Journal of Alzheimer's Disease 94 (2023) S267–S287
DOI 10.3233/JAD-221076
IOS Press

Systematic Review

Effects of S-Adenosylmethionine on Cognition in Animals and Humans: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Accepted 24 February 2023
Pre-press 24 March 2023

Abstract.
Background: There is increasing evidence that supplementation of S-adenosylmethionine (SAM) can improve cognitive function in animals and humans, although the outcomes are not always inconsistent.
Objective: We conducted a systematic review and meta-analysis to evaluate the correlation between SAM supplementation and improved cognitive function.
Methods: We searched studies in the PubMed, Cochrane Library, Embase, Web of Science, and Clinical Trials databases from January 1, 2002 to January 1, 2022. Risk of bias was assessed using the Cochrane risk of bias 2.0 (human studies) and the Systematic Review Center for Laboratory Animal Experimentation risk of bias (animal studies) tools; and evidence quality was evaluated using the Grading of Recommendations Assessment, Development, and Evaluation. STATA software was employed to perform meta-analysis, and the random-effects models was used to evaluate the standardized mean difference with 95% confidence intervals.
Results: Out of the 2,375 studies screened, 30 studies met the inclusion criteria. Meta-analyses of animal ($p = 0.213$) and human ($p = 0.047$) studies showed that there were no significant differences between the SAM supplementation and control groups. The results of the subgroup analyses showed that the animals aged $\leq$8 weeks ($p = 0.027$) and the intervention duration >8 weeks ($p = 0.009$) were significantly different compared to the controls. Additionally, the Morris water maze test ($p = 0.005$) used to assess the cognitive level of the animals revealed that SAM could enhance spatial learning and memory in animals.
Conclusion: SAM supplementation showed no significant improvement in cognition. Therefore, further studies are needed to assess the effectiveness of SAM supplementation.

Keywords: Cognition, meta-analyses, Morris water maze test, randomized controlled trials, S-adenosylmethionine

PROSPERO registration number: CRD42022316443

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INTRODUCTION

"Cognitive frailty", which is a common clinical symptom, is defined by the presence of cognitive function decline and physical frailty simultaneously in older adults, without a clear diagnosis of dementia [1]. It is a precursor to numerous neurodegenerative diseases, including Parkinson's disease, mild cognitive impairment (MCI), and Alzheimer's disease (AD). As it is reversible, it is an available objective in terms of prevention [2]. AD is a chronic neurodegenerative disease that manifests in gradual cognitive function decline, such as memory and learning, progressing to dementia. With the rapid aging of the population, approximately one new case of AD every 3 seconds, and the number of cases is expected to increase to 150 million by 2050, imposing a significant economic burden on families and society [3]. However, early prevention can effectively control the progression of cognitive decline [4]. Therefore, there is an urgent need to identify effective interventions or supplements for delaying cognition decline.

Recently, S-adenosylmethionine (SAM), which was discovered by Italian scientists in 1952 [5], has emerged as a key factor influencing neurophysiological and psychophysiological functions in animals and humans, including neurodevelopment, emotion, and cognition [6]. SAM is a natural compound produced in the liver from adenosine triphosphate and methionine under enzymatic catalysis. As a methyl donor, SAM participates in deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) methylation. Methylation refers to methyl group transfer from the active methyl compounds to other compounds through catalysis, including proteins and nucleic acids. These compounds can be chemically modified to generate important substances [7].

Several studies [5, 8] have shown that SAM can cross the blood-brain barrier in animals and humans, and plays an integral role in slowing cognitive decline

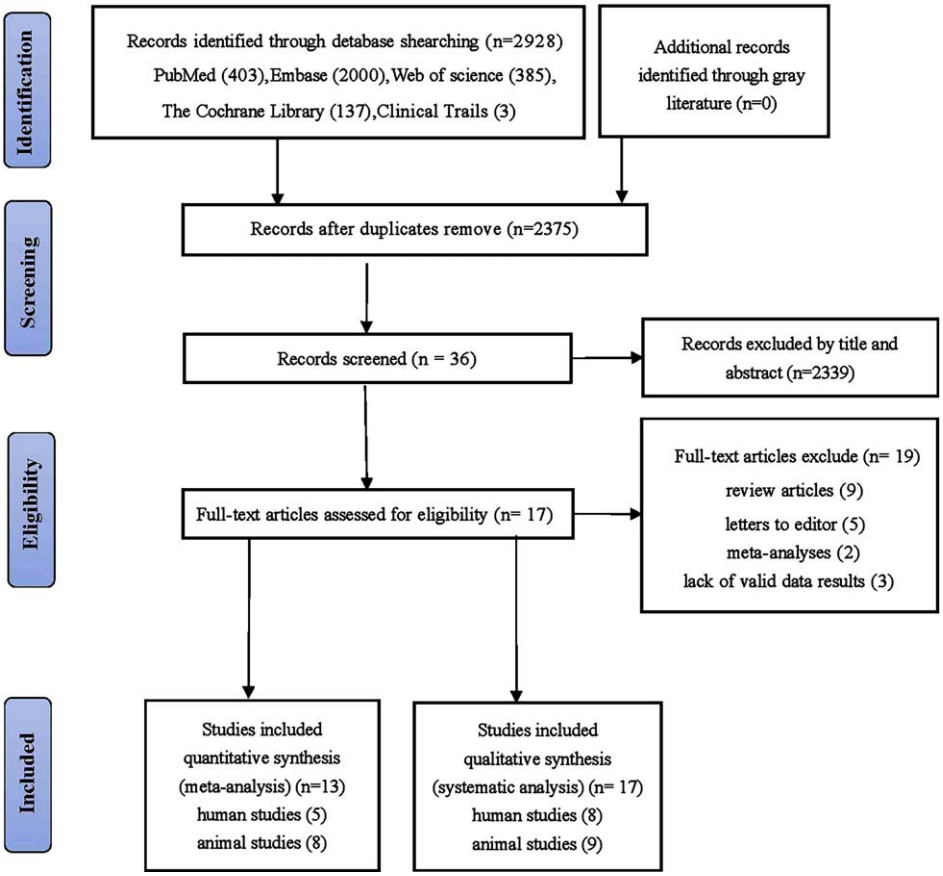

Fig. 1. Flowchart for searching and selection of the included studies.

Table 1
Characteristics of included animal studies.

Study	Study design	Region	Animal models and Diseases	Sample size		Age (weeks)	Duration (weeks)	Measurement of cognition / cognitive tests	Included in meta-analyses?
				Control	Experimental				
Tillmann et al., 2019 [24]	RCT	Denmark	FSL	10	9	10.4 ± 2.1 weeks	4 weeks	NOR; Y-Maze	yes
Chan et al., 2008A [19]	RCT	USA	C57B/6	7	7	36–48 weeks	4 weeks	Y-maze	yes
Chan et al., 2008B [19]	RCT	USA	ApoE –/–	7	7	36–48 weeks	4 weeks	Y-maze	yes
Chan et al., 2008C [19]	RCT	USA	ApoE2	7	7	36–48 weeks	4 weeks	Y-maze	yes
Chan et al., 2008D [19]	RCT	USA	ApoE3	7	7	36–48 weeks	4 weeks	Y-maze	yes
Chan et al., 2008E [19]	RCT	USA	ApoE4	7	7	36–48 weeks	4 weeks	Y-maze	yes
Chan et al., 2008F [19]	RCT	USA	C57B/6	7	7	104–128 weeks	4 weeks	Y-maze	yes
Chan et al., 2008G [19]	RCT	USA	MTHFR+/–	7	7	36–48 weeks	4 weeks	Y-maze	yes
Chan et al., 2008H [19]	RCT	USA	MTHFR+/+	7	7	36–48 weeks	4 weeks	Y-maze	yes
Tchantchou et al., 2004 [23]	RCT	USA	ApoE–/–	3-4	3-4	36–48 weeks	4 weeks	Y-maze; T-maze	yes
Shea 2007A [20]	RCT	USA	normal C57B/6	–	8	36–48 weeks	2 weeks-4 weeks	Y-maze	no
Shea 2007B [20]	RCT	USA	ApoE4	6	6	36–48 weeks	2 weeks-4 weeks	Y-maze	no
Cao et al., 2008A [18]	RCT	China	Control	10	9	3 weeks	3 weeks	MWM	yes
Cao et al., 2008B [18]	RCT	China	Pb exposure	9	9	3 weeks	3 weeks	MWM	yes
Wan et al., 2020A [25]	RCT	China	C57	20	20	8 weeks	28 weeks	MWM	yes
Wan et al., 2020B [25]	RCT	China	APP/PS1	9–15	9–15	8 weeks	28 weeks	MWM	yes
Fuso et al., 2012A [21]	RCT	Italy	TgCRND8	10	9	12 weeks	12 weeks	PAT; MWM	yes
Fuso et al., 2012B [21]	RCT	Italy	129Sv	15	12	12 weeks	12 weeks	PAT; MWM	yes
Beauchamp et al., 2020A [17]	RCT	Australia	WT	6	6	24 weeks	3 weeks	Y-maze	no
Beauchamp et al., 2020B [17]	RCT	Australia	rTg4510	7	7	24 weeks	3 weeks	Y-maze	yes
Gregoire et al., 2017A [22]	RCT	Canada	CD1	7	8	10–12 weeks	12 weeks	PAT; NOR	yes
Gregoire et al., 2017B [22]	RCT	Canada	CD1	6	6	10–12 weeks	12 weeks	PAT; NOR	yes

FSL, Flinders Sensitive Line; *APOE*, apolipoprotein; MTHFR, methylene tetrahydrofolate reductase; C57, wild-type C57BL/6J mice; APP/PS1, APPswe/PS1dE9 (APP/PS1) mice; WT, wild-type mice; NOR, novel object recognition; MWM, Morris water maze tests; PAT, passive avoidance test; –, data not available.

by modulating important factors, such as the methionine metabolic cycle, methylation, and oxidation metabolism [9, 10]. It has been confirmed that low SAM levels in cerebrospinal fluid in some patients with dementia may lead to disorders of methylation metabolism in the nervous system, including hyperhomocysteine, folic acid, and vitamin B_{12} deficiency [8]. However, some studies have shown [9] that SAM does not affect the cognitive function of some patients. To date, animal and human studies have reported conflicting results, which present a challenge in drawing definitive conclusions regarding SAM's improvement in cognitive performance.

