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Systematic Review Article

The Correlation between Probiotic Consumption and Sleep Quality among Adults : A Systematic Review and Meta-Analysis

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ABSTRACT

This study aims to determine the relationship between probiotic consumption and an individual's sleep quality. A systematic search for relevant articles was conducted in Scopus, PubMed, Cochrane Library, and ScienceDirect databases for publication between 2013 and 2023. The article selection process is presented using a PRISMA diagram. Data analysis was performed using Review Manager Version 5.4 and publication bias was assessed using Comprehensive Meta-Analysis Software (CMA) V4. This systematic review and meta-analysis included 10 studies examining the effect of probiotic consumption on sleep quality measured by Pittsburgh Sleep Quality Index (PSQI) and 3 studies assessing the effect measured by Electroencephalogram (EEG). Based on the PSQI results, the findings indicate that probiotics considerably enhance sleep quality, with the pooled odds ratio of -0.32 (95% CI:-0.64–0.01; p=0.04). However, probiotic consumption shows no significant effect on sleep quality measured by EEG. Further studies exploring the relationship between probiotic consumption and sleep quality using objective methods and larger samples are necessary to confirm the impact of probiotic supplementation on sleep quality. While these findings suggest that probiotic supplementation could be a potential strategy for improving sleep quality, additional research is required to strengthen these conclusions and investigate the underlying mechanisms.

INTRODUCTION

Sleep plays various important roles in humans, reflecting both physical and psychological conditions. As a result, good sleep is essential for maintaining physical health, mental well-being, and quality of life. Sleep quality refers to an individual's satisfaction with all aspects of their sleep experience. It encompasses key attributes: sleep efficiency, sleep latency, total sleep time, and wake time after sleep onset. The quality of sleep can be evaluated using both objective and subjective methods. Subjective methods involve self-assessment of sleep quality using sleep diaries . The most frequently used tool is the Pittsburgh Sleep Quality Index (PSQI) questionnaire. In contrast, objective methods involve measuring sleep quality using tools such as traditional Polysomnography (PSG) macrostructural sleep measures and techniques that further analyze the microstructures of PSG-measured sleep, including Electroencephalography (EEG). Factors influencing sleep quality are diverse and can vary, including sociodemographic variables, way of life propensities, wellbeing status, stress, cortisol levels, and natural variables.

Recent research has demonstrated that probiotics can improve sleep quality (Lee *et al.* 2022). Previous studies on the relationship between probiotic consumption and sleep quality have yielded various conclusions. For example, Putriningtyas and Astuti (2019) find that yogurt containing *L. bulgaricus* and *S. thermophilus* significantly enhances both the elderly's immune system and quality of sleep. A study by Sawada *et al.* (2017) implies that taking probiotics will reduce stress biomarkers such as salivary cortisol and chromogranin A, leading to improved sleep quality. However, Marotta *et al.* (2019) found no significant difference between the control and experimental groups, likely due to their study's small sample size and the use of multiple probiotics over different time periods. Similarly, Shafie *et al.* (2022) reports that probiotic yogurt does not affect depression or sleep quality, but reduces lower anxiety, tension, and improves the quality of life in postmenopausal women.

Previous research by Haarhuis *et al.* (2022) has examined the relationship between traditional prebiotics, postbiotics, and probiotics such as *Lactobacilli* and *Bifidobacteria* in improving sleep quality and stress. However, the studies have been limited to systematic reviews and have not utilized a meta-analysis approach. Chu *et al.* (2023) conducted a meta-analytical research on the daily consumption of *Lactobacillus gasseri CP2305* for improving sleep quality in adults. However, this study only focuses on a single type of probiotic using a smaller sample size. While numerous studies have investigated the effects of various probiotics on sleep quality, the findings remain inconsistent, often limited by small sample sizes or a focus on single probiotic strains. Moreover, there is a lack of comprehensive meta-analyses that encompass a broader range of probiotic strains and larger sample sizes to provide more conclusive evidence. This meta-analysis research aims to address these gaps by including a larger number of subjects and a variety of probiotic strains. The additional number of subjects and broader scope provided in this study will generate stronger evidence and identify methodological gaps in understanding the relationship between probiotic consumption and sleep quality.

