Supplementary Material

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

Supplementary File 1. Electronic search strategy for five databases.

Supplementary File 1. Electronic search strategy for PubMed

Search number	Query	Results
#1	(((((S-adenosylmethionine) OR (S-adenosyl methionine)) OR (S-adenosyl-L-methionine)) OR (SAM)) OR (SAM-e)) OR (AdoMet)	43,003
#2	((((Alzheimer Disease[MeSH Terms]) OR (Alzheimer*)) OR (dementia)) OR (cognitive)) OR (cognition)	854,062
#3	(((RCT) OR (random*)) OR (control*)) OR (randomised controlled trial)	6,478,484
#4	("2002/01/01"[Date - Publication] : "2022/01/01"[Date - Publication])	18,970,636
#5	(((((((Alzheimer Disease[MeSH Terms]) OR (Alzheimer*)) OR (dementia)) OR (cognitive)) OR (cognition)) AND ((((RCT) OR (random*)) OR (control*)) OR (randomised controlled trial))) AND (("2002/01/01"[Date - Publication] : "2022/01/01"[Date - Publication]))) AND ((((((S-adenosylmethionine) OR (S-adenosyl methionine)) OR (S-adenosyl-L-methionine)) OR (SAM)) OR (SAM-e)) OR (AdoMet))	403

Supplementary File 1. Electronic search strategy for Cochrane Library

Search number	Query	Results
#1	S-adenosylmethionine OR S-adenosyl methionine OR S-adenosyl-L-methionine OR SAM OR SAM-e OR AdoMet	1,805
#2	Alzheimer Disease OR Alzheimer* OR dementia OR cognitive OR cognition	104,424
#3	RCT OR Random* OR control* OR randomized controlled trial	1,867,838
#4	#1 AND #2 AND #3 with Publication Year from 2002 to 2022, with Cochrane Library publication date Between Jan 2002 and Jan 2022, in Trials	137

Supplementary File 1. Electronic search strategy for Embase

Search number	Query	Results
#1	('s adenosylmethionine' OR 's-adenosyl methionine' OR 's-adenosyl-l-methionine' OR sam OR 'sam e' OR adomet) AND [2002-2022]/py	80,080
#2	('alzheimer disease' OR alzheimer* OR dementia OR cognitive OR cognition) AND [2002-2022]/py	1,012,806
#3	(rct OR random* OR control* OR 'randomised controlled trial') AND [2002-2022]/py	10,487,030
#4	#1 AND #2 AND #3	2,000

Supplementary File 1. Electronic **s**earch strategy for Web of science

Search number	Query	Results
#1	S-adenosylmethionine (Topic) or S-adenosyl methionine (Topic) or S-adenosyl-L-methionine (Topic) or SAM (Topic) or SAM-e (Topic) or AdoMet (Topic) and 2002-01-01/2022-01-01 (Publication Date)	41,542
#2	Alzheimer Disease (Topic) or Alzheimer* (Topic) or dementia (Topic) or cognitive (Topic) or cognition (Topic) and 2002-01-01/2022-01-01 (Publication Date)	1,026,975
#3	RCT (Topic) or Random* (Topic) or control* (Topic) or randomised controlled trial (Topic) and 2002-01-01/2022-01-01 (Publication Date)	10,228,607
#4	#1 AND #2 AND #3	385

Supplementary File 1. Electronic search strategy for Clinical Trials.gov

Advanced Searches

1. Condition: Alzheimer Disease

Intervention: S-adenosylmethionine OR S-adenosyl methionine OR S-adenosyl-L-methionine OR SAM OR SAM-e OR AdoMet

Recruitment: All studies

Study results: All studies

Study type: All studies

Gender: All studies

2. Condition: Alzheimer*

Intervention: S-adenosylmethionine OR S-adenosyl methionine OR S-adenosyl-L-methionine OR SAM OR SAM-e OR AdoMet