Therefore, this systematic review and meta-analysis aimed to provide qualitative and quantitative results on the effects of SAM supplements on the cognition of animals and humans, to provide reliable references for subsequent studies.

MATERIALS AND METHODS

This meta-analysis was registered in PROSPERO (CRD42022316443) and was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines [11].

Literature search strategy

A systematic literature search was conducted to identify studies on the effect of SAM supplementation on cognitive function in animals and humans. Five electronic databases were searched (PubMed, Cochrane Library, Embase, Web of Science, and Clinical Trials [https://clinicaltrials.gov/]) to identify potentially eligible articles from January 1, 2002 to January 1, 2022, using the following terms: ("S-adenosylmethionine" OR "S-adenosyl methionine" OR "S-adenosyl-L-methionine" OR "SAM" OR "SAM-e" OR "AdoMet") AND ("Alzheimer Disease" OR "Alzheimer*" OR "dementia" OR "cognitive" OR "cognition") AND ("RCT" OR "Random*" OR "control*" OR "randomised controlled trial"). The language of the study was limited to English. We screened the titles to exclude duplicate studies and reviews, and then screened the titles and abstracts to exclude inappropriate articles. Subsequently, the final inclusion was determined by reviewing the full text of the remaining studies. Gray literature and references of the selected articles were also examined to glean other possible publica-

Table 2
Characteristics of included human studies

Study	Study design	Region	Diseases	Sample size		Age (mean ± SD)		Duration (weeks)	Measurement of cognition/ cognitive tests	Included in meta-analyses?
				Control	Experimental	Control	Experimental			
Chanet et al., 2008 [26]	Open-Label Study	USA	AD		21		–	48 weeks	DRS; NPI; Clox; ADCS-ADL	no
Remington et al., 2009 [28]	RCT	USA	AD	6	6		–	36 weeks	DRS; NPI; Clox; ADCS-ADL	yes
Remington et al., 2015A [29]	RCT	USA	AD	44	62	79.7 ± 8.6	78.7 ± 7.9	24 weeks	DRS; NPI; Clox; ADL	yes
Remington et al., 2015B [30]	RCT	USA	MCI	12	22	79.7 ± 8.6	78.7 ± 7.9	24 weeks	DRS; Clox	yes
Remington et al., 2016 [31]	Open-Label Study	USA	AD	24		78.4 ± 5.7		52 weeks	ADL; NPI	no
Chan et al., 2010 [6]	RCT	USA	subjects without dementia	56	59	–		12 weeks	CVLT II; Trail-making test	yes
Strous et al., 2009 [9]	RCT	Israel	schizophrenia	8	7	43.7 ± 14.8	39 ± 8.9	9 weeks	Global cognitive scores	no
Levkovitz et al., 2012 [27]	RCT	USA	MDD	19	27	50.5 ± 9.7	54.3 ± 13.5	6 weeks	CPFQ	yes

RCT, randomized controlled trial; SD, standard deviation; AD, Alzheimer's disease; MCI, mild cognitive impairment; MDD, Major depressive disorder; DRS, Dementia Rating Scale; NPI, Neuropsychiatric Inventory; Clox, Clock Drawing Tests; ADCS-ADL, Alzheimer's Disease Cooperative Study–Activities of Daily Living; CVLT II, California Verbal Learning Test II; CPFQ, Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire; –, data not available.

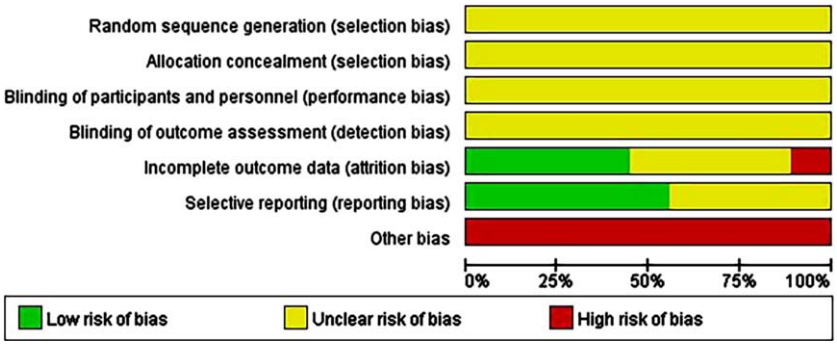

Fig. 2A. Risk-of-bias assessments of the included animal studies (domains from the Cochrane Handbook for Systematic Reviews of Interventions).

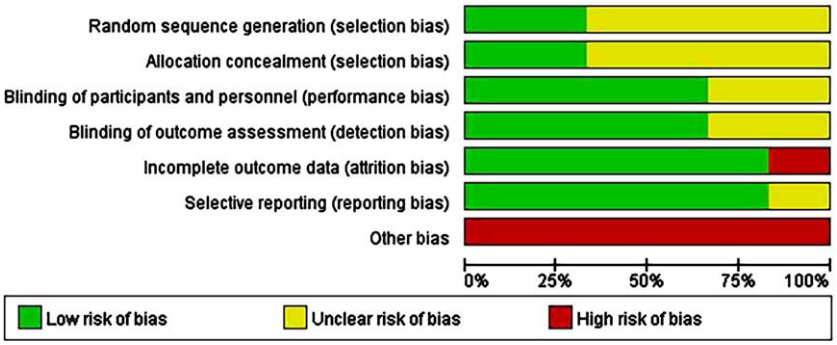

Fig. 2B. Risk-of-bias assessments of the included human studies (domains from the Cochrane Handbook for Systematic Reviews of Interventions).

tions (for a detailed description, see Supplementary File 1).

Inclusion and exclusion criteria

All studies included in the initial search strictly met the criteria of the Population, Intervention, Comparison, Outcome, and Study design framework, according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses recommendations [11].

Animals

a) Subjects were female or male rodents with or without cognitive impairment; b) The intervention was SAM supplements; c) Randomized controlled trials, including control and experimental groups; d) The outcome was a cognitive function test, including the Morris water maze (MWM) test, T- or Y-maze test, Novel Object Recognition (NOR) test, or passive avoidance test; and e) Studies without full text or primary data that could not be extracted electronically were excluded.

Humans

a) Participants were older than 18 years. There were no restrictions on baseline cognitive status due to the differences in the cognitive assessment criteria; b) Pregnant or lactating women, epilepsy, mania, bipolar affective disorder, and other potentially dangerous conditions were excluded; c) Experiments that including SAM intervention alone or in a nutritional supplement form (any dose or method of administration) to improve cognitive function; d) The same conditions were applied to the control group, except that there was no SAM or nutritional supplementation intervention; e) At least one cognitive function outcome was assessed; and f) Randomized controlled trials and open-label experiments were included.

Data extraction

The following information was extracted independently and cross-checked by two reviewers: Author(s), year, country, study design, sample size, age, diagnosis, intervention duration, and measurement of cognition. Furthermore, animal

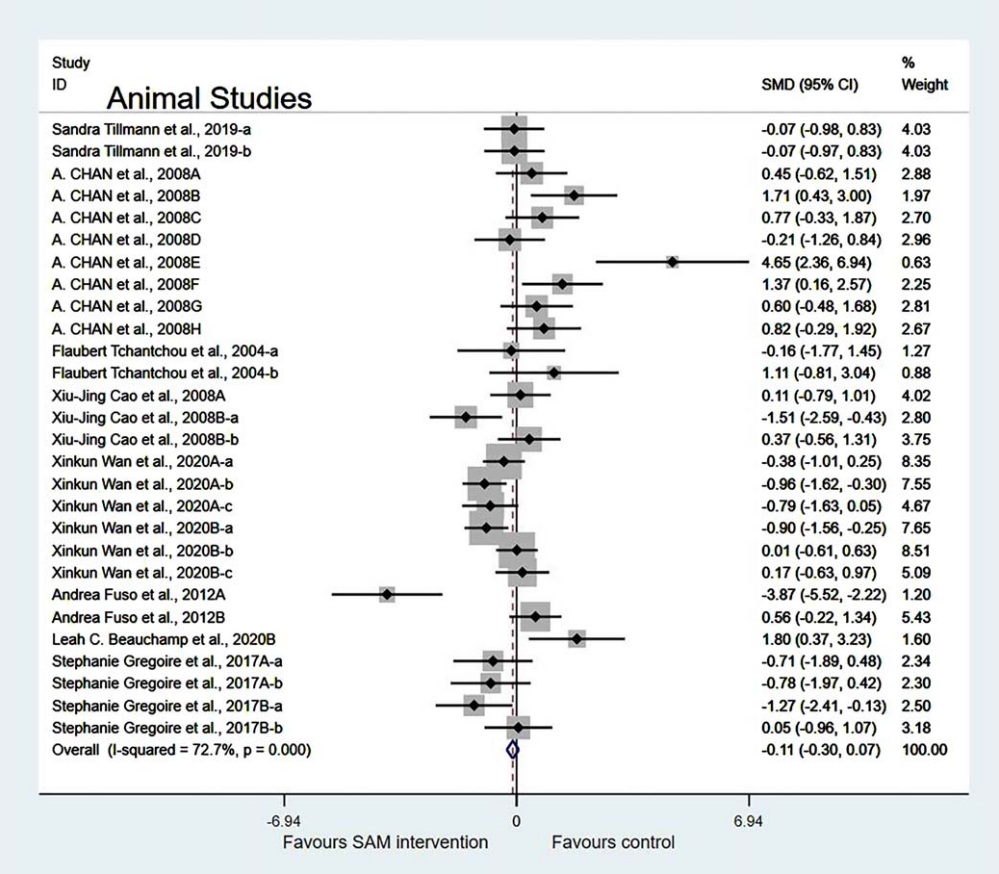

Fig. 3. Forest plot of 28 animal studies of overall effect of S-adenosylmethionine on cognition. SMD, Standardized mean difference; CI, confidence interval; p: heterogeneity *p*-value; SAM: S-adenosylmethionine; Control: placebo.

