.

All tests were two-tailed, with statistical significance set at $p \leq 0.05$, except where otherwise specified.

A standardized mean difference (SMD) is appropriate when studies evaluate the same parameter (e.g., depression severity score) with various measuring tools [36]. Thus, for a continuous variable, SMDs and 95% confidence intervals (CIs) were estimated for each trial using the inverse variance analysis method. When the standard deviation (SD) of the change in depressive symptoms from baseline to endpoint was not provided in the original studies, we calculated it according to the formula recommended by the Cochrane Handbook. A global estimation of 0.6 was adopted to estimate the SD [42]. For dichotomous variables, pooled odds ratios (ORs) with 95% CIs were calculated to assess the incidence of depression, response rate, and all-cause discontinuation. The Z-test was used to evaluate the statistical significance of the summarized ORs. The between-trial heterogeneity was assessed by Cochrane's χ^2 test and I^2 statistics. The existence of notable heterogeneity is defined as $I^2 \geq 50\%$ or $p \leq 0.1$. However, considering the expected heterogeneity due to different anti-inflammatory regimens and evaluation tools, the more conservative random-effects model was used for all meta-analyses.

Meta-regression analyses were conducted to investigate potential heterogeneity utilizing the STATA software (version 18, StataCorp LLC, College Station, TX, USA) based on the following potential factors: (1) publication year; (2) gender (% female); (3) sample size; (4) treatment duration; (5) country; (6) age; (7) risk of bias and (8) comorbidity. In addition, subgroup meta-analyses were conducted based on the type of control group (placebo or active control) and type of anti-inflammatory treatment. Sensitivity analyses were performed by sequentially omitting individual trials in each comparison. The results of sensitivity testing were regarded as credible if the summarized p-value was not substantially different (data not shown). Potential publication bias was identified by visual inspection of the funnel plot in comparisons that contained more than 10 trials. Funnel plots with symmetrical scatter and the p-value more than 0.05 of Begg's test were regarded as having a low risk of publication bias. Furthermore, the quality of evidence for primary outcome will be assessed by two authors (H. Gong and S.-L. Deng) independently utilizing the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) framework [43] in the GRADE Pro (McMaster University, Ontario, Canada). Consequently, the quality of evidence will be categorized into four different levels: high, moderate, low, and very low.
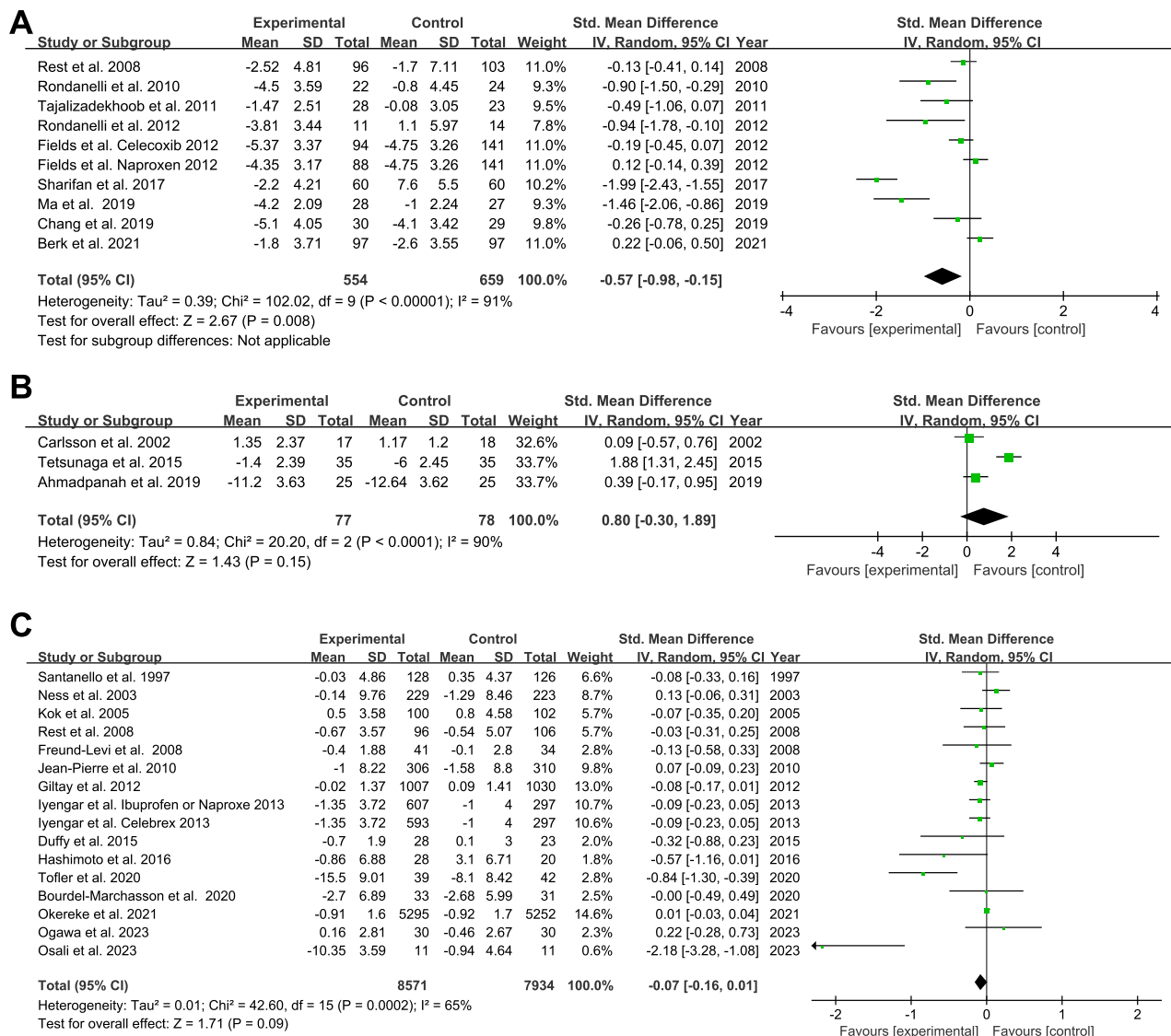
RESULTS
Study selection
The literature selection process was carried out as shown in the flow diagram of PRISMA (Fig. 1). The literature search yielded a total of 3116 citations, of which 1980 were from Embase, 700 were from PubMed, 267 were from the Cochran Library, 169 were from PsycINFO, and 81 were from other sources. Following duplicate removal using EndNote X9 software, 2644 unique records were eligible for screening by title and/or abstract. Full-text identification of 136 studies was further performed, of which 31 RCTs met the criteria and were included in this meta-analysis. One article reported both the score changes of depressive symptoms and the number of patients with severe depressive symptoms after treatment with EPA-DHA [44], which was included in the meta-analyses of the treatment and prevention of depression.