Recruitment: All studies

Study results: All studies

Study type: All studies

Gender: All studies

3. Condition: dementia

Intervention: S-adenosylmethionine OR S-adenosyl methionine OR S-adenosyl-L-methionine OR SAM OR SAM-e OR AdoMet
Recruitment: All studies
Study results: All studies
Study type: All studies
Gender: All studies
4. Condition: cognitive
Intervention: S-adenosylmethionine OR S-adenosyl methionine OR S-adenosyl-L-methionine OR SAM OR SAM-e OR AdoMet
Recruitment: All studies
Study results: All studies
Study type: All studies
Gender: All studies
5. Condition: cognition
Intervention: S-adenosylmethionine OR S-adenosyl methionine OR S-adenosyl-L-methionine OR SAM OR SAM-e OR AdoMet
Recruitment: All studies
Study results: All studies
Study type: All studies
Gender: All studies

Supplementary File 2. Quality assessment of included animal studies

Quality assessment	Selection bias			Performance bias		Detection bias				
References	**Random sequences generation**	**Baseline characteristics**	**Allocation Concealment**	**Random housing**	**Blinding**	**Random outcome assessment**	**Blinding**	**Incomplete outcomes data**	**Selecting report**	**Bias from other resources**
Tillmann et al., 2019 [24]	Unclear	Low risk	Unclear	Low risk	Unclear	Unclear	Low risk	Low risk	Low risk	High risk
Chan et al., 2008 [19]	Unclear	Low risk	Unclear	Unclear	Unclear	Unclear	Unclear	High risk	Unclear	High risk
Tchantchou et al., 2004 [23]	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	High risk
Shea 2007 [20]	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low risk	Unclear	High risk
Cao et al., 2008 [18]	Unclear	Low risk	Unclear	Low risk	Unclear	Unclear	Unclear	Unclear	Low risk	High risk
Wan et al., 2020 [25]	Unclear	Low risk	Unclear	Low risk	Unclear	Unclear	Unclear	Unclear	Low risk	High risk
Fuso et al., 2012 [21]	Unclear	Low risk	Unclear	Low risk	Unclear	Unclear	Unclear	Low risk	Unclear	High risk
Beauchamp et al., 2020 [17]	Unclear	High risk	Unclear	Low risk	Unclear	Unclear	Unclear	Low risk	Low risk	High risk
Gregoire et al., 2017 [22]	Unclear	Low risk	Unclear	Low risk	Unclear	Unclear	Unclear	Low risk	Low risk	High risk

