



The Effect of Spermidine Supplementation on Cognitive Function in Adults: A Mini-Review

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Abstract

Introduction: Spermidine, a naturally occurring polyamine found in various foods, has been linked to enhanced autophagy and has shown potential cognitive benefits in previous human studies. This mini-review aimed to evaluate the evidence on spermidine's effect on the adult population's cognitive functions.

Methods: Randomized clinical trials, controlled cohort/cross-sectional, and controlled before-after studies assessing spermidine consumption/supplementation compared to placebo, non-placebo comparators, or regular diet evaluating cognitive function in adults were included. A comprehensive search in MEDLINE, EMBASE, and CENTRAL yielded 1726 records. After duplicate title/abstract and full-text screening, 17 studies were assessed for eligibility, and three were included in the review.

Results: All studies were randomized controlled trials in adults aged 60-96. Doses of spermidine supplementation ranged from 0.9mg to 3.3mg. Wirth 2018 (30 participants) and Pekar 2021 (85 participants) showed an improvement in cognitive performance after three months of spermidine supplementation measured with the Mnemonic Similarity Task (MST) and the CERAD-Plus test, respectively. Schwarz 2022 (100 participants) did not find a significant change in memory performance after 12 months of spermidine supplementation compared to placebo measured with MST. Two studies were at high risk of bias, while one study was judged to have a low risk of bias using the Cochrane risk-of-bias tool for randomized trials 2 (RoB 2).

Discussion: Current evidence of the effect of spermidine on cognitive function shows inconsistent results based on a few studies with low spermidine doses and a small number of participants. Further evidence is needed to assess its actual effect.

Introduction

Healthy aging, as defined by the World Health Organization (WHO), consists of cultivating functional well-being as adults enter the senior phase. Solid evi-

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dence shows that aging has many modifiable aspects that can prolong lifespan, promote healthy aging, and reduce morbidity (Kennedy et al., 2014; Longo et al., 2015). Effective interventions could reduce the socioeconomic burden caused by many diseases associated with aging (Madeo et al., 2018).

Spermidine is a naturally occurring polyamine derived from various sources such as plant-derived foods, fungi, soybeans, some aged cheeses (among other), and from gut microbiota (Madeo et al., 2018; Rubinsztein, Marino, & Kroemer, 2011; Zou et al., 2022). Spermidine has been found to induce autophagy, which plays a crucial role in cellular renewal and maintenance (Eisenberg et al., 2009). Autophagy has been found to decrease with age, and impaired autophagic activity has been linked to several age-related diseases (Barbosa et al., 2018; Bhukel et al., 2017; Ekmekcioglu, 2020). Autophagy involves the sequestration and subsequent degradation of cellular components within specialized vesicles called autophagosomes (Mizushima & Klionsky, 2007; Thellung et al., 2019). However, levels of different types of polyamines, including spermidine, tend to decrease with age, partly due to reduced enzyme activity responsible for their production, potentially influencing the aging process (Minois, Carmona-Gutierrez, & Madeo, 2011; Nishimura et al., 2006). Recent research has even suggested a connection between autophagy and memory capacity, a cognitive aspect of aging (De Risi et al., 2020).

Animal studies have shown promising results regarding the positive effects of spermidine on the nervous system, supporting its potential to promote cognitive health (De Risi et al., 2020; Filfan et al., 2020; Gupta et al., 2013; Schroeder et al., 2021; Vemula et al., 2019; Xu et al., 2020). In humans, a cross-sectional and longitudinal study with 3,774 adult participants older than 35 demonstrated that higher spermidine levels (from participants' regular oral diet) might reduce the incidence of Mild Cognitive Impairment associated with aging (Xu et al., 2022). One study examined the association of self-reported dietary spermidine intake and structural brain measures of Alzheimer's Disease vulnerable regions among adults aged 60 to 90 years. (Schwarz et al., 2020), They were showing larger hippocampal volumes and greater cortical thickness.