METHODS

Design, location, and time

This study followed The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines as outlined by (Koutsos *et al.* 2019). The design criteria were based on the following basic framework step: 1) Scoping; 2) Planning; 3) Searching; 4) Screening; 5) Eligibility and; 6) Interpretation.

The selection of studies was based on the following inclusion criteria: 1) research investigates the connection between probiotic intake and the quality of sleep; 2) studies conducted on adults with sample size greater than 10; 3) use of a randomized controlled trial design; 4) availability of a sufficient data for analysis and publishing in English. The exclusion criteria were as follows: 1) studies that do not primarily investigate the relationship between probiotic intake and sleep quality; 2) literature with a "low" quality rating (a Joanna Briggs Institute (JBI) score of less than four Indicating low quality). The data search was conducted for publications from 2013–2023, focusing on data from the last decade to ensure the validity, reliability, and relevance of research findings.

Data collection

The research data were obtained through literature searches using databases such as Scopus, Pubmed, Cochrane Library, and ScienceDirect. The search strategy involved using the keywords: "probiotics" or "bacteria" or "microbiome" or "*lactobacillus*" or “*streptococcus*" or "*saccharomyces*" or "*bifidobacteria*" and "tired" or "sleep" separately or combined in the title, abstract, and keywords.

Quality assessment

The Joanna Briggs Institute (JBI) Tool was used to assess the quality of the studies. JBI critical appraisal tool for RCTs (Randomized Controlled Trials) presents 13 questions. These questions aim to identify whether certain safeguards have been implemented to minimize the risk of bias and address other aspects related to the validity or quality of the study. Each question can be scored as met (yes), unmet (no), unclear, or not applicable. According to JBI scoring systems, a score of less than four is considered low quality, a score between four and six is considered medium quality, and a score of seven or even higher is considered high quality. In the current Systematic Review and Meta Analysis only studies with scores of four or higher were included.

Data analysis

The meta-analysis was conducted using Revman 5.4.1 with a random effect model. Statistical significance was determined when a p-value is less than 0.05, the Confidence Interval (CI) was set at 95%. Publication bias testing was conducted using Comprehensive Meta-Analysis Software (CMA) V4. The I^2 statistic values of

25%, 50%, and 75% were considered indicative of mild, moderate, and high heterogeneity, respectively (Higgins 2023). Egger's test was conducted to detect publication bias. The test indicated statistical significance ($p<0.05$), suggesting the publication bias (Egger *et al.* 1997). Additionally, the Fail safe N-Method was used for bias analysis. This method is defined as, "the number of new, unpublished, or un-retrieved non-significant or "null result" studies that would be required to exist to lower the significance of a meta-analysis to some specified level".

RESULTS AND DISCUSSION

The total of 1,520 articles were identified: 501 from Scopus, 97 from PubMed, 422 from Cochrane Library, and 560 from ScienceDirect. After removing 15 duplicates using Mendeley Reference Manager, 1,505 articles remained. Title screening based on the study's scope narrowed this down to 188 papers. Ultimately, 10 studies of the effect of probiotic consumption on sleep quality measured by PSQI and 3 studies of the effect of probiotic consumption on sleep quality measured by EEG were included. Using the PRISMA flowchart as a guide, the study selection process is illustrated in Figure 1 (Page *et al.* 2021). The detailed characteristics of the included studies (PICOS) are summarized in Table 1 and Table 2.