Characteristics of eligible studies
The characteristics of eligible studies are shown in Table 1. Twenty-eight eligible studies were published between 1997 and 2023 from various countries (7 from United States, 5 from

Fig. 2 Forest plots showing summary effect sizes for the primary efficacy outcomes. A Meta-analysis of anti-inflammatory interventions vs. placebo in older patients with depression. **B** Meta-analysis of anti-inflammatory interventions vs. active control in older patients with depression. **C** Meta-analysis of anti-inflammatory interventions vs. placebo in non-depressed elderly adults. SD standard deviation, CI confidence interval.
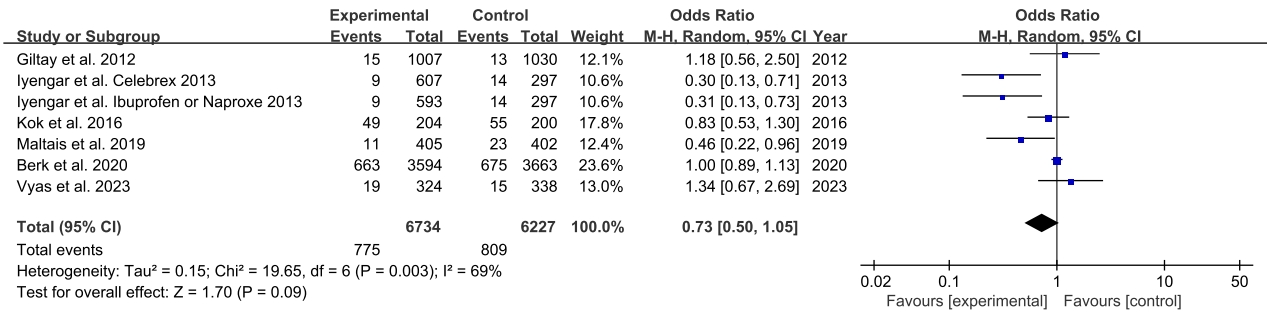
Australia, 4 from Netherlands, 4 from Iran, 2 from France, 2 from China, 3 from Japan, 2 from Italy, 1 from United Kingdom, and 1 from Sweden). The total sample consisted of 28,727 participants, and female subjects comprised 51.48% (n = 14,788) of them. Most selected studies enrolled participants aged 60 or over, except one that included patients aged 55 or over [45]. Besides, to enlarge sample size, several studies with a mean age over 60 were also included in this meta-analysis [46–52]. Participants from 11 studies were diagnosed with depression by DSM-V, DSM-IV, GDS, SDS, HADS, HDRS, or CESD. Twenty-five studies reported depressive score changes, allowing meta-analysis of the efficacy of anti-inflammatory agents. Besides, a meta-analysis was conducted to evaluate the preventive effects of anti-inflammatory management based on 7 included studies. Seven studies looked at nonsteroidal anti-inflammatory drugs (NSAIDs), 15 at omega-3 fatty acids (FA), 5 at botanical drugs or dietary interventions, 3 at statins, and 1 at dexamethasone. Most studies adopted placebos as the control groups. Besides outcomes related to depressive symptoms, some studies also reported the quality of life and adverse effects.
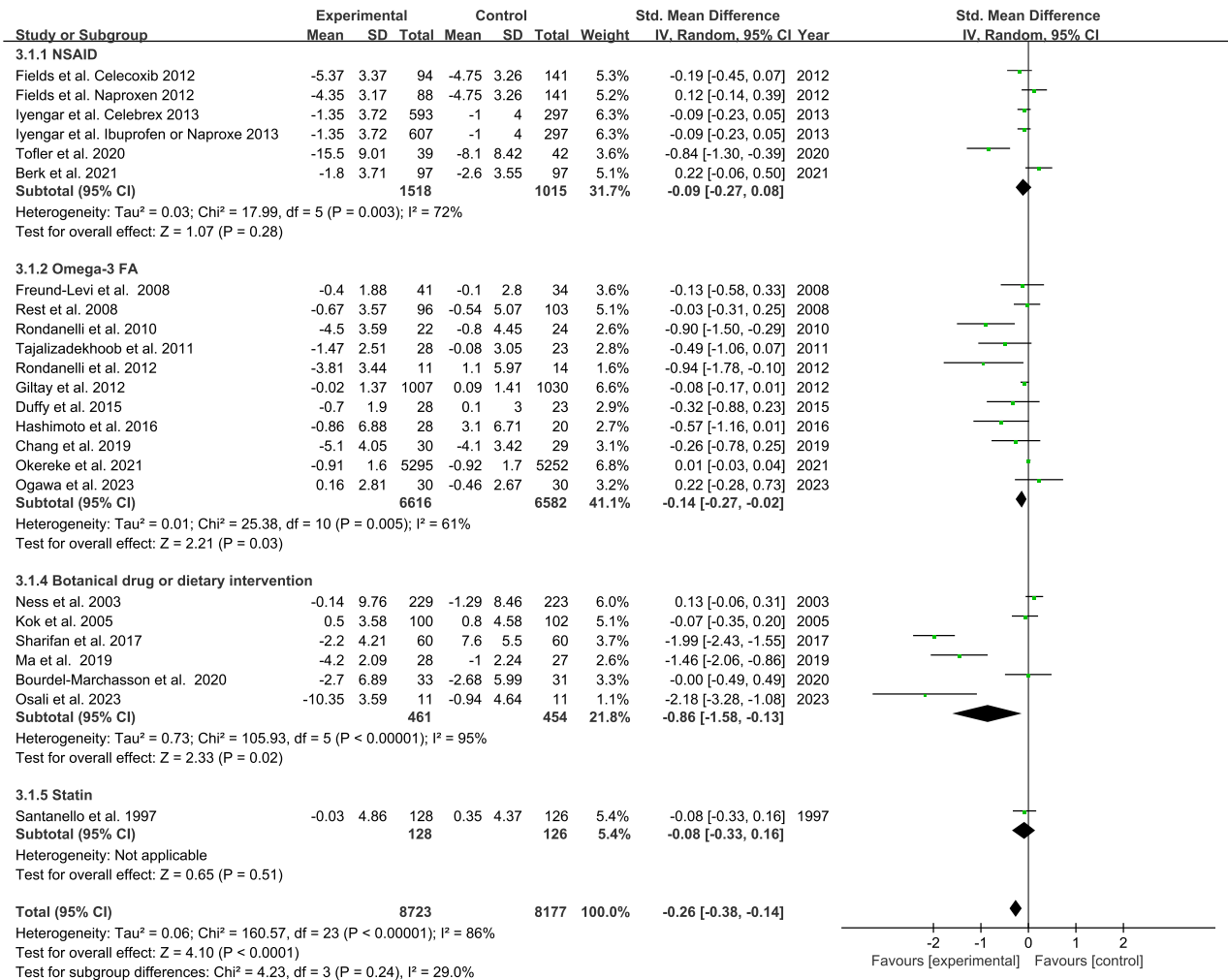
Risk of bias