Nonetheless, current literature about the impact of oral supplementation of spermidine on cognitive functions in humans is scarce. Understanding the effects of spermidine on cognitive processes in humans is crucial to developing interventions that promote healthy aging and address age-related cognitive decline. Evaluating the existing evidence will allow us to gain breakthrough knowledge on the role of

spermidine supplementation in maintaining mental health during aging. Therefore, this mini-review aims to examine existing human studies about spermidine and cognition, providing insights into the potential benefits of spermidine supplementation for supporting cognitive well-being in the context of aging.

Materials and Methods

This mini-review is based on recommendations of the Cochrane Handbook (Higgins JPT, Cochrane, 2023) and PRISMA guidelines for reporting systematic reviews (Page et al., 2021). Appendix 1A and 1B provide the PRISMA abstract and main checklists.

Literature search and study selection

Based on the research question and a predefined search strategy, systematic searches were conducted in MEDLINE, EMBASE, and CENTRAL from database inception to July 14th, 2023. The Search strategy concepts were appropriately explored using specific indexed vocabulary (MeSH-terms and free text), Boolean operators, truncation, parentheses, and quotation marks. The search strategy is shown in Appendix 2. The literature search was not restricted by language and did not use additional filters. The results were exported via the literature management system EndNote 21® after eliminating the duplicates. Following agreement on a standard approach for the screening procedure, the searched results were first screened in terms of titles and abstracts by two reviewers (IP and GK) and secondly in terms of full texts (MH and PC) using Rayyan, a web and mobile app for systematic reviews ([www.https://www.rayyan.ai/](https://www.rayyan.ai/)) (Ouzzani et al., 2016). A third reviewer resolved any disputes between the two reviewers.

Eligibility criteria

The research question and eligibility criteria were compiled using the PICOS framework as follows:

Inclusion criteria

We included studies with adult participants of any age, healthy or diseased, assessing spermidine supplementation in any form, dose, or setting, using placebo, non-placebo comparators, or regular diet as the control, and evaluating the effect on any mental process or cognitive function as an outcome. Study designs included Randomized Clinical Trials (RCTs), controlled Cohort/Cross-Sectional studies, and controlled before-after studies.

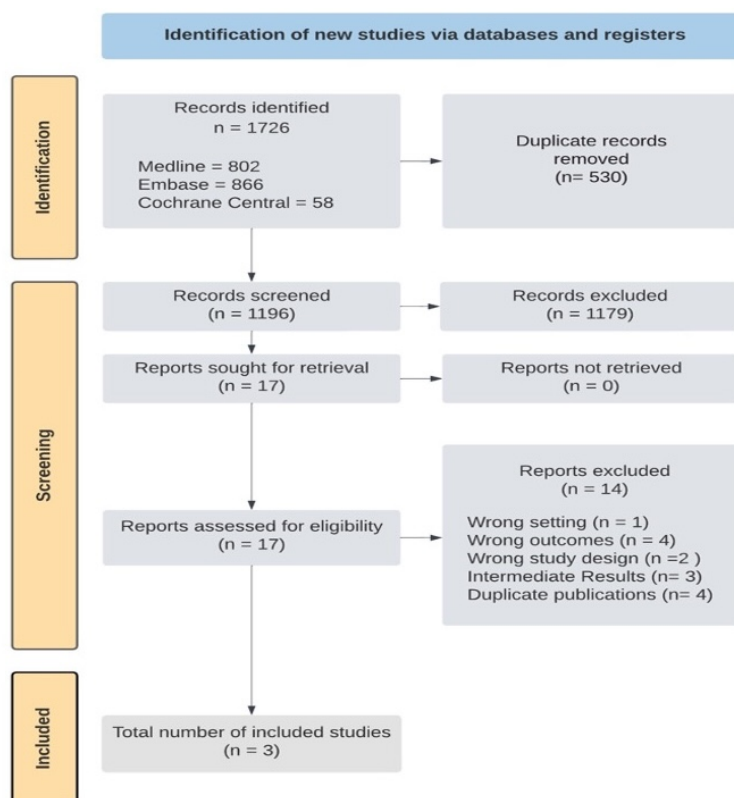


Figure 1: PRISMA Flowchart.