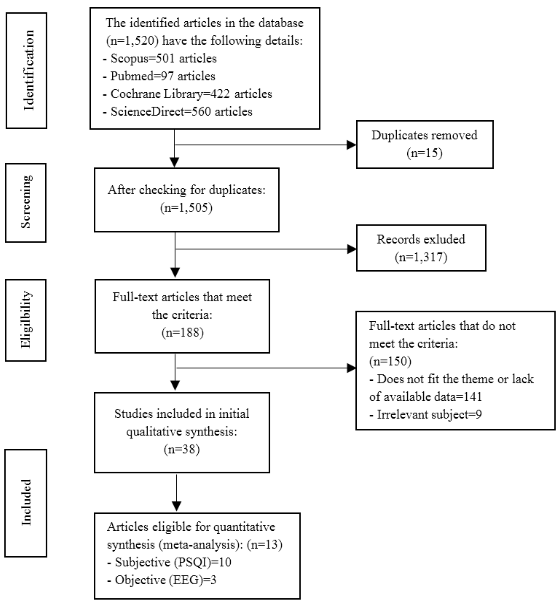


Figure 1. Flow chart of study selection results

Publication bias relationship between probiotic consumption and sleep quality measured by PSQI and EEG

According to Egger regression test, the p-value for the effect of probiotic consumption and sleep quality measured by PSQI is 0.455. Meanwhile for the effect of p-value of probiotic consumption and sleep quality measured by EEG is 0.144 for sleep latency, 0.210 for total sleep time, and 0.202 for wake time after sleep. Since these p-values are above 0.05 statistical significance was not attained, indicating no evidence of publication bias. However, the result of fail-safe N method suggest that the observed significant effect in our meta analysis is highly sensitive to presence of unpublished or unretrieved studies with null results.

Probiotic consumption on sleep quality measured by PSQI

Figure 2. shows the forest plot illustrating the relationship between probiotic consumption and sleep quality measured by PSQI. It indicates high heterogeneity among the studies ($p<0.00001$, $I^2=83\%$). The high heterogeneity may be attributed to variations in population characteristics (demographic differences), differences in intervention protocols, and sample size. The data analysis indicates a significant correlation between the subjective sleep quality measured with PSQI and probiotics, with a pooled odds ratio of -0.32 (95% CI:-0.64–0.01; $p=0.04$). This suggests that the intervention group has a significant effect of 0.32 better than the control. These results align with a meta-analysis conducted by Chu *et al.* (2023), which found that the administration of *Lactobacillus gasseri CP2305* improved adult's sleep quality.

Several mechanisms can link probiotic effects to sleep quality. Higher stress level is associated with lower perceived sleep quality (Horvath *et al.* 2023). Following a 12-week intervention, *L. plantarum P8* (2×10^{10} CFU/day) can enhance the gut's synthesis of neurotransmitters or neuroactive substances, which can improve mood, reduce stress and anxiety, and positively impact neural and psychological function (Ma *et al.* 2021). Randomized controlled placebo trials with stressed-out students have shown that three weeks of *L. plantarum JYLP-326* administration resulted in a reduction in the symptoms of anxiety, depression, and sleeplessness (Zhu *et al.*

Table 1. Characteristic of included studies by Pittsburgh Sleep Quality Index (PSQI)