Table 3
GRADE quality of evidence assessment of outcome indicators for the efficacy of SAM in the treatment of cognition

Outcome indicator	Number of included cases	Heterogeneity		Model of analysis	Group effect value		Estimated value	95% CI	Grade
		I^2	*p*		Z	*p*			
Between SAM intervention versus Control for animals	537	72.7%	<0.0001	Random effect	0.02	0.984	0.00 (SMD)	–0.36, 0.36	Moderate
Between SAM intervention versus Control for human	1296	41.4%	0.025	Random effect	1.32	0.186	0.10 (SMD)	–0.05, 0.26	High

SMD, standardized mean difference; CI, confidence interval; GRADE, Grading of Recommendation Assessment, Development and Evaluation.

models were extracted for animal studies. Data were collected from the graph using the GetData software. The primary data were estimated based on the coordinate axis, and the mean and standard deviation were calculated statistically. If the data were unavailable, we contacted authors further.

Risk of bias and quality assessment

Two authors independently assessed the risk of bias in human studies using the Cochrane RoB 2.0 tool [12] per protocol for parallel-group randomized trials, and in animal studies using the Systematic Review Centre for Laboratory Animal Experimen-

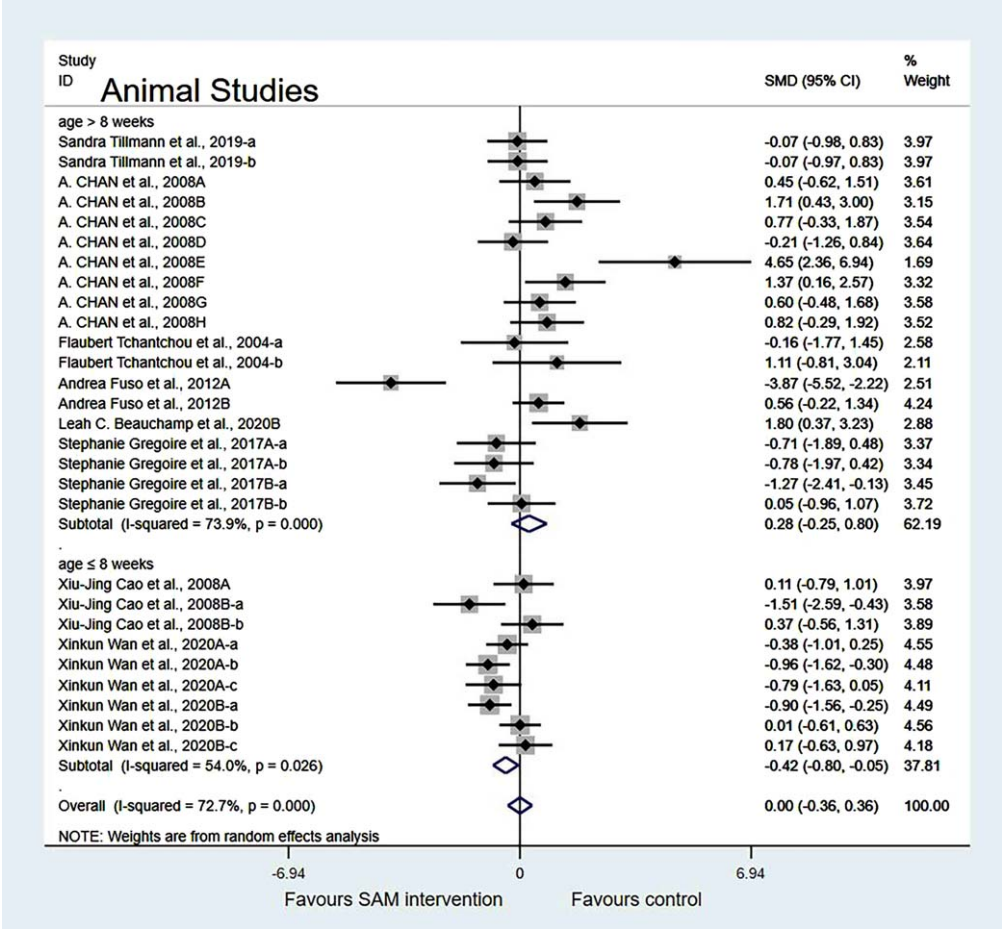

Fig. 4. Forest plot of 28 animal studies of random-effects model subgroup analysis according to animal age. SMD, Standardized mean difference; CI, confidence interval; p: heterogeneity *p*-value; SAM: S-adenosylmethionine; Control: placebo.

tation tool [13]. The reviewers assessed each study item as "high risk", "low risk", or "unclear risk" of bias. A third reviewer discussed the results if any disagreements existed. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology was used to evaluate the quality of the body of retrieved evidence (GRADEpro; https://gdt.gradepro.org/app/#projects). The GRADE system assessed evidence quality in the following four classes: high, moderate, low, or very low. The initial grading would decrease if there were study limitations, inconsistencies, imprecision, indirectness, or publication bias [14].

Data synthesis and analysis

Statistical analysis was performed using the Stata software version 16.0 (StataCorp, College Station, TX, USA). Data were described as the standardized mean difference (SMD) and the effect size 95% confidence intervals (CI). A random effects model [15] was used to present the data. Statistical significance was set at $p < 0.05$. Furthermore, the degree of heterogeneity was assessed using the I^2 statistic, with I^2 values of 25, 50, and 75% being considered to indicate low, moderate, and high heterogeneity, respectively [16]. A sensitivity analysis was performed when high heterogeneity was present. In addition, subgroup analyses were performed by animal age, cognitive tests, intervention duration, cognitive domains, or cognitive scales. Funnel plots were used to examine the potential publication bias.

RESULTS

Study selection

The initial search identified 2,928 articles, with 403, 137, 2,000, 385, and 3 from PubMed, Cochrane,

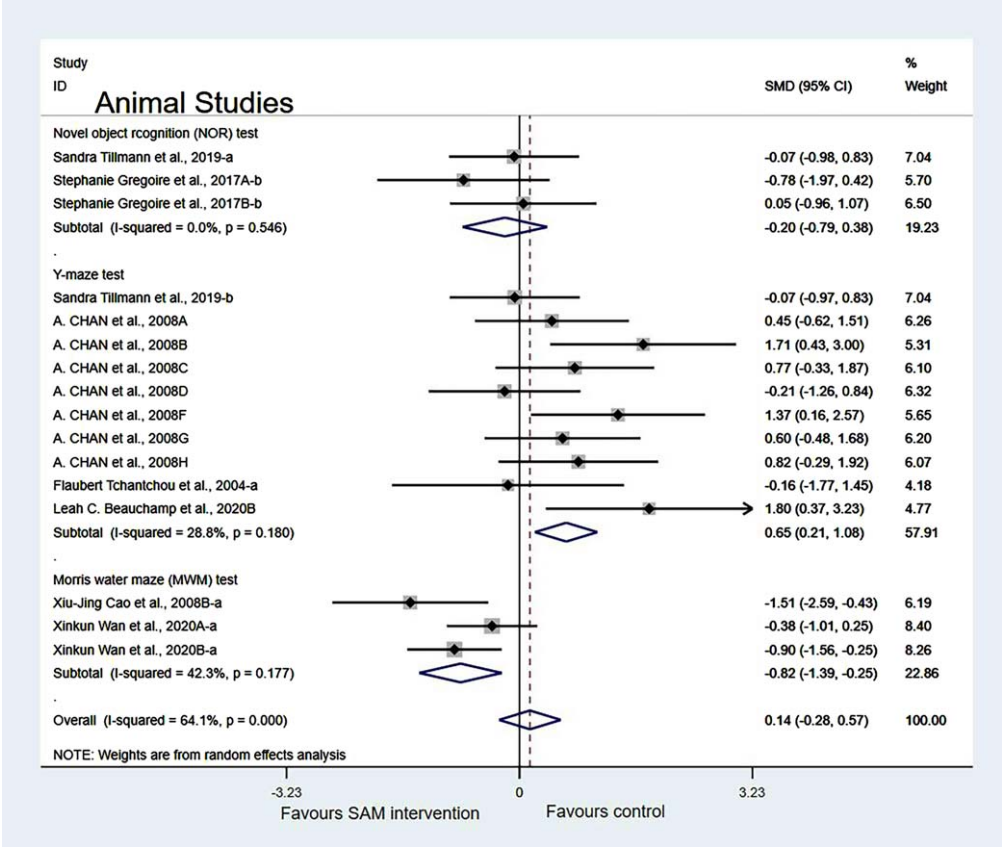

Fig. 5. Forest plot of 16 animal studies of random-effects model subgroup analysis according to cognitive tests. SMD, Standardized mean difference; CI, confidence interval; p: heterogeneity *p*-value; SAM: S-adenosylmethionine; Control: placebo.