We excluded case reports, case series, and narrative or systematic reviews. We also excluded studies that measured biomarkers or intermediate outcomes of cognitive function and duplicate publications on the same study population.

Data extraction

Two independent reviewers (AL and LC) conducted data extraction using a standardized data extraction template within the web-based software platform Covidence ([www.https://www.covidence.org/](https://www.covidence.org/)). The characteristics shown in Table S1: (1) study design, (2) population, (3) intervention, (4) control, (5) sample size, (6) age of participants, (7) gender, (8) follow-up and (9) primary outcome. Disagreements were addressed by consensus between reviewers. If no agreement was reached, a third independent reviewer was designated arbitrator.

Risk of bias assessment

The ROB (Risk of Bias assessment)-2 tool was used to assess the risk of bias (RoB) of each study (Sterne et al., 2019). The risk of bias was assessed in five domains (prejudice arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in

measurement of the outcome, and bias in selection of the reported result). Two independent reviewers conducted the risk of bias assessment and, for each domain, answers to a series of signaling questions led to the judgments of “low risk of bias,” “some concerns,” or “high risk of bias.” Disagreements were resolved by consensus of two reviewers. Rob assessment was recorded in the Covidence software platform and presented in a graph and table form using Robvis, a web app designed to visualize risk-of-bias assessments performed as part of a systematic review (<https://www.riskofbias.info/welcome/robvis-visualization-tool>) (McGuinness & Higgins, 2021).

Results

Description of studies

After a comprehensive search in three databases (MEDLINE, EMBASE, and CENTRAL), we identified 1,726 studies, from which 530 duplicate reports were removed. Title and abstract screening were conducted on 1,196 records, from which 1,179 studies were excluded, 17 were considered relevant for assessing eligibility and full-text review, and three were included. Search results are summarized in Figure 1, showing the flow diagram according to the PRISMA guidelines (Page et al., 2021). Key charac-

A. Risk of bias assessment summary table

| Study | Risk of bias domains | | | | | Overall |
|--------------|----------------------|----|----|----|----|---------|
| | D1 | D2 | D3 | D4 | D5 | |
| Wirth 2018 | + | + | + | + | ⊗ | ⊗ |
| Pekar 2021 | ⊗ | + | ⊗ | + | - | ⊗ |
| Schwarz 2022 | + | + | + | + | + | + |

Domains:
 D1: Bias arising from the randomization process.
 D2: Bias due to deviations from intended intervention.
 D3: Bias due to missing outcome data.
 D4: Bias in measurement of the outcome.
 D5: Bias in selection of the reported result.

Judgement
 ⊗ High
 - Some concerns
 + Low

B. Risk of bias assessment Plot

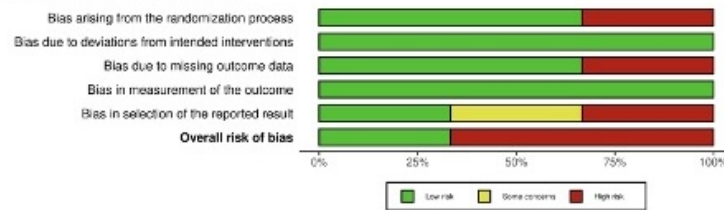


Figure 2. (A) Risk of bias summary table: review authors' judgements about each risk of bias item for each included study. (B) Risk of bias graph: review authors' judgements about each risk of bias item across studies.

Figure 2: Risk of bias of the included studies.

teristics of the studies are described in Table 1. The list of excluded studies and reasons for exclusion are summarized in Table S1 of the supplementary material.

Three randomized controlled studies were included. Two studies were conducted in Germany (Schwarz et al., 2022; Wirth et al., 2018) and one in Austria (Pekar et al., 2021). A fourth study was a follow-up of Pekar 2021 and was considered along with the previous one (Pekar, Wendzel, & Jarisch, 2023). Two studies were single-center (Schwarz et al., 2022; Wirth et al., 2018), and one was multicentric (Pekar et al., 2021). Funding sources were reported in all three studies and were government agencies, foundations, and universities. Additional information on the study's methodology is provided in Table S2 of the supplementary material.