The assessment of the risk of bias showed that 19 studies (61.2%) had a low risk of bias, and 6 studies (19.4%) had an unclear risk of bias. The remaining 6 studies (19.4%) were classified as having a high risk of bias owing to the presence of both performance bias and attrition bias. Overall, most of the RCTs included in this meta-analysis were rated as high-quality studies, as evidenced by the low risk of bias. Supplementary Fig. 1 shows the detailed risk-of-bias assessment, and Supplementary Fig. 2 shows the summary bias risk of the included studies.

Antidepressant effect of anti-inflammatory treatments in older adults
For studies with older patients with a diagnosis of depression, most of them (9 trials) used a placebo as the control group, except for two studies [46, 53, 54]. Compared with the placebo group, older patients administered anti-inflammatory interventions showed significantly lower depressive symptom scores (SMD = −0.57, 95% CI = −0.98 to −0.15, p = 0.008; Fig. 2A). Heterogeneity among the 9 studies was identified as significant (I² = 92%, p < 0.00001).

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Giltay et al. 2012	15	1007	13	1030	12.1%	1.18 [0.56, 2.50]	2012
Iyengar et al. Celebrex 2013	9	607	14	297	10.6%	0.30 [0.13, 0.71]	2013
Iyengar et al. Ibuprofen or Naproxe 2013	9	593	14	297	10.6%	0.31 [0.13, 0.73]	2013
Kok et al. 2016	49	204	55	200	17.8%	0.83 [0.53, 1.30]	2016
Maltais et al. 2019	11	405	23	402	12.4%	0.46 [0.22, 0.96]	2019
Berk et al. 2020	663	3594	675	3663	23.6%	1.00 [0.89, 1.13]	2020
Vyas et al. 2023	19	324	15	338	13.0%	1.34 [0.67, 2.69]	2023
Total (95% CI)		6734		6227	100.0%	0.73 [0.50, 1.05]	
Total events	775		809				

Heterogeneity: Tau² = 0.15; Chi² = 19.65, df = 6 (P = 0.003); I² = 69%
Test for overall effect: Z = 1.70 (P = 0.09)

Odds Ratio M-H, Random, 95% CI — Favours [experimental] / Favours [control] (scale 0.02 0.1 1 10 50)

Fig. 3 Forest plots showing summary effect sizes for the prevention outcomes of anti-inflammatory interventions in older adults. CI confidence interval.