Study	Study country (Study design)	Population (Duration)	Sample size (Age)/ Intervenation	Type and amount of probiotics	PSQI score
(Shafie *et al.* 2022)	Iran (Randomized, Triple-Blind, Placebo-Controlled Trial)	Postmenopausal women who have medical records at the health center (6 weeks)	66 (45–55)/ 100 mL yogurt daily	1x10^8 C CFU *Bifidobacterium lactis* & *L. acidophilus*	PRO: 3.46±1.81 PLA: 3.77±1.32
(Davoodabadi *et al.* 2021)	Iran (Randomized, Double-Blind, Placebo-Controlled Trial)	Women suffering from cyclical mastalgia that associated with a diagnosis of breast FCC (12 weeks)	45 (18–40)/ 1 capsule daily	2x10^9 CFU *Lactobacillus Acidophilus, Lactobacillus Fermentum, Lactobacil-lus Reuteri, & Bifidiobacterium Bifidum*	PRO: 7.4±2.2 PLA: 8.5±2.6
(Fei *et al.* 2023)	China (Randomized, Double-Blind, Placebo-Controlled Trial)	Meets Peterson MCI diagnostic criteria; no serious problems with the heart, lungs, liver or kidneys; do not have chronic disease exacerbations or seizures; have no visual or hearing impairment. (12 weeks)	40 (>60)/ 2 g probiotics daily	>2x10^{10} CFU *Bifidobacterium lactis HNO19, Lactococcus lactis LY-66, Lactobacillus rhamnosus HNO01, Bifidobacterium animalis BB-115, Lactobacillus paracasei GL-156, Lactobacillus fermentum TSF331, Lactobacillus casei CS-773, Bifidobacterium infantis BLI-02, Lactobacillus reuteri TSR332, Lactobacillus rhamnosus Bv-77, Lactobacillus plantarum CN2018, Lactobacillus plantarum BioF-228, Lactococcus lactis BioF224, Bifidobacterium lactis CP-9, Lactobacillus acidophilus TYCA06, Lactobacillus johnsonii MH-68, Lactobacillus paracasei MP137, Lactobacillus salivarius AP-32*	PRO: 5.35±2.78 PLA: 8.40±1.76
(Kinoshita *et al.* 2021)	Japan (Randomized, Double-Blind, Placebo-Controlled Trial)	Women who work as medical professionals or related to welfare in the medical field (16 weeks)	961 (20–71)/ 112 mL yogurt daily	≥1.12x10^9 CFU *L. bulgaricus* & *S. Thermophilus*	PRO: 5.03±2.68 PLA: 5.22±2.68
Matsuura *et al.* 2022)	Japan (Double-Blind and Placebo-Controlled Clinical Trial)	Healthy young male (8 weeks)	27 (>23.5)/ 1 capsule daily	(-) *Lactococcus lactis subsp. cremoris (YRC3780)*	PRO: 3.3±1.6 PLA: 3.8±2.0
(Önning *et al.* 2023)	Ireland (Randomized, Double-Blinded, Placebo-Controlled, and Parallel-Designed Study)	Healthy adult men and women (12 weeks)	132 (21–52)/ 1 capsule daily	1x10^{10} CFU (10B CFU) *Lactiplantibacillus plantarum HEAL9* (*LPHEAL9, HEAL9™, DSM 15312*)	PRO: 4.94±0.32 PLA: 5.36±0.36

Continue from Table 1

Study	Study country (Study design)	Population (Duration)	Sample size (Age)/ Intervenation	Type and amount of probiotics	PSQI score
(Lee *et al.* 2021)	South Korea (Randomized, Double-Blind, Placebo-Controlled Trial)	Healthy adults with subclinical symptoms of depression, anxiety, and insomnia (8 weeks)	156 (19–65)/ 2 capsules daily	Each 500 mg contains $2.5x10^9$ CFU (2.0x109 CFU *Lactobacillus reuteri NK33* & $0.5x10^9$ CFU *Bifidobacterium adolescentis NK98*)	PRO: 6.83±2.79 PLA: 6.80±2.36
Nishida *et al.* 2019)	Japan (Double-blind, Placebo-Controlled, Parallel-Group Clinical Trial)	Japanese medical students preparing for national exams (24 weeks)	60 (23–25)/ 1 tablet daily	Per 2 tablets contains $1x10^{10}$ *Lactobacillus gasseri CP2305*	PRO: 3.9±0.4 PLA: 4.1±0.5
(Boehme *et al.* 2023)	Switzerland (Double-blind, Placebo-Controlled, Parallel-Group Clinical Trial)	Healthy adults with mild stress (6 weeks)	45 (25–65)/ 1 sachet daily	$1x10^{10}$ CFU *Bifidobacterium longum NCC3001*	PRO: 5.2±1.8 PLA: 4.3±1.7
Sawada *et al.* 2019)	Japan (Double-Blind, Randomized, and Placebo-Controlled Clinical trial)	Male students who do not suffer from psychological or physical disorders, or have a history of serious illness (12 weeks)	49 (18–22)/ 200 mL daily	$1x10^{10}$ CFU *Lactobacillus gasseri CP2305*	PRO: 5.0±1.9 PLA: 4.8±2.3

-: Not provided; CFU: Colony-Forming Unit ; PRO: Probiotic ; PLA: Placebo

2023). The relationship between stress and sleep is well documented (Önning *et al.* 2023). One of the reasons for this relationship is that stress response can elevate blood pressure, heart rate, cortisol levels, and adrenaline response, all of which negatively impact sleep quality (Martire *et al.* 2020).