Participants

Participants in all three studies were older adults between 60 and 96 years of age. Two studies included cognitively intact participants but presented with subjective cognitive decline. (Schwarz et al., 2022; Wirth et al., 2018), And the other study included nursing home patients without dementia (Pekar et al., 2021).

Interventions and comparators

Interventions included oral spermidine in its natural

food form or as plant extract, with doses ranging from 0.9 mg to 3.3 mg. The main comparator was placebo in the form of cellulose capsules, except in Pekar 2021, which used oral spermidine 1.9 mg as the control group. In two studies, the follow-up time was three months and 12 months in the third study (Schwarz et al., 2022).

Outcome measurement

In the studies conducted by Schwarz in 2022 and Wirth in 2018, cognitive function was assessed using the Mnemonic Similarity Task (MST), which served as the primary outcome measure. On the other hand, Pekar's study in 2021 opted for the CERAD-plus test for this purpose. Both Schwarz 2022 and Wirth 2018 explored additional neuropsychological factors as secondary outcomes. Specifically, the 2022 study by Schwarz delved into areas such as verbal and visual-spatial memory, attention, executive functions, and sensorimotor speed. Meanwhile, Wirth's study in 2018 incorporated the German version of the Rey Auditory Verbal Learning Test (RAVLT) to assess verbal episodic memory and the digit symbol substitution test to gauge executive functions.

Furthermore, Schwarz's study in 2022 went a step further by evaluating lifestyle-related behaviors, psycho-affective traits, perceived quality of life, various blood parameters, markers indicating vascular damage, and cardiovascular risk factors, including vital signs and weight. In contrast,

| Study | Country | Study design | Population | Intervention (Spermidine Dose) | Control | Number of participants (n) | Age of participants (years)* | Female n (%) | Follow-up time | Primary outcome |
|--------------|---------|---|--|--------------------------------|-------------------|----------------------------|---|--------------|----------------|---|
| Wirth 2018 | Germany | RCT, double-blind, placebo-controlled, phase 2a Pilot trial | Older adults of 60-80 years, cognitively intact with subjective cognitive decline. | 1.2 mg | Placebo | 30 | Spermidine 70.4 (SD 5.2) Placebo 69.4 (SD 5.6) | 67 (78.8) | 3 months | Memory performance (Mnemonic Similarity Task) |
| Pekar 2021 | Austria | RCT, double-blind | Older adults of 60-90 years in nursing homes with or without dementia. | 3.3 mg | 1.9 mg spermidine | 85 | 83.1 (IQR 79-89.5) | 28 (64.3) | 3 months | Cognitive performance (CERAD-Plus test) |
| Schwarz 2022 | Germany | RCT, double-blind, placebo-controlled, phase 2b | Older adults of 60-90 years with subjective cognitive decline. | 0.9 mg | Placebo | 100 | 69 (SD 5) | 49 (49) | 12 months | Memory performance (Mnemonic Similarity Task) |

RCR: Randomized Controlled Trial; **CERAD:** The Consortium to Establish a Registry for Alzheimer's Disease

* Mean (SD) or median (IQR)

Table 1: Key characteristics of the included studies.

Pekar's 2021 study focused on metabolic parameters, including Vitamin B12, Ferritin, Folic acid, and TSH levels. Notably, all of these studies performed measurements of their secondary outcomes at the start and end of their respective investigations.

Risk of bias of included studies

The risk of bias was assessed using the Cochrane RoB 2 tool, as described in the methods section (Sterne et al., 2019). We judged one study to be at low risk of bias in all domains (Schwarz et al., 2022). However, the other two studies were considered at high risk of bias. Review authors' judgments about each risk of bias item for each included study, and the conclusions about each bias item across studies are depicted in Figures 2A and 2B.