Embase, Web of Science, and Clinical Trials respectively (Fig. 1). After removing duplicates, 36 articles were screened based on their titles and abstracts, and 2,339 were excluded. The full texts of the remaining 36 articles were reviewed, and 19 were excluded because they did not meet the inclusion criteria. Overall, 17 studies were included in the systematic review and 13 in the meta-analysis.

Study characteristics

Across the nine animal articles [17–25] included in the systematic review, eight studies [17–19, 21–25] contained meta-analysis that met the eligibility criteria (with some articles comprising of multiple eligible experiments or datasets). Three of the studies [19, 20, 21] were conducted in the United States, one in Denmark [22], two in China [18, 25], one in Italy [21], one in Australia [17], and one in Canada [21]. All studies were published between 2004 and 2020. Furthermore, the effect of SAM on spatial learning and memory was assessed using extra-maze cues to navigate in the MWM, spontaneous alternation in a T- or Y-maze, or NOR tasks. Moreover, six, three, and thirteen experiments used the MWM, NOR, and the T- or Y-maze, respectively (Table 1).

In this systematic review, eight human articles were included [10, 26–32]. Five articles were included in the meta-analysis. In addition, seven studies were conducted in the United States and one in Israel. All studies were published between 2008 and 2016. The included studies consisted of six randomized controlled trials [6, 10, 27–31] and two open-label trials [26, 31]. Four studies [26, 28, 29, 31] examined cognition in patients with AD, whereas four [6, 10, 27, 30] were conducted on MCI, depression, schizophrenia, or patients without dementia. Six studies [6, 26, 28–31] investigated the effect of a nutriceutical formulation diet containing SAM; only two studies [10, 27]evaluated the effect of SAM supplementation. Furthermore, the impact of diet intervention on cognition was assessed through the measurement

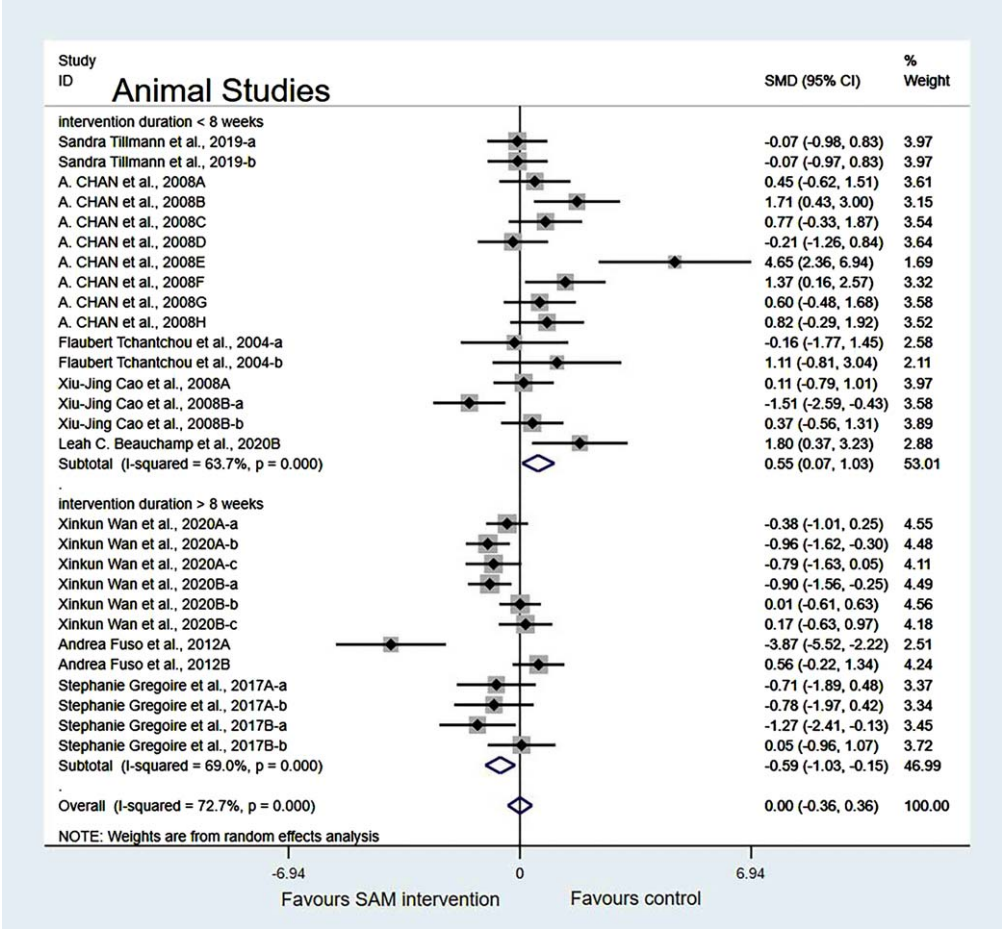

Fig. 6. Forest plot of 28 animal studies of random-effects model subgroup analysis according to intervention duration. SMD, Standardized mean difference; CI, confidence interval; p: heterogeneity *p*-value; SAM: S-adenosylmethionine; Control: placebo.

tool. Four studies [26, 28–30] used the Clock Drawing tests and Dementia Rating Scale, one study [31] used the Neuropsychiatric Inventory (NPI), one study [6] employed the California Verbal Learning Test II and Trail-making test, one study [9] used the Global cognitive scores, and one study [27] used the Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire (Table 2).

Study quality

Animals

All nine animal studies included showed that the selection bias resulting from random sequences was unclear. Although randomization was reported in most articles, the method was not described in sufficient detail. Overall, 100% of the allocation concealment (selection bias) and blinding (performance bias) results showed an unclear risk. Approximately 40% of the studies showed a low risk of attrition bias in follow-up with missing or incomplete outcome data. In addition, 55% of the studies indicated a low risk of reporting bias. We considered that other bias tests were at high risk because none of the articles provided sufficient information regarding the results. (Supplementary File 2; Fig. 2A).

Humans

In six human studies, the minority described randomization methods. In addition, 50% of the studies did not describe the allocation concealment methods in sufficient detail; 70% of human studies were regarded as having an unclear risk of selection bias. Overall, 60%–90% of the included studies were considered to have a low risk of bias for blinding of outcome assessments (detection bias), incomplete outcome data (attrition bias), and selective reporting (reporting bias). All human studies considered

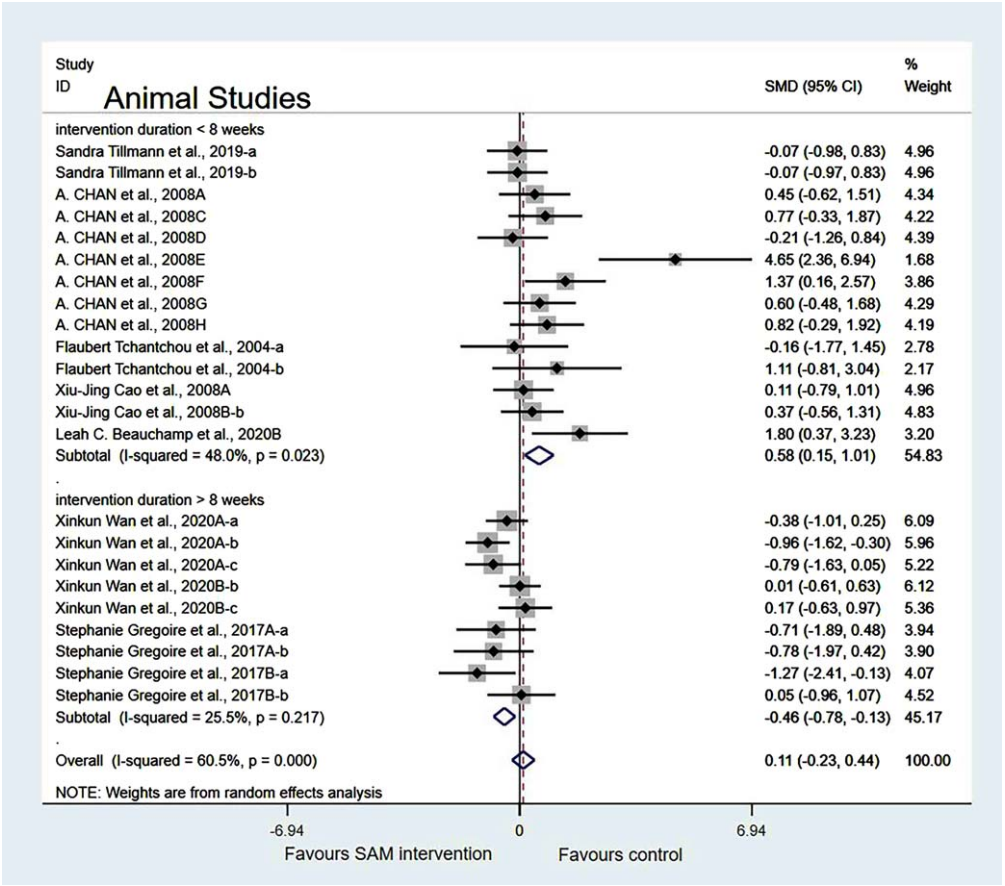

Fig. 7. Sensitivity meta-analysis of 23 animal studies between SAM intervention versus control according to intervention duration. SMD, Standardized mean difference; CI, confidence interval; p: heterogeneity *p*-value; SAM: S-adenosylmethionine; Control: placebo.

as a high risk of other biases included those lacking sample size analysis and those with images rather than concrete data (Supplementary File 3; Fig. 2B).