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI	Year
3.1.1 NSAID									
Fields et al. Celecoxib 2012	-5.37	3.37	94	-4.75	3.26	141	5.3%	-0.19 [-0.45, 0.07]	2012
Fields et al. Naproxen 2012	-4.35	3.17	88	-4.75	3.26	141	5.2%	0.12 [-0.14, 0.39]	2012
Iyengar et al. Celebrex 2013	-1.35	3.72	593	-1	4	297	6.3%	-0.09 [-0.23, 0.05]	2013
Iyengar et al. Ibuprofen or Naproxe 2013	-1.35	3.72	607	-1	4	297	6.3%	-0.09 [-0.23, 0.05]	2013
Tofler et al. 2020	-15.5	9.01	39	-8.1	8.42	42	3.6%	-0.84 [-1.30, -0.39]	2020
Berk et al. 2021	-1.8	3.71	97	-2.6	3.55	97	5.1%	0.22 [-0.06, 0.50]	2021
Subtotal (95% CI)			1518			1015	31.7%	-0.09 [-0.27, 0.08]	

Heterogeneity: Tau² = 0.03; Chi² = 17.99, df = 5 (P = 0.003); I² = 72%
Test for overall effect: Z = 1.07 (P = 0.28)

3.1.2 Omega-3 FA									
Freund-Levi et al. 2008	-0.4	1.88	41	-0.1	2.8	34	3.6%	-0.13 [-0.58, 0.33]	2008
Rest et al. 2008	-0.67	3.57	96	-0.54	5.07	103	5.1%	-0.03 [-0.31, 0.25]	2008
Rondanelli et al. 2010	-4.5	3.59	22	-0.8	4.45	24	2.6%	-0.90 [-1.50, -0.29]	2010
Tajalizadehkoob et al. 2011	-1.47	2.51	28	-0.08	3.05	23	2.8%	-0.49 [-1.06, 0.07]	2011
Rondanelli et al. 2012	-3.81	3.44	11	1.1	5.97	14	1.6%	-0.94 [-1.78, -0.10]	2012
Giltay et al. 2012	-0.02	1.37	1007	0.09	1.41	1030	6.6%	-0.08 [-0.17, 0.01]	2012
Duffy et al. 2015	-0.7	1.9	28	0.1	3	23	2.9%	-0.32 [-0.88, 0.23]	2015
Hashimoto et al. 2016	-0.86	6.88	28	3.1	6.71	20	2.7%	-0.57 [-1.16, 0.01]	2016
Chang et al. 2019	-5.1	4.05	30	-4.1	3.42	29	3.1%	-0.26 [-0.78, 0.25]	2019
Okereke et al. 2021	-0.91	1.6	5295	-0.92	1.7	5252	6.8%	0.01 [-0.03, 0.04]	2021
Ogawa et al. 2023	0.16	2.81	30	-0.46	2.67	30	3.2%	0.22 [-0.28, 0.73]	2023
Subtotal (95% CI)			6616			6582	41.1%	-0.14 [-0.27, -0.02]	

Heterogeneity: Tau² = 0.01; Chi² = 25.38, df = 10 (P = 0.005); I² = 61%
Test for overall effect: Z = 2.21 (P = 0.03)

3.1.4 Botanical drug or dietary intervention									
Ness et al. 2003	-0.14	9.76	229	-1.29	8.46	223	6.0%	0.13 [-0.06, 0.31]	2003
Kok et al. 2005	0.5	3.58	100	0.8	4.58	102	5.1%	-0.07 [-0.35, 0.20]	2005
Sharifan et al. 2017	-2.2	4.21	60	7.6	5.5	60	3.7%	-1.99 [-2.43, -1.55]	2017
Ma et al. 2019	-4.2	2.09	28	-1	2.24	27	2.6%	-1.46 [-2.06, -0.86]	2019
Bourdel-Marchasson et al. 2020	-2.7	6.89	33	-2.68	5.99	31	3.3%	-0.00 [-0.49, 0.49]	2020
Osali et al. 2023	-10.35	3.59	11	-0.94	4.64	11	1.1%	-2.18 [-3.28, -1.08]	2023
Subtotal (95% CI)			461			454	21.8%	-0.86 [-1.58, -0.13]	

Heterogeneity: Tau² = 0.73; Chi² = 105.93, df = 5 (P < 0.00001); I² = 95%
Test for overall effect: Z = 2.33 (P = 0.02)

3.1.5 Statin									
Santanello et al. 1997	-0.03	4.86	128	0.35	4.37	126	5.4%	-0.08 [-0.33, 0.16]	1997
Subtotal (95% CI)			128			126	5.4%	-0.08 [-0.33, 0.16]	

Heterogeneity: Not applicable
Test for overall effect: Z = 0.65 (P = 0.51)

| **Total (95% CI)** | | | 8723 | | | 8177 | 100.0% | -0.26 [-0.38, -0.14] | |

Heterogeneity: Tau² = 0.06; Chi² = 160.57, df = 23 (P < 0.00001); I² = 86%
Test for overall effect: Z = 4.10 (P < 0.0001)
Test for subgroup differences: Chi² = 4.23, df = 3 (P = 0.24), I² = 29.0%