Administration of red bean yogurt containing *Lactobacillus bulgaricus* and *Streptococcus thermophilus* has been shown to improve sleep quality (Putriningtyas & Astuti 2019). The fermentation process of red bean yogurt produces bioactive peptides and minerals, such as zinc, which can directly impact sleep and nervous system function. Bioactive peptides may be linked to GABAergic or serotonergic neurons, such as melatonin, which help regulate the body's circadian cycle (Codoñer-Franch *et al.* 2023).

Another mechanism that may occur is that various types of microbiomes can generate the neurotransmitters and precursors that are important in controlling sleep (Haarhuis *et al.* 2022). Through the synthesis of SCFA, the microbiome can affect neurotransmitter release by enterochromaffin cells in addition to directly generating neurotransmitters. Gastrointestinal neurons in the vagus nerve, have receptors that can be activated by neurotransmitters. These activated neurotransmitters send signals from the central terminals of the vagus nerve, to the brain (Breit *et al.* 2018). By acting on the vagus nerve, these neurotransmitters play a role in regulating sleep.

Probiotic consumption with sleep quality measured by EEG

Figure 3 (A) presents funnel plot and forest plot of the relationship between probiotic consumption in sleep latency. The analysis indicates low heterogeneity among the studies (p=0.31, I^2=14%). The pooled odds ratio is 0.36 (95% CI:-0.04–0.77; p=0.08). Sleep latency, which measures the time it takes to fall asleep, can indicate sleep quality. Very short sleep latency may suggests excessive daytime

Table 2. Characteristic of included studies by Electroencephalogram (EEG)

Study	Study country (Study design)	Population (Duration)	Sample size (Age)/ Intervenation	Type and amount of probiotics	ECG score
(Nakagawa *et al*. 2018)	Japan (Randomized, Double-Blind, Placebo-Controlled Trial	Adults who face sleeping difficulty every day (4 weeks)	38 (20–64)/ 8 tablets daily	(-) *Lactobacillus helveticus MIKI-020* (LBH MIKI-020)	- Sleep latency PRO: 18.14±15.98 PLA: 15.86±12.30 -Total sleep time PRO: 323.93±81.44 PLA: 317.67±77.26 -Wake time after sleep PRO: 3.64±4.24 PLA: 4.57±4.85
(Monoi *et al*. 2016)	Japan (Randomized, Double-Blind, Placebo-Controlled Trial)	Healthy man suffering sleep disorders (4 weeks)	68 (Average 38)/ 4 sake yeast tablets (125 mg each tablet)	(-) *Saccharomyces cerevisiae*	- Sleep latency PRO: 17.1±10.9 PLA: 18.6±10.7 - Total sleep time PRO: 334±67 PLA: 341±78 - Wake time after sleep PRO: 6.32±3.65 PLA: 6.21±3.36
Nakakita *et al*. 2016)	Japan (Randomized, Double-Blind, Placebo-Controlled Trial)	Full-time employees who have good sleep quality (10 days)	14 (40–69)/ 25 mg daily	(-) *Lactobacillus brevis SBC8803* (SBL88™)	- Sleep latency PRO: 11±1 PLA:10±2 -Total sleep time PRO: 340±7 PLA: 334±7 - Wake time after sleep PRO : 16±1 PLA : 17±1

-: Not provided; CFU: Colony-Forming Unit ; PRO: Probiotic ; PLA: Placebo

sleepiness or pathological sleep conditions such as narcolepsy. The meta-analysis results on sleep quality measured using the EEG are inversely proportional to the meta-analysis results on sleep quality measured using the PSQI method and the study reported by Nishida *et al.* (2019) which measured sleep quality using EEG before (0) and after 6 or 12 weeks of consuming *Lactobacillus gasseri CP2305*. *Lactobacillus gasseri CP2305* significantly reduced sleep latency. Takada *et al.* (2017) also reported that prolonged sleep latency was lowered by taking *Lactobacillus casei* daily.