Qualitative analysis

Qualitative analysis of animal studies

Overall, nine studies reported an association between SAM supplements and enhanced cognitive function. Four studies [17, 18, 20, 25] revealed that SAM could improve the spatial memory deficit of animals; however, SAM might have neuroprotective effects only in some kinds of cognitive disorder and does not affect learning and memory under normal conditions [18, 21]. Fuso et al. [21] clearly demonstrated that SAM inhibits the progression of Alzheimer-like features. Furthermore, Gregoire et al. [22] reported that chronic systemic administration of SAM reduces cognitive impairment. A study showed that mice at 9 months of age do not exhibit signs of neuronal trauma when maintained on deficient SAM, whereas increases oxidative damage and impairs performance in the Y-maze and T-maze in normal mice aged 2–2.5 years [23]. Therefore, this indicates that SAM effects may depend on age. In contrast, Tillmann et al. [24] reported that monotherapy with SAM had no impact on cognition.

Qualitative analysis of human studies

In human studies, SAM can delay cognitive decline (including baseline cognitive performance, behavioral and psychological symptoms of dementia, AD Cooperative Study–Activities of Daily Living, MCI, Chronic Schizophrenia and Depression) [10, 26, 27–29]. Simultaneously, Chan et al. [26] reported that cognitive improvement in SAM is closely related to supplementation time. Three studies [26, 28, 29] used the NPI to evaluate cognitive improvement in patients with AD. The results revealed that patients

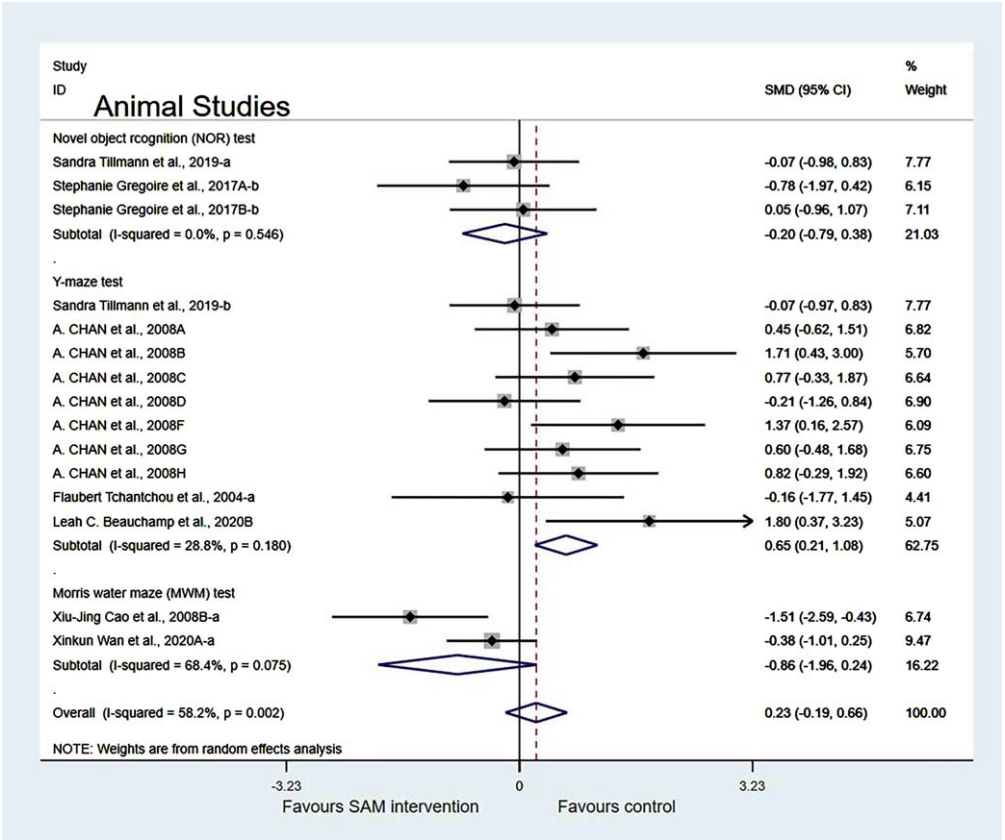

Fig. 8. Sensitivity meta-analysis of 15 animal studies between SAM intervention versus control according to cognitive tests. SMD, Standardized mean difference; CI, confidence interval; p: heterogeneity *p*-value; SAM: S-adenosylmethionine; Control: placebo.

who received SAM for 9 months improved by approximately 30% in NPI, and those who received SAM for 1 year improved in many areas of NPI. However, a study [29] indicated that no significant improvement was observed in NPI after 3 months of SAM supplementation. An analysis of adults without dementia showed that participants supplemented with SAM had statistical significance and clinical improvement in the California Language Learning Test II and trail-making test [6]. Nevertheless, participants older than 74 years showed no significant improvements, which could be attributed to age-related cognitive decline.

Results of the meta-analysis

Meta-analysis of animal studies

Experimental versus controls. The overall data from the eight animal studies involving 28 comparisons suggested that SAM supplements did not significantly improve cognition (SMD = –0.12, 95% CI: [–0.30, 0.07], $p = 0.213$), and moderate heterogeneity was present ($\chi^2 = 99.05$, $p < 0.001$) (Fig. 3). The quality of evidence using the GRADE summary between SAM intervention and control for animals was considered to be moderate (Table 3).

Subgroup analyses by animal age. The animal studies were divided into two subgroups based on animal age. The forest plot indicated that age of animals ≤8 weeks showed a significant difference (SMD = –0.42, 95% CI: [–0.80, –0.05], $p = 0.027$). Meanwhile, age >8 weeks showed no significant difference in cognition (SMD = 0.28, 95% CI: [–0.25, 0.80], $p = 0.304$) (Fig. 4).

Subgroup analyses by cognition tests. Animal studies were categorized into the following three subgroups based on cognitive tests. Those using NOR (SMD = –0.20, 95% CI: [–0.79, 0.38], $p = 0.500$) showed no significant difference in cognition; however, the Y-maze test (SMD = 0.65, 95% CI: [0.21, 1.08], $p = 0.003$) and the MWM test (SMD = –0.82, 95% CI: [–1.39, –0.25], $p = 0.005$) showed significant differences, which indicated that SAM significantly enhanced spatial cognitive function (Fig. 5).

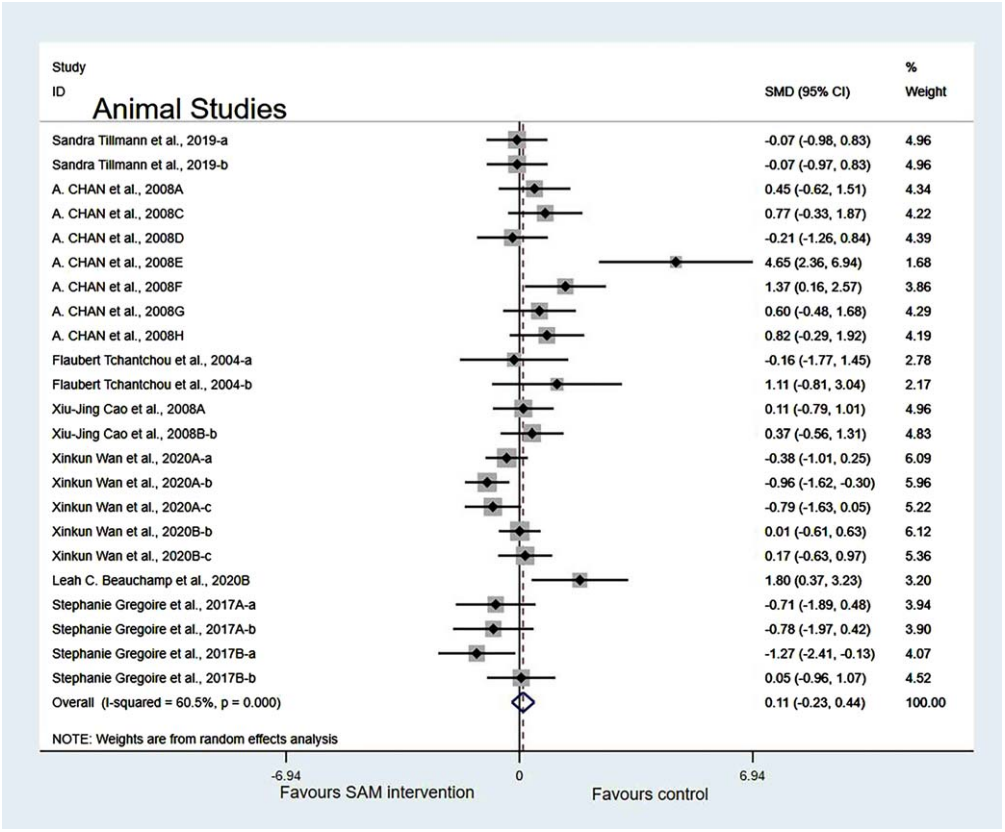

Fig. 9. Forest plot of 23 animal studies of overall effect of S-adenosylmethionine on cognition. SMD, Standardized mean difference; CI, confidence interval; p: heterogeneity *p*-value; SAM: S-adenosylmethionine; Control: placebo.

Subgroup analyses by intervention duration. When we analyzed the data according to SAM intervention duration (<8 weeks or >8 weeks), the forest plot showed that the duration of <8 weeks was not significantly different (SMD = 0.55, 95% Cl: [0.07, 1.03], $p = 0.025$). However, the duration of >8 weeks had a significant effect on cognition in animals (SMD = –0.59, 95% Cl: [–1.03, –0.15], $p = 0.009$) (Fig. 6).

Sensitivity analysis. In the intervention duration of the subgroup, when we removed Chan et al. [18], Cao et al. [19], Wan et al. [21], and Fuso et al. [25] datasets, a slight decrease in the heterogeneity occurred when the test results were changed to 60.5% ($\chi^2 = 55.73$, $p < 0.001$). The combined effect sizes showed no significant differences (SMD = 0.11, 95% CI: [–0.23, 0.44], $p = 0.251$) (Fig. 7).