Std. Mean Difference IV, Random, 95% CI — Favours [experimental] / Favours [control] (scale -2 -1 0 1 2)
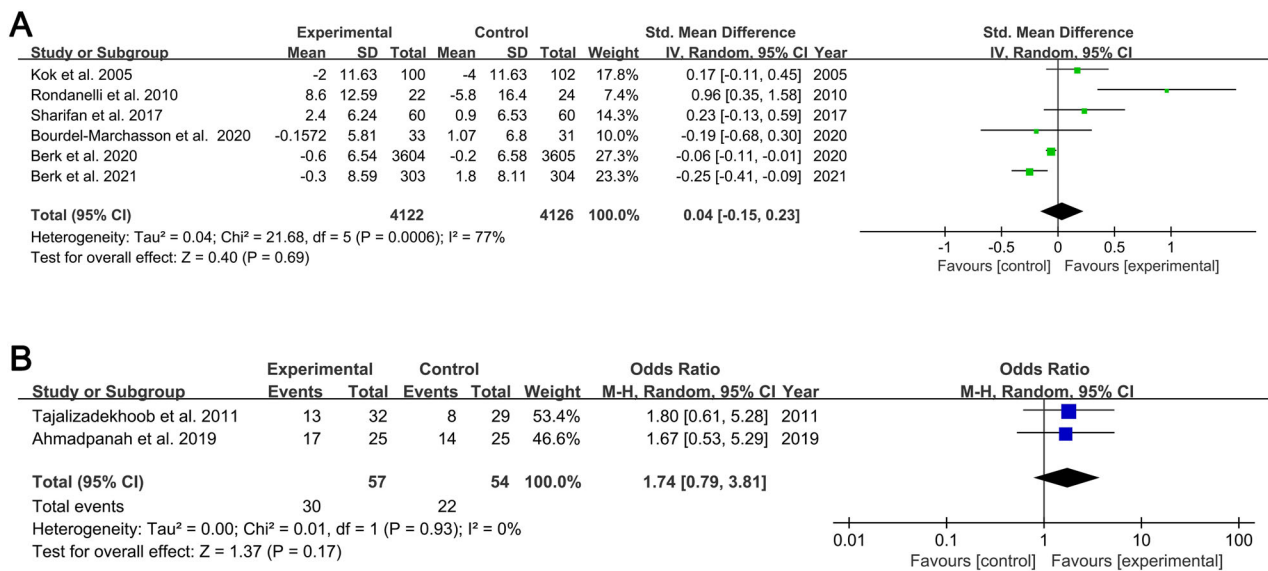
Fig. 4 Antidepressant activity of anti-inflammatory interventions vs. placebo. SD standard deviation, CI confidence interval, NSAID nonsteroidal anti-inflammatory drugs, FA fatty acid.

While compared with the active group (sertraline, tocopherol or tramadol and acetaminophen), the severity of depression in patients from the anti-inflammation group was similar (SMD = 0.80, 95% CI = −0.30 to 1.89, p = 0.15; Fig. 2B). Heterogeneity among the 3 studies was deemed significant (I² = 90%, p < 0.0001).

In addition, 15 studies enrolled 16,505 participants who were not suffering from depression at baseline. All 15 studies compared the effects of anti-inflammatory interventions with a placebo. As shown in Fig. 2C, significant heterogeneity was detected, as evidenced by I² = 65% (p = 0.0002). Pooling analysis with a random effects model revealed a lower trend in depressive score in the older subjects treated with anti-inflammatory agents compared with the placebo group (SMD = −0.07, 95% CI = −0.16 to 0.01, p = 0.09). Sensitivity analysis of each study yielded very similar findings to those of the original analysis, except for two RCTs from Ness et al. (SMD = −0.09, 95% CI = −0.18 to −0.00, p = 0.04) [51] and Jean-Pierre et al. (SMD = −0.09, 95% CI = −0.18 to 0.00, p = 0.05) [50].

Fig. 5 Forest plots showing summary effect sizes for the secondary efficacy outcomes. A Meta-analysis of anti-inflammatory interventions on mental health quality in older participants. **B** Meta-analysis of anti-inflammatory interventions on response rate in older participants. SD standard deviation, CI confidence interval.

Preventive effect of anti-inflammatory interventions on geriatric depression

Seven of the 31 available trials reported several cases of depression at the end of treatment, allowing us to summarize the preventive effect of anti-inflammatory interventions. From the results of these studies, pooling analysis indicated a moderate but not significant difference in the incidence of depression between anti-inflammatory treatment and placebo, with a pooled OR of 0.73 (95% CI = 0.50 to 1.05, p = 0.09; Fig. 3). This effect estimate was calculated based on a total of 12,961 subjects using a random effects model (I^2 = 69%, p = 0.003). Sensitivity analysis of each study yielded very similar findings to those of the original analysis, except for one outlier RCT [52] (SMD = 0.66, 95% CI = 0.43 to 0.99, p = 0.05).