Figure 3 (B) shows funnel plot and forest plot of the relationship between probiotic consumption and total sleep time. The analysis indicates moderate heterogeneity among the studies (p=0.09, I^2=58%). The pooled odds ratio is 0.37 (95% CI:-0.25–0.98; p=0.24). Total sleep time refers to the total amount of time spent sleeping over the whole recording period, encompassing the interval between the start and the end of sleep. The meta-analysis results are consistent with the study by Takada *et al.* (2017), which found that *Lactobacillus casei* strain Shirota did not affect total sleep time measured by EEG, but had a significant effect on total sleep time as measured subjectively using the Oguri-Shirakawa-Azumi (OSA) score.

Figure 3 (C) shows the funnel plot and forest plot of the relationship between probiotic consumption and wake time after sleep. The analysis indicates moderate heterogeneity among the studies (p=0.08, I^2=61%). The pooled odds ratio is -0.48 (95% CI:-1.12–0.17; p=0.15). The data analysis reveals no significant relationship between probiotic consumption and sleep quality

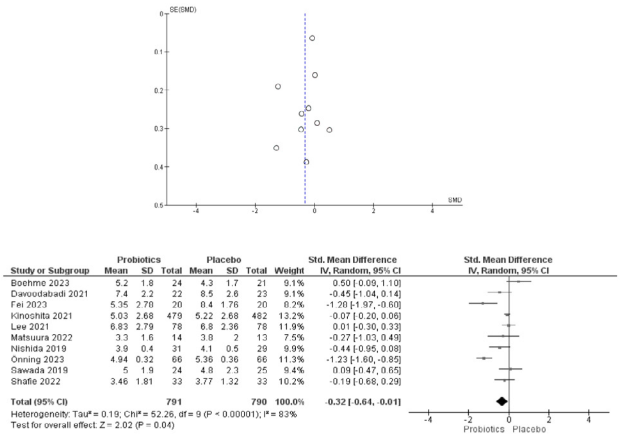


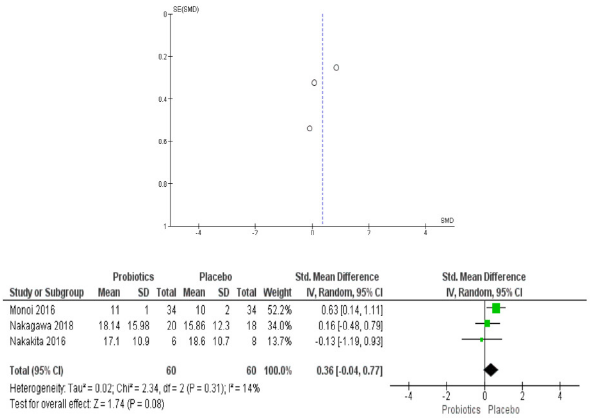
Figure 2. Funnel plot and Forest plot of the meta-analysis on the effect between probiotic consumption and sleep quality measured by pittsburgh sleep quality index

measured by EEG. Wake time after sleep refers to the period of wakefulness occuring after the beginning of sleep cycle. A high percentage of total sleep time is generally associated with a low percentage of wake time after sleep, and vice versa. This measures describes the amount of time spent awake following the start of a particular sleep cycle (Shrivastava *et al.* 2014).