In the cognitive test subgroup, when Xinkun et al. [25] was removed[21, 22], the heterogeneity test results changed to 58.2% ($\chi^2 = 33.48$, $p = 0.002$); however, the difference was not statistically significant (SMD = 0.23, 95% CI: [–0.19, 0.66], $p = 0.283$) (Fig. 8).

Finally, when Chan et al. [18], Cao et al. [19], Wan et al. [21], and Fuso et al. [25] were deleted simultaneously, the results of the meta-analysis did not change significantly (Fig. 9).

Publication bias. A funnel plot test on animal studies showed that eight datasets were located outside the dashed line, indicating a slight publication bias (Supplementary Figure 1).

Meta-analysis of human studies

Experimental versus controls. A meta-analysis of the five included human studies found no significant difference in cognitive function between the experimental and control groups (SMD = 0.10, 95% Cl: [–0.05, 0.26], $p = 0.047$), and there was a low heterogeneity ($\chi^2 = 41.4\%$, $p = 0.025$) (Fig. 10). In addition, the quality of evidence using the GRADE summary between SAM intervention and control for humans was considered to be high (Table 3).

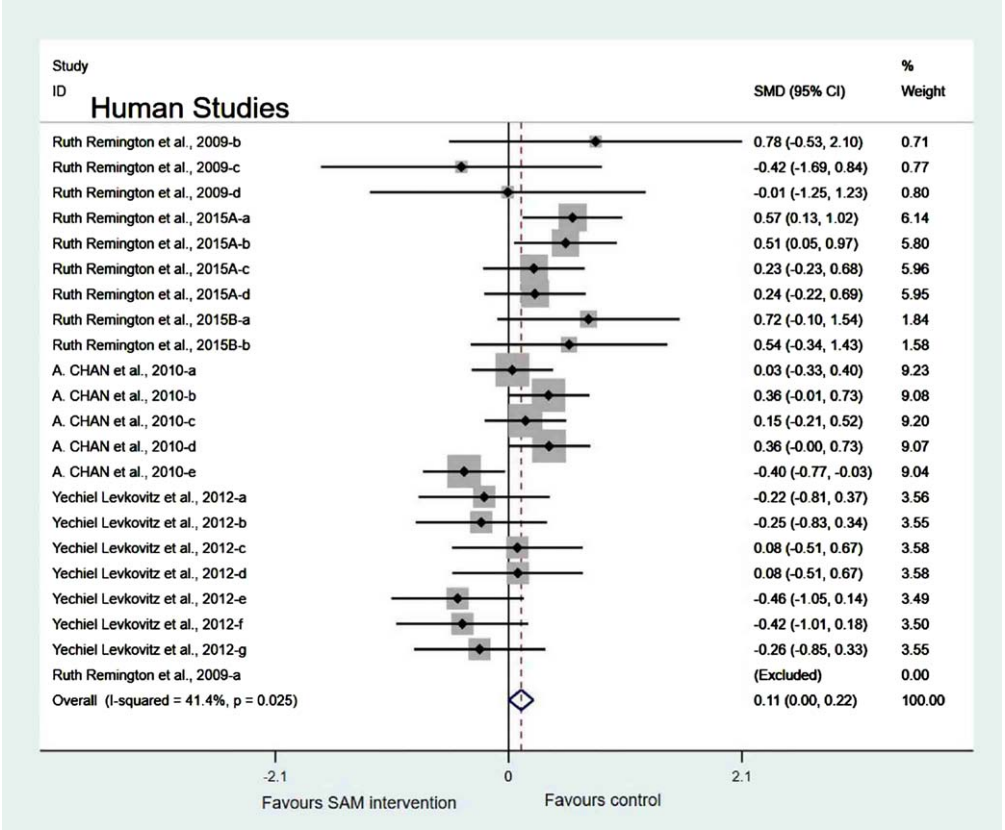

Fig. 10. Forest plot of 22 human studies of overall effect of S-adenosylmethionine on cognition. SMD, Standardized mean difference; CI, confidence interval; p: heterogeneity *p*-value; SAM: S-adenosylmethionine; Control: placebo.

Subgroup analyses by cognitive domains. Human studies were categorized into three subgroups based on various cognitive domains. Global cognition was measured and the results showed a significant difference (SMD = 0.41, 95% Cl: [0.11, 0.70], $p = 0.007$). However, in the other two subgroups, different cognitive domains were measured using corresponding tests. Furthermore, executive function was measured and the results were insignificant (SMD = 0.25, 95% Cl: [–0.51, 1.02], $p = 0.515$), and the memory subgroup was evaluated to have no difference (SMD = 0.17, 95% Cl: [–0.03, 0.36], $p = 0.098$) (Fig. 11).

Subgroup analysis by measurement tool of cognition. Human studies were classified into two subgroups based on different cognitive scales for further investigation. Those using the Dementia Rating Scale (SMD = 0.36, 95% Cl: [0.11, 0.61], $p = 0.005$) and Clock Drawing test (SMD = 0.61, 95% Cl: [0.21, 1.00], $p = 0.002$) to assess cognitive level showed a significant difference (Fig. 12).

Sensitivity analyses. In the cognitive domains of the subgroup, when one of the Chan et al. [6] and Levkovitz et al. [27] datasets were eliminated, the heterogeneity significantly decreased ($\chi^2 = 7.08$, $I^2 = 0\%$, $p = 0.718$). The combined effect sizes showed higher cognitive function in the control group than in the experimental group, with significant differences (SMD = 0.31, 95% CI: [0.18, 0.45], $p < 0.001$) (Fig. 13).

In the measurement tool of cognition, when two of the Remington et al. [29] datasets were removed, the heterogeneity test results were changed to 0% ($\chi^2 = 0.29$, $I^2 = 0\%$, $p = 0.991$). Additionally, the difference was statistically significant (SMD = 0.57, 95% CI: [0.30, 0.85], $p < 0.001$) (Fig. 14).

Finally, when we removed the Chan et al. [6], Levkovitz et al. [27], and Remington et al. [29] datasets simultaneously, the results of the meta-analysis were not significantly changed (Fig. 15).

Publication bias. A funnel plot test on human studies showed that one study was located outside

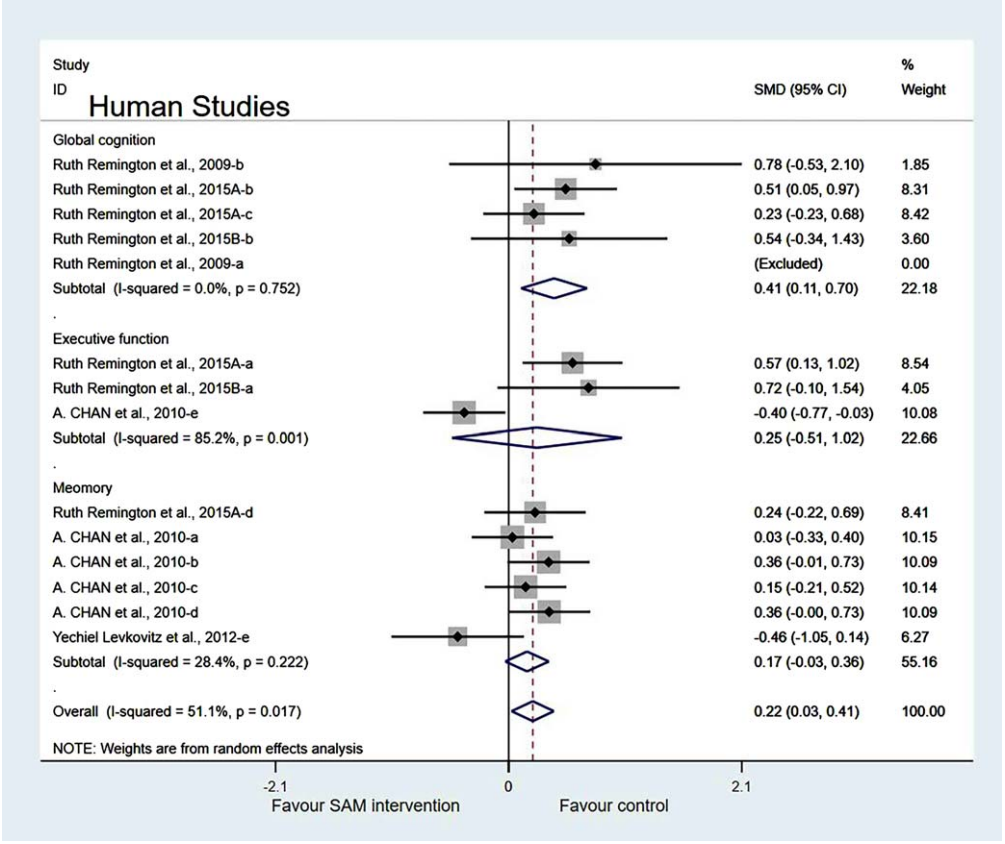

Fig. 11. Forest plot of 14 human studies of random-effects model subgroup analysis according to cognitive domains. SMD, Standardized mean difference; CI, confidence interval; p: heterogeneity *p*-value; SAM: S-adenosylmethionine; Control: placebo.

the dashed line and one study intersected with the dashed line; heterogeneity in others appeared approximately symmetric. This finding suggests that there was no significant publication bias (Supplementary Figure 2).

Results of evidence quality

Four outcomes were evaluated using the GRADE system. According to the evaluation results, high-quality evidence was found and one outcome provided moderate evidence. (Details in Supplementary File 4.)

DISCUSSION

We included all available animal and human data to provide the most comprehensive assessment to date of the effects of SAM supplementation on cognition in this systematic review and meta-analysis. Overall, according to our study, SAM supplementation improved the cognitive performance of animals, particularly regarding spatial learning and memory. In contrast, in human studies, the SAM intervention group showed no significant cognitive differences compared with the control group.