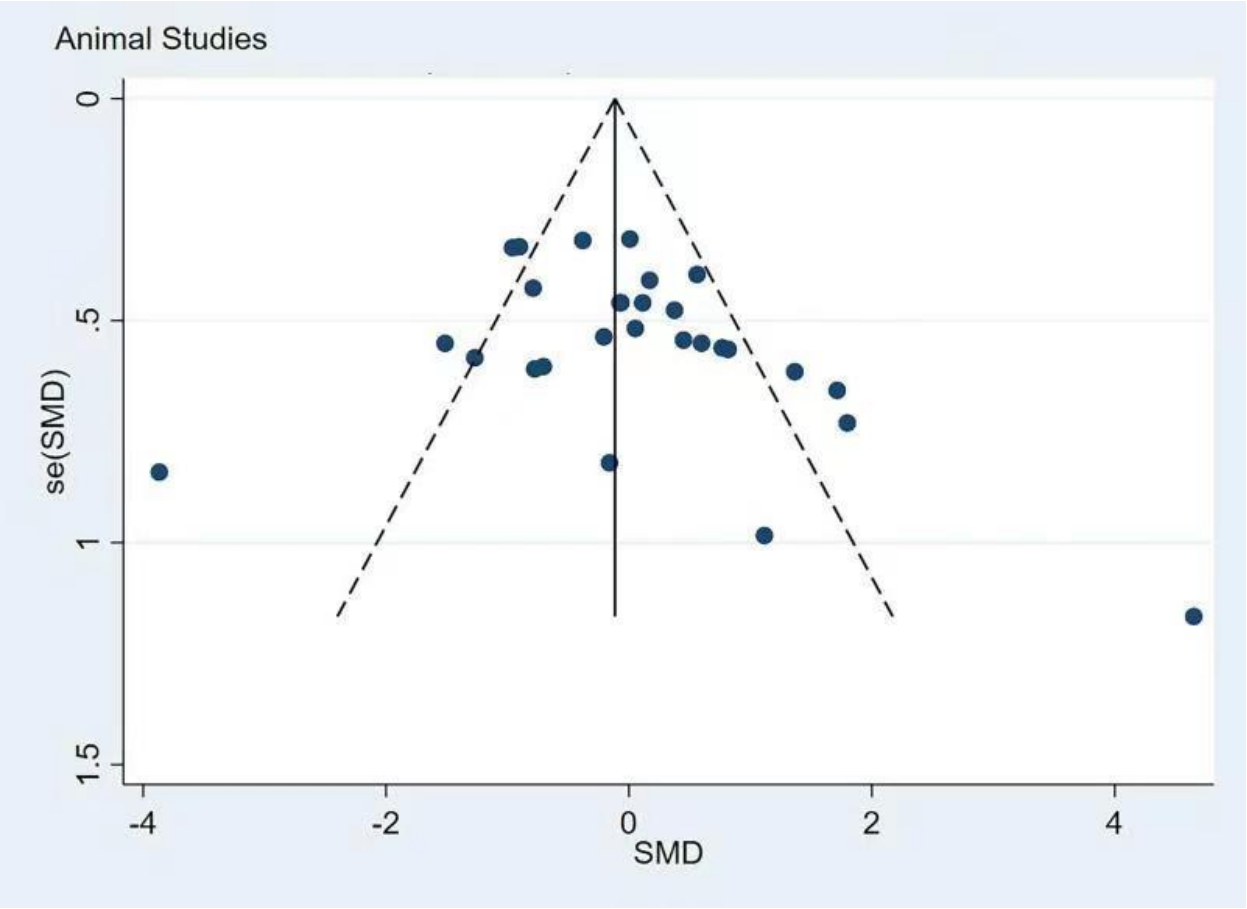
Supplementary File 3. Quality assessment of included human studies

References	Random sequences generation	Allocation Concealment	Blinding	Incomplete outcomes data	Selecting report	Bias from other resources
Chanet et al., 2008 [26]	Unclear	Unclear	High risk	Low risk	Unclear	High risk
Remington et al., 2009 [28]	Unclear	Unclear	Unclear	High risk	Low risk	High risk
Remington et al., 2015A [29]	Low risk	Low risk	Low risk	Low risk	Low risk	High risk
Remington et al., 2015B [30]	Low risk	Low risk	Low risk	Low risk	Low risk	High risk
Remington et al., 2016 [31]	Unclear	Unclear	High risk	Low risk	Unclear	High risk
Chan et al., 2010 [6]	Unclear	Unclear	Unclear	Low risk	Unclear	High risk
Strous et al., 2009 [9]	Unclear	Unclear	Low risk	Low risk	Low risk	High risk
Levkovitz et al., 2012 [27]	Unclear	Unclear	Low risk	Low risk	Low risk	High risk