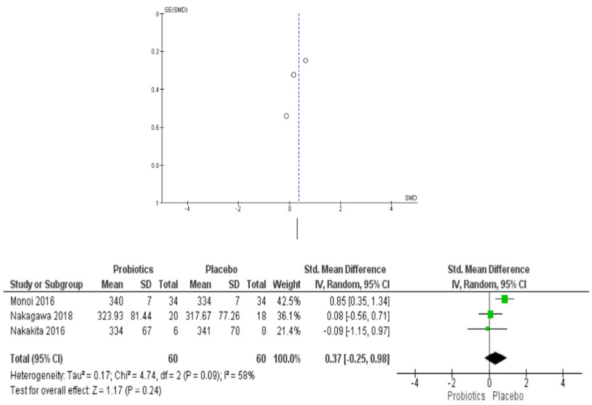
There is a difference between the results of the meta-analysis of subjective (PSQI) and objective (EEG) sleep quality measurements. The meta-analysis results found that probiotic administration had no significant effect on objective sleep quality (sleep latency, total sleep time, and wake time after sleep). In contrast, people assess their sleep quality using the PSQI questionnaire, which evaluates sleep over the past month (Pilz *et al.* 2018). In comparison, objective measurements are gathered in advance and only collected for three (Nakagawa *et al.* 2018) or four (Monoi *et al.* 2016) consecutive nights of the entire experimental trial. However, participants often report advantages from taking probiotics for improved sleep quality. Consequently, the limited duration of objective measurements may restrict the ability to detect subtle changes in sleep characteristics following probiotic ingestion. Another contributing factor could be the smaller sample sizes and fewer studies using the objective methods. The impact sizes reported in the meta-analysis represent the weighted averages of the effect sizes from each study. The weights are assigned based on how well each study predicts the impact size. In meta-analysis, larger studies typically receive more weight and contribute significantly to the overall effect size, primarily based on their sample size (Schober & Vetter 2020). Other factors such as dietary influences and emotional factors may affect sleep quality and contribute to the inconsistencies. These factors might be more controlled or reported in subjective assessments like the PSQI compared to objective measurements.

Strength and limitations of the review

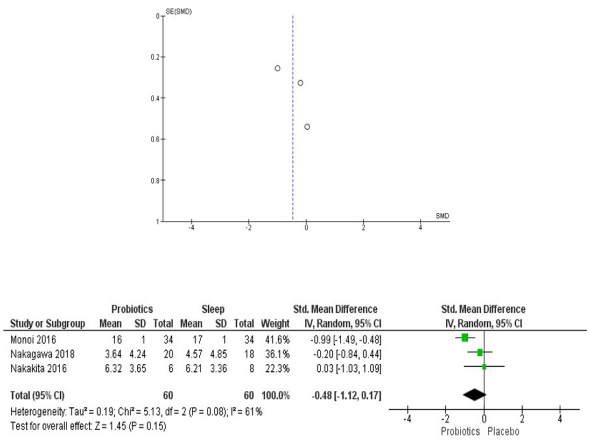
The key strength of this study is its comprehensive approach, incorporating both subjective (PSQI) and objective (EEG) measures to assess the relationship between probiotic consumption and human's sleep quality. This dual approach provides a more nuanced understanding of how probiotics may influence sleep quality. However, this systematic review and meta-analysis had several limitations. First, this systematic review and meta-analysis remain general and do not categorize results based on other factors such as gender or age, due to the limited number of available studies. Additionally, potential confounding factors were not considered, which could have influenced the results. More studies of the relationship between probiotic consumption and sleep quality measured by objective method with large samples are required to verify the impact of probiotic use on the quality of sleep. This study did not include probiotic-containing foods such as kimchi and kombucha, which could have provided additional insights. Moreover, some studies exhibited heterogeneity in their results, to mitigate this, future research should focus on standardizing methodologies and consider potential confounding variables.



(A) Funnel plot and Forest plot of sleep latency



(B) Funnel plot and Forest plot of total sleep time



(C) Forest plot of wake time after sleep

Figure 3. Funnel plot and forest plot of the meta-analysis on the effect between probiotic consumption and sleep quality measured by electroencephalogram

CONCLUSION

Based on the results of the meta-analysis, probiotics have a significant impact on sleep quality measured by subjective methods (PSQI). The research indicates that probiotics are effective in improving sleep quality. However, the current evidence suggests that probiotics intake does not significantly influence responses measured by objective methods (EEG). There is currently a scarcity of well-designed research studies in this area. Further research is warranted to gain a deeper understanding of the effects of probiotics on objective sleep characteristics.

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DECLARATION OF CONFLICT OF INTERESTS

The authors have no conflict of interest.

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