The following three points for qualitative analysis were concluded: a) According to the Y-maze and MWM tests, supplementation with SAM-containing feed or injection in mice and rats significantly improved spatial memory; b) Studies have shown that animal age influences the effects of SAM interventions; and c) Overall, SAM supplementation delayed cognitive decline in animals.

Our meta-analysis indicated the following five points: a) the age of animals $\leq$8 weeks and intervention duration >8 weeks could significantly improve the cognitive ability of animals; b) According to the MWM test subgroup analysis of animal studies, the escape latency in the experimental group was significantly better than that in the control group, implying that SAM supplementation improved spatial mem-

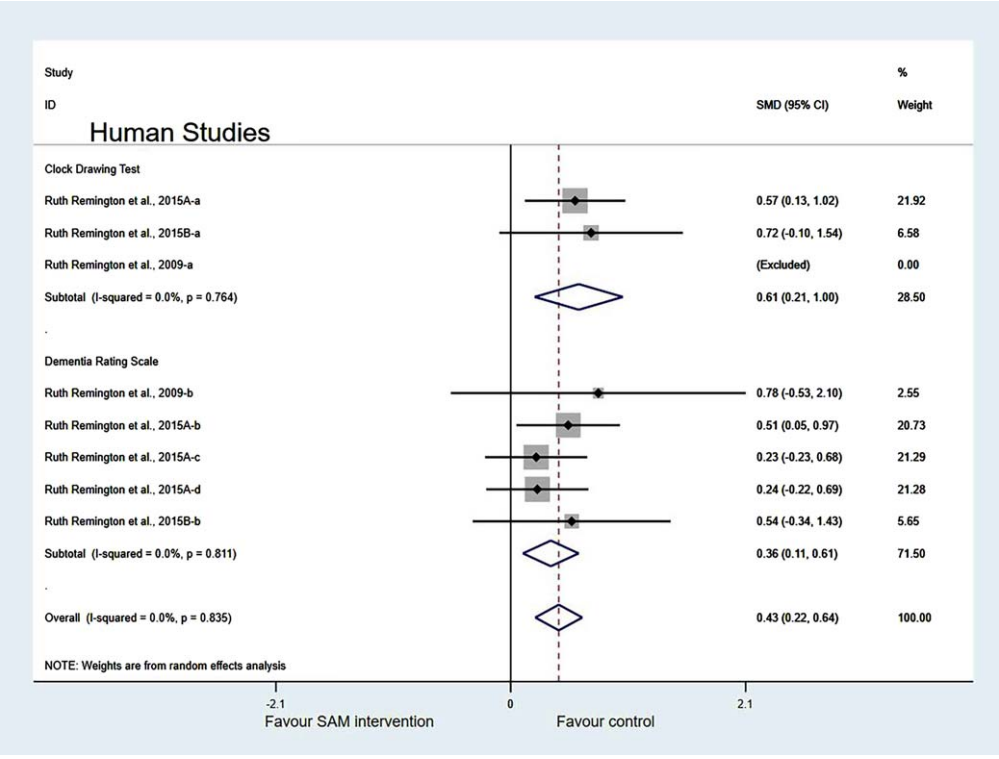

Fig. 12. Forest plot of 8 human studies of random-effects model subgroup analysis according to cognitive scales. SMD, Standardized mean difference; CI, confidence interval; p: heterogeneity *p*-value; SAM: S-adenosylmethionine; Control: placebo.

ory; the Y-maze showed a significant difference when SAM intervention was used to promote cognition; c) Subgroup analysis of human studies showed the same overall results, and SAM intervention had no significant effect on human cognition; d) Various cognitive tests have different effects on experimental results, whether in animal or human studies; and e) Sensitivity analyses suggested that the primary outcomes of the meta-analysis were affected by some studies; however, the results remained stable after excluding these studies.

SAM is a metabolite found in all living cells, and the adenosyl derivative of the amino acid methionine. It is a principal methyl-group donor in epigenetic regulation. Furthermore, SAM plays a central role in cellular biochemistry as a precursor to methylation, aminopropylation, and transsulfuration pathways [32–34]. It is widely used as a food supplement and marketed as a drug in some countries [33].

Neurodegenerative diseases, including MCI and AD, manifest as progressive cognitive decline and functional impairment. According to Talal et al. [35], DNA/RNA methylation plays a vital role in neurodegenerative processes. Furthermore, some studies have shown that decreased cognitive function pathogenesis is correlated with changes in DNA or RNA methylation [36–39]. DNA methyltransferase, which transfers the methyl group from SAM, the principal methyl donor, to the fifth position of cytosine (5-methylcytosine, 5-mC) on the DNA strand, performs DNA methylation, where SAM is the donor of methyl groups [35, 41, 42]. Hence, SAM will affect methylation as a methyl donor. But the research of Anier et al. [43] deemed that SAM only affected the expression of a limited number of genes and did not affect the vast majority of the genome, suggesting that SAM treatments, despite their global nature, do not result in a general silencing of gene expression. Thus, exogenous SAM treatment induces minor effects on whole-genome gene expression [43].

Some studies have demonstrated that the methylation levels of patients with AD continuously decrease with increasing age [44–46]. In addition, the methyl group is catalyzed by a donor substrate SAM to an adenosine residue of an RNA moiety along a specific sequence [47]. N^6-methyladenosine (m^6A), the addition of methyl groups to adenine residues, is

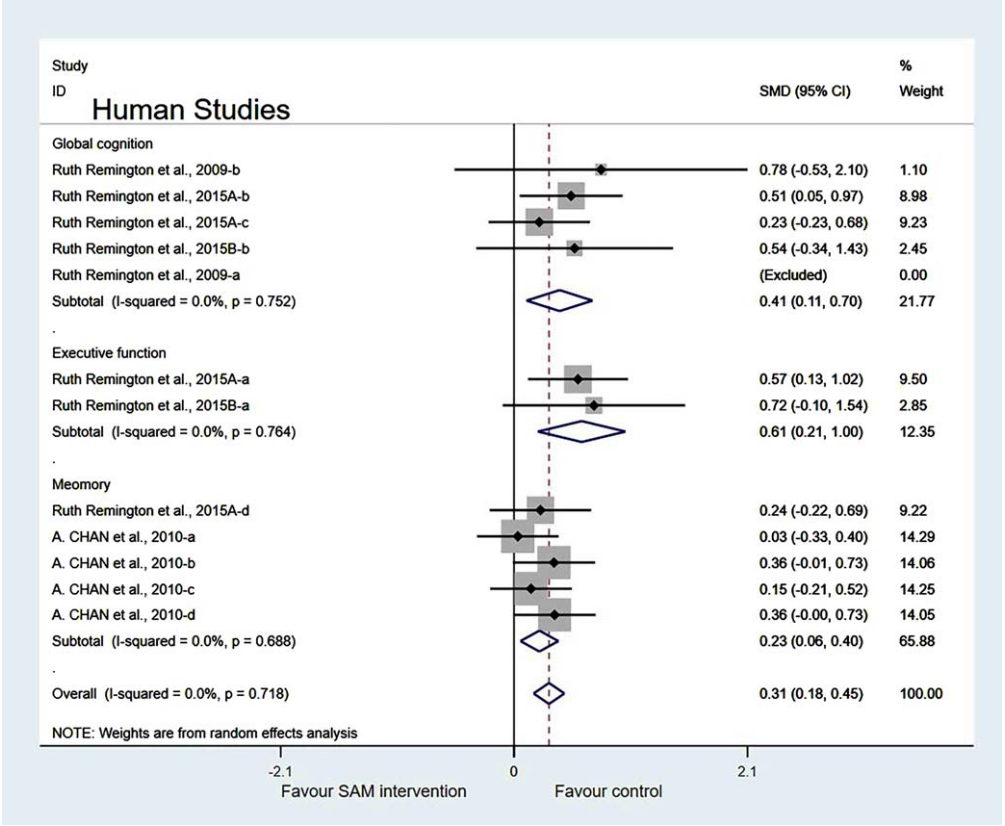

Fig. 13. Sensitivity meta-analysis of 12 human studies between SAM intervention versus control according to cognitive domains. SMD, Standardized mean difference; CI, confidence interval; p: heterogeneity *p*-value; SAM: S-adenosylmethionine; Control: placebo.

the most abundant and is prevalent in brain tissue [47]. m^6A modification is involved in various RNA mechanisms, most notably RNA stability and translational efficiency [48, 49]. Brain processes affected by m^6A methylation may be involved in cognitive functions, including learning and memory, neurogenesis, neurodevelopment, stress response, myelination, and axon plasticity [8]. Moreover, it has been shown that enhanced memory retention of m^6A plays a critical role in memory formation and consolidation [50, 51]. However, the results of the total meta-analysis showed that cognitive function was not significantly improved after SAM supplementation. We speculated that this was due to pathological changes of the participants developing into an irreversible stage or a small sample size. Although the specific mechanisms are yet to be fully elucidated, SAM levels can influence DNA/RNA methylation differently, which in turn affects cognitive levels.

In subgroup analyses, SAM intervention could significantly improve the cognitive function of animals when they were ≤8 weeks of age, which is probably because SAM can promote the development of cognition in mice or rats and prevent age-related cognitive decline [52]. Additionally, age is the greatest risk factor for AD [53]. The incidence of cognitive decline increases with increasing age. It has been confirmed that the pathological changes associated with ageing are similar to those of AD, including loss of brain size and weight, microglial degeneration, and breakdown of white matter fiber bundles [54].