Subgroup analyses

Subgroup analyses were only conducted for the efficacy outcome because of the limited data on prevention. To avoid the disturbance from active control interventions, only studies with placebo control were included in subgroup analyses based on the type of anti-inflammatory treatment. As shown in Fig. 4, four studies with 6 comparisons and 2533 participants investigated the efficacy of NSAIDs, including celecoxib [49, 55], naproxen [49, 55], ibuprofen [49], and aspirin [56, 57]. Subgroup analysis demonstrated that NSAIDs failed to exert antidepressant effects concerning the primary outcome of changes in depressive symptom severity (SMD = −0.09, 95% CI = −0.27 to 0.08, p = 0.28). Significant heterogeneity was detected among studies (I^2 = 72%, p = 0.003).

Of the studies included in the meta-analysis, 11 trials with 13,198 participants compared the effects of omega-3 FA with placebo [44, 48, 58–66]. Heterogeneity among the 11 comparisons was identified as significant (I^2 = 61%, p = 0.005). Subgroup meta-analysis for the primary outcome revealed that omega-3 FA outperformed placebo in terms of antidepressant effects (SMD = −0.14, 95% CI = −0.27 to −0.02, p = 0.03). However, sensitivity analyses showed the results could be affected by omitting one of several studies of omega-3 FA [60, 63–65]. A descriptive study [67] was excluded in the meta-analysis. This study demonstrated that the GDS scores were significant improved after treatment with EPA (p = 0.04) and DHA (p = 0.01) [67], suggesting the potential benefits of omega-3 FA intakes in reducing depressive symptoms.

In addition, 6 studies with 915 participants focused on the effects of botanical drugs or dietary interventions, including Xinkeshu tablets [47], nanocurcumin [68], argan oil [69], Soy protein [70], and fish dietary [45, 51]. Subgroup analysis of these studies yielded a moderate but significant improvement in depressive symptom scores, with a pooled SMD of −0.86 (95% CI, −1.58 to −0.13, p = 0.02). A significant heterogeneity was found among these studies (I^2 = 95%, p < 0.00001). However, sensitivity analyses performed by excluding each study seriatim in the software could change the results significantly (data not shown) [47, 68]. The remaining study explored the potential anti-depressant effects of lovastatin [71]. No significant effects of this drug were found in this single study (SMD = −0.08, 95% CI = −0.33 to 0.16, p = 0.51).

Mental health quality

Six studies [45, 57, 63, 69, 70, 72] collected the data for the changes in mental health quality as measured by the corresponding component of the SF-12 or SF-36. Meta-analysis showed no difference in score changes of mental health quality between the anti-inflammatory treatment and placebo groups (SMD = 0.04, 95% CI = −0.15 to 0.23, p = 0.69; Fig. 5A). Heterogeneity among these trails was high (I^2 = 77%, p = 0.0006).

Response rate

Only two studies [53, 65] provided the number of participants who responded to the anti-inflammatory treatment. Pooling results indicated that the response rate was similar between the two groups (OR = 1.74, 95% CI = 0.79 to 3.81, p = 0.17; Fig. 5B). A random-effects model was used due to the presupposed heterogeneity from the different interventions and treatment durations.

All-cause discontinuation

We further analyzed the all-cause discontinuation, which may help to evaluate the acceptability/safety of these treatments. For these studies missing data about the drop-out participants in each group, they were not synthesized in the meta-analysis. As shown in Fig. 6, the overall all-cause discontinuation was comparable between control group and anti-inflammatory intervention group (OR = 0.99, 95% CI = 0.95 to 1.04, p = 0.75). The similar all-cause discontinuation was also found in each subgroup, including

Fig. 6 All-cause discontinuation of anti-inflammatory interventions of the included studies. CI confidence interval, NSAID nonsteroidal anti-inflammatory drugs, FA fatty acid.

NSAID, omega-3 FA, botanical drug or dietary intervention, statin, modafinil and dexamethasone (Fig. 6).

Meta-regression analyses
Considering the obvious heterogeneity across studies, the meta-regression analyses were performed and the results were presented in the Supplemental Table 2. It showed that most modifiers did not significantly affect the effect of anti-inflammatory interventions in the indices of primary outcome and mental health quality. However, we found that age and risk of bias influenced the antidepressant effect size of anti-inflammatory interventions compared to placebo group in older patients with depression, while country influenced in older patients without depression. The anti-inflammatory interventions seem to be more effective in the younger old patients with depression. More evidence is needed to clarify the impacts of age following anti-inflammatory treatments.

Publication bias and GRADE assessment

Assessment of publication bias was conducted for the effects of anti-inflammatory interventions vs. placebo in older participants without depression at baseline. The inverted funnel plots of these studies presented significant asymmetry ($p = 0.035$), suggesting the publication bias should not be ignored (Supplementary Fig. 3). The results of GRADE assessment were shown in the Supplementary Table 3. The evidence regarding the comparison of anti-inflammatory interventions with placebo in older adults, both with and without depression, demonstrated low certainty when assessing the antidepressant effect. The low certainty of the evidence is mainly attributed the inadequate allocation concealment, substantial heterogeneity, publication bias, lack of blinding of participants and outcome assessors, etc. Furthermore, the certainty of evidence concerning the antidepressant effect of anti-inflammatory interventions relative to active control in older patients with depression was classified as very low, which is attributed to limitations in study design, significant heterogeneity, and small sample size. Additionally, considering the comorbidities and underlying diseases among the healthy elderly, we upgraded the evidence when evaluating the antidepressant and preventive effects of anti-inflammatory interventions in older adults who did not present with depression at baseline.