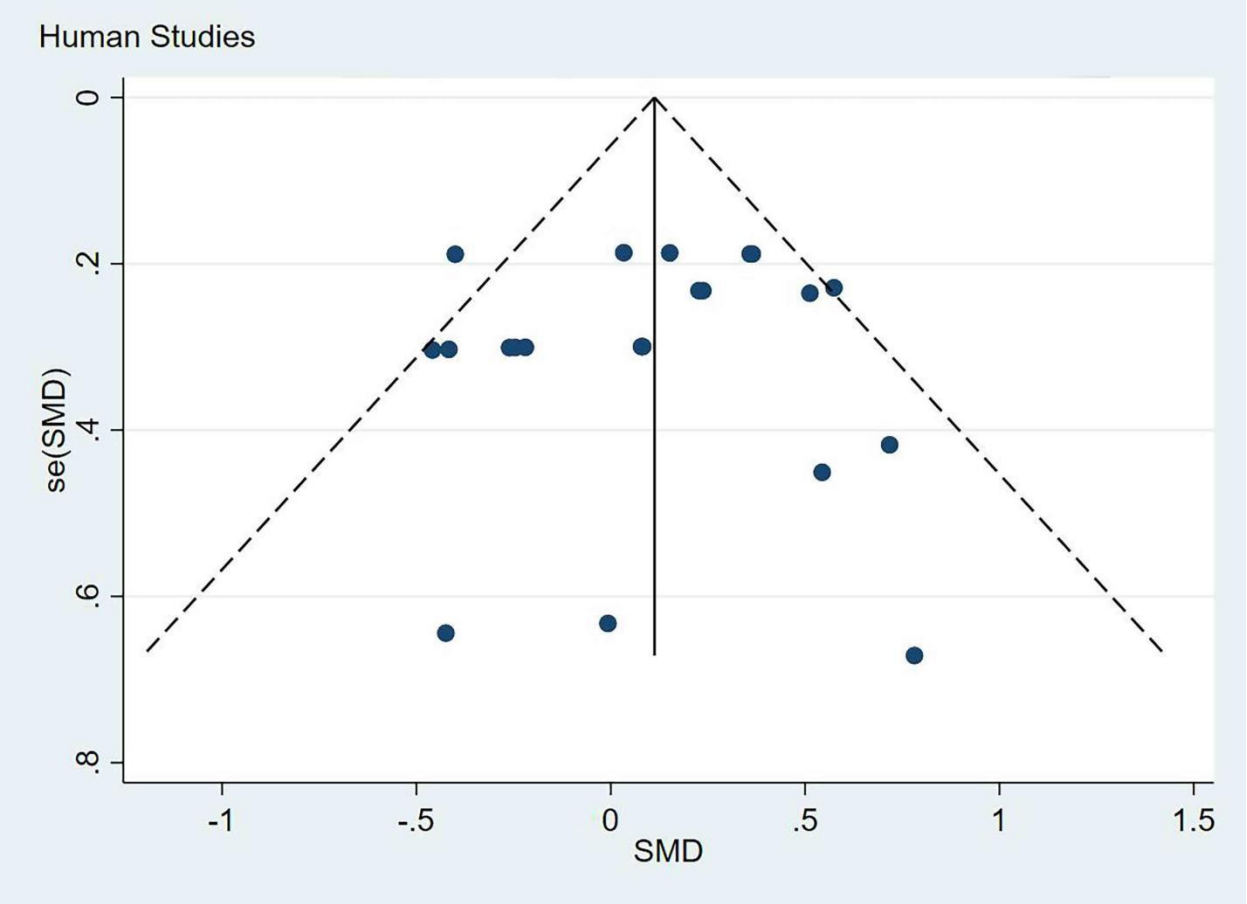
Supplementary File 4. Results of evidence quality
Author(s): Meng Sijia, Dong Xinyi
Question: Used to compare AD and Control
Setting: -
Bibliography: -

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	[intervention]	[comparison]	Relative (95% CI)	Absolute (95% CI)		
Between SAM intervention versus Control for animals												
28	randomized trials	not serious	serious	not serious	not serious	none	-/266	-/271	-- (-0.36 to 0.36)	**-- per 1,000** (from -- to --)	⊕⊕⊕◯ Moderate	CRITICAL
Between SAM intervention versus Control for human												
22	randomized trials	not serious	not serious	not serious	not serious	none	0/712 (0.0%)	0/584 (0.0%)	**0.00** (-0.05 to 0.26)	**-- per 1,000** (from -- to --)	⊕⊕⊕⊕ High	CRITICAL

CI, confidence interval; -, data not available.



Supplementary Figure 1. Funnel plot of animal studies comparing cognitive function between experiment versus control. SMD, Standardized mean difference.



Supplementary Figure 2. Funnel plot of human studies comparing cognitive function between experiment versus control. SMD, Standardized mean difference.