In Wirth 2018, there was a low risk of bias in the randomization process, deviations from intended intervention, missing outcome data, and measurement of the outcome domains. Nevertheless, the registered protocol for the trial (NCT02755246) stated that the primary outcome was the change in cognitive function measured with a neuropsychological test battery. However, the direct result of the published study 2021 was the assessment of memory performance with the MST test. Hence, there may be a high risk of bias for selection in the reported result. In Pekar 2021, the authors mention that participants were randomized to both groups. However, there is no information on the randomization process or allocation concealment. There is also an imbalance in the baseline characteristics of both groups, with

5 (15%) participants in Group A having severe dementia compared to Group B, which had no participants with severe dementia. Consequently, this domain was judged to be at high risk of bias. After randomization, 14% of participants were excluded from the analysis because blood sampling was not done (7 patients) or follow-up was not completed (6 patients). More information on the distribution of missing data by treatment groups is needed to assess the potential effect. A description of methods to handle missing data is required, and a complete case analysis was carried out. Therefore, we judged this domain to be at high risk of bias. Finally, there is no available protocol to assess selective outcome reporting. With no information to compare the outcomes to those published in the report, we judged this domain to have some bias concerns. Overall, the Pekar 2021 study was considered at high risk of bias.

Effect of intervention

The primary outcome of the three studies is summarized in Table 2.

Wirth 2018 used Memory performance (Mnemonic Similarity Task) to evaluate cognitive function. The trial featured two arms: arm one (1) involved spermidine intervention, and arm two (2) served as a control group. Measurements were obtained before and post-intervention. For the baseline measurements, the mean score for the spermidine intervention arm was 0.32 (SD=0.11), and for the control group, it was 0.33 (SD=0.17). Following the intervention, the mean

| Study ID | Cognitive Function Test | Spermidine Intervention | | Control | | Outcome |
|--------------|---|---|-------------------|--|-------------------|---|
| | | Baseline | Post-Intervention | Baseline | Post-Intervention | |
| Wirth 2018 | Memory performance (Mnemonic Similarity Task) | 0.32 (0.11)* | 0.43 (0.15)* | 0.33 (0.17)* | 0.26 (0.29)* | Mean Difference 0.17 (0.01 to 0.35) Cohen's d 0.77 |
| Pekar 2021 | Cognitive performance (CERAD-Plus test) | High-dose group Improved by 6.25 points (p=0.030) | | Low dose group Improved by 4.00 points (p=0.041) | | NA |
| Schwarz 2022 | Memory performance (Mnemonic Similarity Task) | - 0.02 (-0.08 to 0.04)† | | 0.01 (- 0.04 to 0.06)† | | Mean Difference - 0.03 (- 0.11 to 0.05)† p value = 0.47 |

CERAD: The Consortium to Establish a Registry for Alzheimer's Disease.

*Mean and Standard Deviation (SD)

†Mean and 95% Confidence Interval

Table 2: Effect of intervention.

score for the spermidine intervention arm increased to 0.43 (SD=0.15), while for the control group, it decreased to 0.26 (SD=0.29). The author does not state a possible reason for this decrease. The mean difference between the groups was 0.17, with a 95% confidence interval ranging from 0.01 to 0.35. The effect size (Cohen's d) was 0.77. Ultimately, Wirth 2018 found memory performance exhibited moderate improvement within the spermidine group compared to the placebo group by the conclusion of the intervention period.

Pekar 2021 used CERAD-plus scores to evaluate cognitive function. The trial also involved two arms (high and low dose spermidine). They assessed the score pre and post-intervention and found increased scores in both groups, but the improvement was higher within the high-dose spermidine group (6.25 points, p= 0.030) compared to the low-dose group (4.00 points, p= 0.041). The study found a positive correlation between spermidine intake and enhanced cognitive performance among subjects with dementia.

Schwarz 2022 also used Memory performance (Mnemonic Similarity Task) to evaluate cognitive function. They also featured two arms: spermidine intervention and placebo. Measurements were taken at both baseline and post-intervention stages. The findings showed that the mean change from baseline to post-intervention in the spermidine intervention arm was -0.02 (95% CI: -0.08 to -0.04). Conversely, the control group exhibited a mean change from baseline to post-intervention 0.01 (95% CI: -0.04 to 0.06). This led to an adjusted treatment effect of -0.03 (95% CI: -0.11 to 0.05; p-value for primary efficacy outcome = 0.47). Furthermore, Schwarz 2022 found that after 12 months of spermidine supplementation, no discernible impact on memory performance or other neuropsychological, behavioral, or physiological measures was observed compared to a placebo,

as indicated by intention-to-treat analyses.