DISCUSSION

This meta-analysis represents the most comprehensive summary of currently available data for the treatment and prevention of anti-inflammatory interventions for depression among older adults. Our review of 31 RCTs demonstrated that anti-inflammatory interventions could be more beneficial than placebo control conditions for older adults with or without depressive disorders, and the corresponding SMDs of -0.57 and -0.07 were medium and trivial effect sizes. Compared with active control regimens (sertraline, tocopherol and tramadol), anti-inflammatory treatments were not significantly more effective in reducing depression symptoms for depressed patients, although the limited number of studies available suggests the need for further research. It should be noted that, the evidence of quality in the above outcome of antidepressant effect were low or very low, which may limit the application of this evidence in clinical practice and guideline development. Overall, our results among older adults are consistent with those of previous meta-analyses [37, 39, 40], which also report small to medium effects of anti-inflammatory treatments for patients with depressive symptoms. Intriguingly, we find beneficial effects of omega-3 FA and botanical drug or dietary intervention, but not NSAIDs and statins, among old population. However, young adult MDD patients may benefit from a broader spectrum of anti-inflammatory agents, including NSAIDs, statins, cytokine inhibitors, etc [39, 40]. This distinction might be partially attributed to the severity of depression. The inflammatory activity may be particularly elevated in these severe MDD patients [73], making them benefits more from the classic anti-inflammatory agents.

The preventative effects of anti-inflammatory management for depression have seldom been investigated in previous meta-analyses. Our findings showed that older participants who administered anti-inflammatory interventions might be less likely to suffer from depression than those in the placebo condition. However, the marginal p-value and the upper limit of the credible interval close to the line of no difference suggest concern about whether this estimate is robust enough to guide clinical practice.

Subgroup analyses indicated that omega-3 FA and botanical drug or dietary intervention significantly improved depressive symptoms in older adults, whereas NSAIDs and statins did not. However, the beneficial magnitude of omega-3 FA and botanical drug or dietary intervention is small. Sensitivity analyses also indicate that the anti-depressant effects could be affected by omitting some included studies. Future high-quality RCTs with large sample size are needed to further verify the efficacy of these anti-inflammatory interventions. The current findings suggest that omega-3 FA and botanical drug or dietary intervention may be a superior option than other anti-inflammatory interventions for older adults, even though the benefits of some types, such as statins, have been confirmed among adults [39]. Two meta-analyses of studies reported similar effects of omega-3 FA on reducing depressive symptoms in the elderly population (Hedges' $g = -0.94$, 95% CI $= -1.37$ to 0.50; $d = -0.428$, 95% CI $= -0.822$ to -0.035) [74, 75]. However, these previous meta-analyses focused on older adults and only investigated the anti-depressant efficacy of omega-3 FA, without evaluating other types of anti-inflammatory regimens or their preventative effects. Besides, omega-3 FA has been recommended for MDD treatment for the elderly, children, and pregnant women, and prevention in high-risk populations [76]. It should be noted that the negative results of statin and NSAIDs are estimated based on very limited data from studies with significant heterogeneity among them. Surprisingly, several main types of anti-inflammatory agents, such as cytokine inhibitors and corticosteroids for adults with depression were not retrieved in the meta-analysis. One possible interpretation for the lack of these studies is the concern about the safety of these drugs for frail seniors. Moreover, we did not conduct subgroup analyses regarding medical comorbidity condition or the treatment duration due to the insufficient data from included original studies. But certain medical comorbidities may moderate anti-inflammatory treatment impact. For instance, some comorbid conditions of depression, including rheumatoid arthritis [77] and vascular disease [78], are characterized by chronic inflammation. The effectiveness of anti-inflammatory treatment for depression might be partially reduced by overwhelming the comorbidity-evoked inflammation. Besides, comorbidities such as gastrointestinal disorders can affect the drug absorption, and kidney diseases can affect the drug metabolism. These pharmacological alterations may attenuate the benefits of anti-inflammatory treatment for late-life depression. Thus, future studies are need to determine whether increasing the dosage and/or prolonging the treatment duration may enhance the anti-depressant effects of anti-inflammatory interventions in such populations.

Regarding the mental health quality, meta-analysis revealed that anti-inflammatory interventions and control conditions had comparable effects. Several factors may explain this finding. First, participants with chronic comorbidities, such as hypertension and diabetes [45], may benefit less than others. Second, the number of trials in this comparison is few. Physical functioning was not pooled for meta-analysis because some studies only focused on the mental health quality [57, 72]. Moreover, anti-inflammatory interventions have no positive effects on response in older adults with depression, owing to the active control (Sertraline) and small sample size ($n = 111$). Only two included studies reported the response rates, but did not provide the range and mode of response rate criteria [53, 65]. Future studies are needed to reveal the response rate using accepted definitions. Specifically, for the clinical research community of depression researchers, response is a widely-used psychometric term that is defined as a $\geq 50\%$ decrease from baseline to endpoint in a rating scale [79, 80]. And the 50% limit for response has been validated in multiple depression rating scales, including HAMD, MADRS and BDI [81]. Moreover, it is also helpful to evaluate the efficacy of anti-inflammatory treatment based on the traditional criteria used for endpoint classification: nonresponse ($< 30\%$ improvement), partial response (30–49% improvement), response ($\geq 50\%$ improvement without reaching remission), and remission (HAMD-17 ≤ 7) [82].