Moreover, our subgroup analyses showed that when the SAM intervention time was >8 weeks, the beneficial effect on animals' cognitive function was more obvious. This is consistent with previous studies [55, 56], which found that the longer the duration, the better the intervention. Thus, this finding may be related to the pathogenesis of AD. In the late stage of AD, synaptic receptors are reduced; protein degeneration and inflammation, intracellular nerve fiber tangles, and excessive phosphorylation are irreversible pathological changes that lead to gradual cognitive decline, making it difficult to reverse this process [57]. Therefore, early intervention is likely to

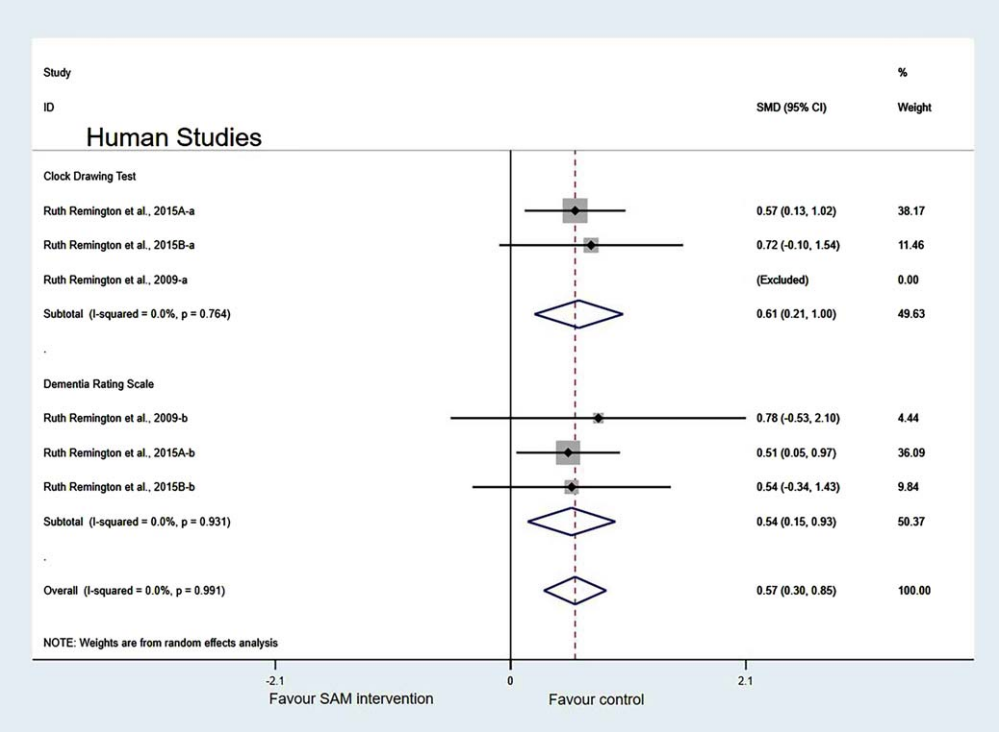

Fig. 14. Sensitivity meta-analysis of 6 human studies between SAM intervention versus control according to cognitive scales. SMD, Standardized mean difference; CI, confidence interval; p: heterogeneity *p*-value; SAM: S-adenosylmethionine; Control: placebo.

be more effective. In animal studies, the reliability of the results was reduced because of the heterogeneity of the included studies. Hence, more rigorous experiments are required to determine the effects of SAM on cognition.

SAM did not improve cognition in animals, but when the cognitive test results were analyzed in subgroups, SAM supplementation significantly improved the animals' cognition. Compared with the control group, MWM tests were more favorable in supporting SAM supplementation in improving cognition, but the results were inconsistent in the test of NOR. The MWM test measures spatial learning and memory, particularly long-term memory, through escape latency and the target quadrant residence time. The NOR detects whether animals have recognition defects [58]. This is consistent with a meta-analysis concluded that SAM supplementation enhanced spatial memory in patients with dementia [59]. Based on this, we inferred that SAM could promote spatial learning and memory abilities instead of animal object recognition. Regarding the subgroups in human studies based on cognitive domains and scales, the effects of SAM on global cognition were more significant than those on cognitive domains. Therefore, we speculate that the cognitive tests are more sensitive to cognitive changes.

However, the meta-analysis of the included human studies revealed that SAM did not significantly improve human cognition. This might be because of the small number of human studies included or that the animal phenotypes included differ from those of patients with AD, representing only a partial AD model and not revealing AD's full pathology [60]. Meanwhile, various interference factors in human research and the unique social attributes of humans can also lead to different results in human and animal studies. Therefore, further studies are required to comprehensively analyze the effects of SAM on cognition in animal and human studies.

With a continuous increase in the degree of ageing, the incidence of chronic neurodegenerative disease is increasing, and cognitive decline is the primary functional disorder. This systematic review and meta-analysis aimed to explore the effects of SAM on cognitive decline. Therefore, this provides novel ideas for interventions to improve cognition. Moreover, conducting further clinical experiments and meta-analyses on the clinical control experiments is warranted.

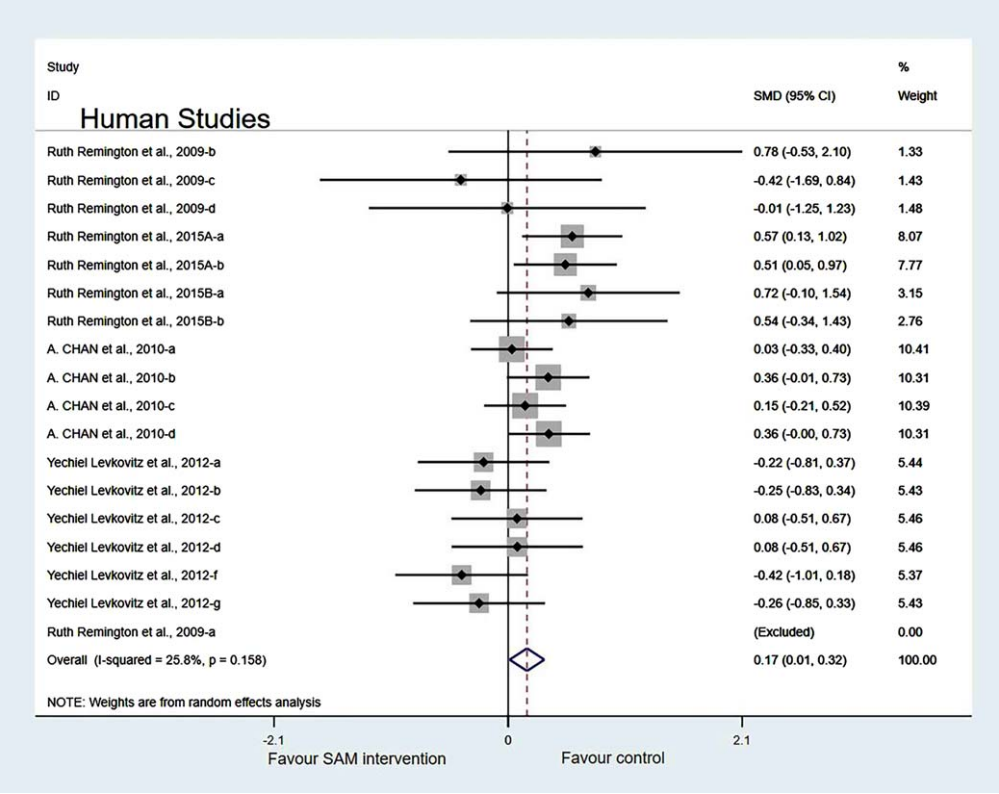

Fig. 15. Forest plot of 18 human studies of overall effect of S-adenosylmethionine on cognition. SMD, Standardized mean difference; CI, confidence interval; p: heterogeneity *p*-value; SAM: S-adenosylmethionine; Control: placebo.

Our study had certain strengths: a) We included only randomized controlled trials in the meta-analysis to improve the accuracy and reliability of the studies; b) Five databases were thoroughly searched to include a large sample and results from multiple measures of cognition and subgroups; and c) The selection and quality assessments of this meta-analysis were performed independently by two researchers, ensuring strict quality control during the study process, including data collection.

However, there were some limitations to the meta-analysis. First, participants were included with different types of diseases, and animal studies used various models of cognitive impairment, making the results less reliable. Second, in most studies, digital software was used to collect data, implying that errors may exist due to differences between the data obtained from the software and the original data. Third, most of the included human studies supplemented SAM in the form of a nutrient mixture, and we cannot be sure that the improvement was due to the total effect of SAM. In addition, human cognitive function evaluation lacks consistency and objectivity, necessitating more accurate methods. Furthermore, because of the included studies did not note the specific dose of SAM per kg body weight in animals, and we also did not describe this content. Finally, due to the limitations of our included literature, any culturing of healthy neurons in presence of various doses of SAM and their effect on overall epigenetics were not mentioned, which would be a limitation of the paper.

The results of our qualitative analyses support the idea that SAM supplementation can effectively improve cognition in animals and humans. However, our meta-analysis revealed that SAM supplementation does not significantly improve cognitive performance in animals or humans. Subgroup analyses of animal studies showed that age $\leq$8 weeks and intervention duration >8 weeks significantly improved spatial learning and memory. Therefore, the efficacy of SAM supplements should be interpreted with caution before definitive conclusions can be drawn, which will require further studies and broader clinical investigations.

ACKNOWLEDGMENTS

We are grateful to the National Natural Science Foundation of China for their financial support. Furthermore, we genuinely appreciate the hard work from the distinguished editor and reviewers.

FUNDING

This work was supported by the National Natural Science Foundation of China (82171582), the Science and Technology Research Project of Higher Education Institutions in Hebei Province (ZD2020105), and the Medical Science Research Project of Hebei Province (20220976).

CONFLICT OF INTEREST

The authors have no conflict of interest to report.

DATA AVAILABILITY

The data supporting the findings of this study are available within the article and/or its supplementary material.

SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: https://dx.doi.org/10.3233/JAD-221076.

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