Discussion

Our goal with this study was to provide an overview of the effect of spermidine supplements on cognitive function in the adult population. A comprehensive search was conducted on three primary databases. After duplicate selection and evaluation of the reports, only three studies met the eligibility criteria and were included in the review. All studies were randomized controlled trials in older adults that ranged from 60 to 96 years old—two studies compared spermidine supplementation to placebo, and a third compared high-dose spermidine to a low-dose group. Two studies showed a positive association between spermidine supplementation and memory performance. Wirth et al., 2018, showed that memory discrimination performance was enhanced after three months of 1.2mg daily spermidine supplements (Cohen's d effect size of 0.77, 95%CI 0 to 1.53) in 28 cognitively intact individuals with subjective cognitive decline (Wirth et al., 2018). Pekar 2021 et al. reported an increase in the CERAD-plus score after three months of daily spermidine supplements in 79 older adults from a nursery home. The CERAD-plus score increased in both groups, the high spermidine dose (3.3mg) and the low spermidine dose (1.9mg) group, but the improvement was more significant within the high dose group (6.25 points, p= 0.030) compared to the low dose group (4.00 points, p= 0.041) (Pekar et al., 2021). Lastly, Schwarz et al., 2022 showed no significant effect on memory performance after 12 months of 0.9 mg daily spermidine supplementation in 100 older adults with subjective cognitive decline. Two of the three studies were judged to be at high risk of bias. Wirth 2018 had a high risk of bias in selecting the reported result. Pekar 2021 was considered at increased risk of bias mainly due to the lack of information in the random-

ization process, an imbalance in the groups' baseline characteristics, and missing outcome data. Schwarz 2022 was judged to be at low risk of bias.

Some additional methodological issues about the three studies are worth mentioning. In Wirth et al., 2018 participants were recruited from the memory clinic of the hospital department of neurology and the general population through advertisement. Therefore, sampling and volunteer bias can limit the generalizability of the findings. Additionally, of 171 adults interviewed by telephone to assess eligibility, 138 were excluded, and only 33 participated in the trial, creating a high chance of selection bias. Finally, for sample size calculation, the authors used the size effect from another study investigating differences between baseline and follow-up spermidine serum levels and not cognitive changes – this indicates that the sample size was likely inadequate due to the total lack of support for correlation between serum levels and cognitive improvement.

According to Pekar et al. 2021, the recruitment strategy introduces potential referral bias. Characteristics of patients referred by nursing home directors may differ from older adults of the general population, limiting the generalizability of the findings. Data on the total recruited population, number, and reason of subjects excluded was not disclosed. Spermidine supplements were given in baked rolls during breakfast, which may have led to variable absorption rates, potentially affecting its bioavailability and, by extension, its therapeutic efficacy (Madeo et al., 2018). Moreover, the sample size ($n=85$) was calculated with a significance of 0.05, a power of only 67%, and an MMSE difference of only 3 points, which is not clinically significant. The age range of the total target population varied from 60 to 100 years. Still, the final sample was not stratified by age, which may lead to bias since cognitive decline rates vary according to the individual's age, and, accordingly, the effect of an anti-aging supplement (spermidine) on cognition would be different across subgroups during a follow-up study.

Notably, a follow-up study of Pekar 2021 was published in 2023, in which 45 participants from the original study were ensured at least 3.3mg of spermidine per day and were followed for 12 months. This study reported a statistically significant improvement in the Mini-Mental State Examination (MMSE) from baseline (MMSE mean score 15) to 12 months (MMSE score 20), $p<0.001$. However, the original study sample had 85 participants, and there needs to be more information on why some individuals were not included; this is difficult to understand since the exclusion criteria are the same for both studies. This creates a severe and potential ascertainment bias, pos-