Even though we tried our best to summarize important indicators as much as possible, some of them were not conducted

due to insufficient reports, including the detailed safety profile and the comorbidity of inflammatory diseases (such as auto-immune disease [83]). Our meta-analysis showed the similar all-cause discontinuation between two groups, indicating the acceptable safety of anti-inflammatory intervention. These findings are in line with previous evidence of these agents in adult patients with MDD [40]. But whether they are safe and which of them have the highest benefit-risk expectations for older adults remain unanswerable questions. Moreover, most included studies only adopted anti-inflammatory monotherapies as interventions. Given that the add-on therapies based on classic antidepressants also improved depressive symptoms for MDD patients [39, 40], further studies are also needed to investigate the efficacy and safety of adjunctive treatments with antidepressants and anti-inflammatory interventions, especially for these older patients with severe MDD.

To capture these heterogenous processes of inflammaging, various biomarkers related to inflammaging have been proposed to date, however, a broad consensus has not been reached due to this complex biological process. It is possible to identify C-reactive protein (CRP), tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) and IL-1 as the most relevant systemic markers related to inflammaging [84]. In the context of depression, previous meta-analysis has also identified several inflammatory markers, including CRP and IL-12 [85]. Since CRP is widely used in clinical and research settings, based on the above evidence, CRP could be regarded as one of the potential inflammatory markers in older adults with depression. According to previous work from our and other teams [21, 86], the cut-off of CRP could be set at 3 mg/L. Among the included studies in the present meta-analysis, three studies reported the CRP levels at baseline [48, 65, 69]. One of them reported the change of CRP levels from baseline, which showed no significant change in both control diet group and anti-inflammatory diet group [69]. Future researches are encouraged to report the detailed changes of common inflammatory markers, which would be helpful for preventing the risk of bias and improve the study quality and credibility. Even more importantly, future clinical trials should pay much attention to investigate the pathophysiologic mechanism of the potential anti-inflammatory interventions and avoid to relegate the field to broad spectrum therapeutics [87]. Specifically, future RCTs with anti-inflammatory agents should identify and enrich for inflammatory subgroups of MDD patients using stratified approaches, for instance, circulating CRP > 3 mg/L. Moreover, in addition to the efficacy and safety files, the relevant inflammatory pathways along the chain of pathology should also been verified after anti-inflammatory intervention. All these efforts will contribute to the precise treatment of depression.

This study provides a new perspective on using anti-inflammatory interventions in the elderly population. The anti-inflammatory regimen can be a potential choice for depression amelioration and prevention in older adults. Considering the limited efficacy of current antidepressant agents, it is warranted to further assess the combined effect of antidepressants and omega-3 FA, botanical drug or dietary intervention. Besides, more high-quality RCTs are needed to answer the following important questions. First, which kind of botanical drug or dietary interventions or what ratio of omega-3 FA is most recommended for older adults? Second, how do we adjust the anti-inflammatory regimens for therapeutic or preventative purposes?

This meta-analysis had several limitations. First, to retrieve as much data as possible from available clinical studies of anti-inflammatory interventions in managing of depressive symptoms in elder subjects, we included subjects with an average age older than 60. The results may be underestimated or overestimated due to this confounding factor, while we took this confounding factor into account in the GRADE assessment. Second, although all the included original studies were RCTs, the baseline depressive scores could be different [45]. Meta-analysis based on the changes

in depressive symptoms from baseline to endpoint could mitigate but could not fully avoid the potential overestimation of our results. Besides, given that most included studies assessed depressive symptoms by GDS > 5 points, our findings could be more applicable for mild to moderate depression in the elderly. The efficacy of anti-inflammatory treatments on severe depression remains to be verified by further clinical trials. Third, substantial heterogeneity was found in most analyses, which could not be effectively avoided by subgroup analysis or sensitivity analysis. Fourth, insufficient data were available to determine the difference in efficacy of anti-inflammatory interventions on older participants with and without high-level baseline inflammation. Fifth, the classification of anti-inflammatory treatments for older adults remains provisional. For instance, the interventions implemented in the studies of this meta-analysis under the heading "botanical drug or dietary intervention" were somewhat heterogeneous.

In conclusion, our findings of the comprehensive meta-analysis support the notion that anti-inflammatory interventions might help to prevent and reduce depressive symptoms in older participants with or without depression. Omega-3 FA and botanical drugs, or dietary intervention, rather than NSAIDs or statins, show promising anti-depressant effects in older adults. However, the results should be interpreted with caution due to significant heterogeneity in most comparisons. Future RCTs are warranted to further assess the safety and efficacy of anti-inflammatory intervention monotherapy or combined treatment with first-line antidepressants.

DATA AVAILABILITY
Data will be made available on request to the author (H. Gong, hgong@tmmu.edu.cn).

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AUTHOR CONTRIBUTIONS

HG, DMZ, and XTF jointly conceptualized the study and wrote the draft of the manuscript. HG, WJS, and SLD conducted the statistical analyses and verified the data. YL and KYL visualized the data in tables and figures. JL and ZLD provided administrative and technical supports. HG, WJS, and XTF obtained funding. All authors revised and approved the final version of the manuscript.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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