sibly leading to a study sample that is systematically different from the general population. The paper provides a boxplot graph indicating that the median baseline Mini-Mental Status Examination (MMSE) score was 15, indicative of dementia. Of note, the use of anti-dementia medication was an exclusion criterion – inferring that the sample included individuals with moderate to severe dementia who were not being treated. Still, there is no explanation for this unexpected finding. According to the graph, the follow-up mean MMSE score was 20, which also means moderate dementia. It can be concluded that although there was a statistically significant change in MMSE scores, individuals still presented with dementia. Also, the visual inspection of the boxplot shows that although MMSE means were statistically different, Q0 and Q4 were quite similar in both groups. Furthermore, the statistical difference does not necessarily mean a clinical difference since inventories addressing Activities of Daily Living [ADL] (or other standard measures of daily functioning) were not used. Finally, there was no correction for multiple testing, which is crucial in such a short-term interval. Schwarz 2022 showed no effect after 12 months of spermidine supplementation on memory performance and any other neuropsychological, behavioral, or physiological parameter in intention-to-treat analyses compared with a placebo. Of note, this study used a lower dose (0.9mg) than the dose used in the pilot study (1.2 mg) (Wirth 2018 et al.). There is no reason provided for this change in the spermidine supplementation dose. Additionally, there is a discrepancy with the dose published in the supplement online content (eMethods 1. Study Design and Participants), where the spermidine dose is said to be 1.2mg.

Interestingly, the spermidine supplementation dose used in these trials could be considered low, taking into account that daily intake of spermidine has been estimated to be highly variable between subjects, ranging from 5 to 15mg (Hofer et al., 2022), currently registered clinical trials are evaluating doses of 4 to 6 mg and that a recent pharmacokinetic study suggested that doses less than 15mg are unlikely to exert any short-term effects. (Senekowitsch et al., 2023). Furthermore, Schwarz 2022, which was methodologically well-designed and had longer follow-up times, used a remarkably low spermidine dose, raising the possibility that the lack of clinical effect may have been associated with the low dose.

On the other hand, studies showing a positive correlation of spermidine supplementation with cognitive function had critical methodological issues and were judged to be at high risk of bias. Thus, the generalizability and interpretation of these findings could be improved. Further evidence and more extensive

randomized controlled trials, possibly higher doses, are needed to assess the actual effect of spermidine supplementation on cognitive function.

This mini-review is subject to certain limitations. The small number of studies and small sample sizes, in conjunction with the methodological issues found in most of them, make it challenging to draw firm conclusions. Furthermore, two of the three included studies were conducted by the same research group and may lead to systematic biases, introducing further limitations in the interpretation. The RCTs differed in their methodologies, populations, and outcome measures, which could introduce heterogeneity to the conclusions drawn. The choice of outcome measures is also discussed across studies. While the Mnemonic Similarity Task (MST) was commonly used, its exclusive application in two studies might introduce potential bias in interpreting results. The geographical regional confinement of the studies to Germany and Austria limits the generalizability of the findings to a broader, global population. Additionally, the population across the studies was older adults, limiting the generalization to other age ranges.

Despite the structured approach and diligence in selection, the reliance on published data might have resulted in missing unpublished or ongoing studies with varied results. The predominant focus on low dosages of spermidine and the limited exploration of cognitive functions beyond memory add uncertainty to our findings. Moving forward, research in this area should prioritize more thorough and precise methodologies, investigate deeper into finding the proper dosage, and expand the range of cognitive evaluations.

Conclusion

This mini-review evaluated the literature on Spermidine and its possible effect on adult cognitive function. Two of the studies in this review were judged to be at a high risk of bias. Though Wirth et al., 2018 and Pekar et al. 2021 spermidine showed an improvement in memory in cognitively intact individuals & individuals with dementia, the sample size was small, and sheer biases within the methodology limited the interpretation of their results. Additionally, the study of Schwartz 2022 did not find significant changes in memory performance after a year of supplementation. Therefore, we conclude that evidence still needs to be more conclusive regarding the effect of spermidine on cognitive function, requiring further research to assess its impact and to understand the potential benefits better.

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Conflicts of Interest

The authors declare no conflict of interest.

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