Special Article

The impact of tryptophan supplementation on sleep quality: a systematic review, meta-analysis, and meta-regression

Clarinda N. Sutanto, Wen Wei Loh, and Jung Eun Kim

Context: *L-tryptophan (Trp) has been documented to aid sleep, but a systematic compilation of its effect on sleep quality is still limited.* ***Objective:*** *We assessed the effect of Trp supplementation on sleep quality via meta-analysis and meta-regression. The effects of daily Trp dose (<1 g and ≥1 g) were also assessed.* ***Data sources:*** *A database search was done in PubMed, Medline (Ovid), Cumulative Index to Nursing and Allied Health Literature (CINAHL), and Cochrane and a total of 18 articles were collected.* ***Data extraction:*** *Extracted data from 4 articles were also analyzed using random-effect meta-analysis and meta-regression. Standardized mean difference (SMD) was used in meta-analysis.* ***Data analysis:*** *Results from the study suggested that Trp supplementation can shorten wake after sleep onset (−81.03 min/g, P = 0.017; SMD, −1.08 min [95%CI, −1.89 to −0.28]). In addition, the group receiving ≥1 g Trp supplementation had a shorter wake after sleep onset than the group with Trp < 1g supplementation (Trp <1 g vs Trp ≥1 g: 56.55 vs 28.91 min; P = 0.001). However, Trp supplementation did not affect other sleep components.* ***Conclusion:*** *Trp supplementation, especially at ≥1 g can help improve sleep quality.*

INTRODUCTION

Continual advances in screen-based devices, such as television and smartphones, along with social and work commitments may contribute to sleep disturbances. Concomitantly, the use of sleep medications and care visits for sleep disturbances have been increasing since the 1990s, which may indicate a decline in sleep quality.[1] Studies have associated sleep disturbance with a range of health-related conditions, such as impaired cognition, obesity, type 2 diabetes mellitus, and cardiovascular disease.[1–3] This association is rationalized by the effect of sleep on various biological processes, such as memory consolidation and attention, appetite, glucose regulation, and inflammation.[1] A meta-analysis showed that individuals who have difficulty maintaining sleep have an 84% increased risk of type 2 diabetes mellitus development.[3] Nondepressed individuals with insomnia are also twice as likely to develop depression as compared with those with normal sleep.[4] Collectively, because sleep is important to overall physical and mental well-being, the decline in sleep quality has raised growing health and economic concerns.[1]

With growing evidence on the contribution of sleep to optimal health, conventional strategies, such as behavioral modification and sleep hygiene techniques, have been recommended to improve sleep quality. For more serious sleep disturbance cases, such as chronic insomnia, pharmacotherapies are also implemented. However, the use of these drugs often come with the

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risk of unwanted side effects.[5] Another treatment alternative is the use of physiological agents that are supposedly involved in sleep regulation. Because a natural metabolic pathway already exists for these agents to modulate sleep, their use may have a reduced risk of undesirable side effects and toxicity.[6] L-tryptophan (Trp) is one of those physiological agents and it can be obtained from protein-rich food and supplementation.[7,8] It has been suggested in previous reviews that consumption of foods high in Trp, such as milk, is linked to improved sleep outcomes.[9,10] In addition, Trp and α-lactalbumin supplementation is reported to improve different measures of sleep quality, such as sleep latency (SL).[11] However, the impact of Trp on sleep is mixed and one of the defining factors of its efficacy is the daily dose. Although 0.25 g of Trp may improve sleep, a 1 g dose had a more consistent favorable effect on sleep.[12] Schneider-Helmert and Spinweber[6] also claimed that a dose of 1–5 g should be applied to treat sleep disturbances.

Although sleep is a multidimensional concept, most of the focus in sleep research has been on sleep duration. Objective measures of sleep continuity, such as SL, wake after sleep onset (WASO), and sleep efficiency (SE) can be appropriate indicators of sleep quality. Therefore, in this review, we systematically compiled relevant published data and evaluated the effect of Trp supplementation on multiple sleep-quality components via meta-analysis and meta-regression analytical techniques. In addition, we compared the effects of a <1 g dose and a ≥1 g dose of Trp to investigate the dose-dependent response of Trp supplementation on sleep outcomes.

METHODS

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement was applied to guide the execution of this systematic review, meta-regression, and meta-analysis.[13]

Literature search and article selection

A participant, intervention, comparison, outcome, and study design (PICOS) statement was established to define the scope of this review (Table 1). This was followed by a literature search in the PubMed, Medline (Ovid), Cumulative Index to Nursing and Allied Health Literature (CINAHL), and Cochrane databases in November 2019. The search query and filters used for each database search are detailed in Table S1 in the Supporting Information online. From this initial search, 255 articles were captured and exported to Endnote X8 (Clarivate; Thomson Reuters, Boston, MA, USA) for duplicate exclusion (n = 101) and article consolidation. As part of the study selection, these articles were screened using the following set of criteria: (1) randomized controlled trial (RCT) study design; (2) adult population aged ≥19 years (mean age); (3) ≥1 group consuming a Trp supplement or Trp-enriched food; and (4) reported ≥1 sleep-quality outcome, such as total sleep time (TST), WASO, SL, SE, rapid eye movement (REM), and nonrapid eye movement (NREM) sleep duration.

During the title and abstract screening, 44 articles were selected. An additional 22 articles from other sources were also identified and added. Collectively, a total of 66 articles were chosen for the full-text screening and, after screening, 18 full-text articles were deemed to have met the requirements for this review. The study selection flow is shown in Figure 1. Of the qualified articles, 18[7,12,14–29] were used in the systematic review and 4 were eligible for the meta-analysis and meta-regression. The literature search and study selection were performed independently by 2 reviewers (C.N.S. and W.W.L) and any discrepancies in the process were discussed until a consensus was reached.

Data extraction

The qualified articles were extracted for: (1) year of publication; (2) first author's name; (3) study design; (4) age; (5) Trp doses administered; (6) duration of the intervention; and (7) pre-intervention, postintervention, and change values of sleep outcome values (mean and standard deviation). Sleep-quality outcomes included TST (h), WASO (min), SL (min), SE (%), REM duration (h), and NREM duration (h). Along with these listed outcomes, sleep outcomes reported as D-time and slow-wave sleep were further classified as REM and NREM, respectively.[14,18] In addition, corresponding authors of the selected articles were contacted when additional data were needed.

Quality assessment

The quality assessment of these selected articles was also performed by 2 independent reviewers (C.N.S. and W.W.L) and any discrepancies were discussed until an agreement was reached. Quality assessment was performed to assess risk of bias of the RCTs. This was conducted with a modified version of the Cochrane risk-of-bias tool.[30] For studies in which multiple intervention phases were conducted, the individual, relevant experimental designs were assessed for their risk of bias.

Selection bias, performance bias, and detection bias were evaluated, and reviewers independently assessed the level of risk in each bias by categorizing each as low,

Table 1 **PICOS criteria for inclusion of studies**

Parameter	Description
Population	Adult ≥19 years old (mean age)
Intervention	Consuming Trp supplement or Trp-enriched food
Comparison	Not consuming Trp supplement or Trp-enriched food
Outcome	Sleep quality outcomes: TST, SL, SE, REM, and NREM sleep duration
Setting	RCT

Abbreviations: NREM, non-rapid eye movement; RCT, randomized controlled trial; REM, rapid eye movement; SL, sleep latency; SE, sleep efficiency; Trp, tryptophan; TST, total sleep time.

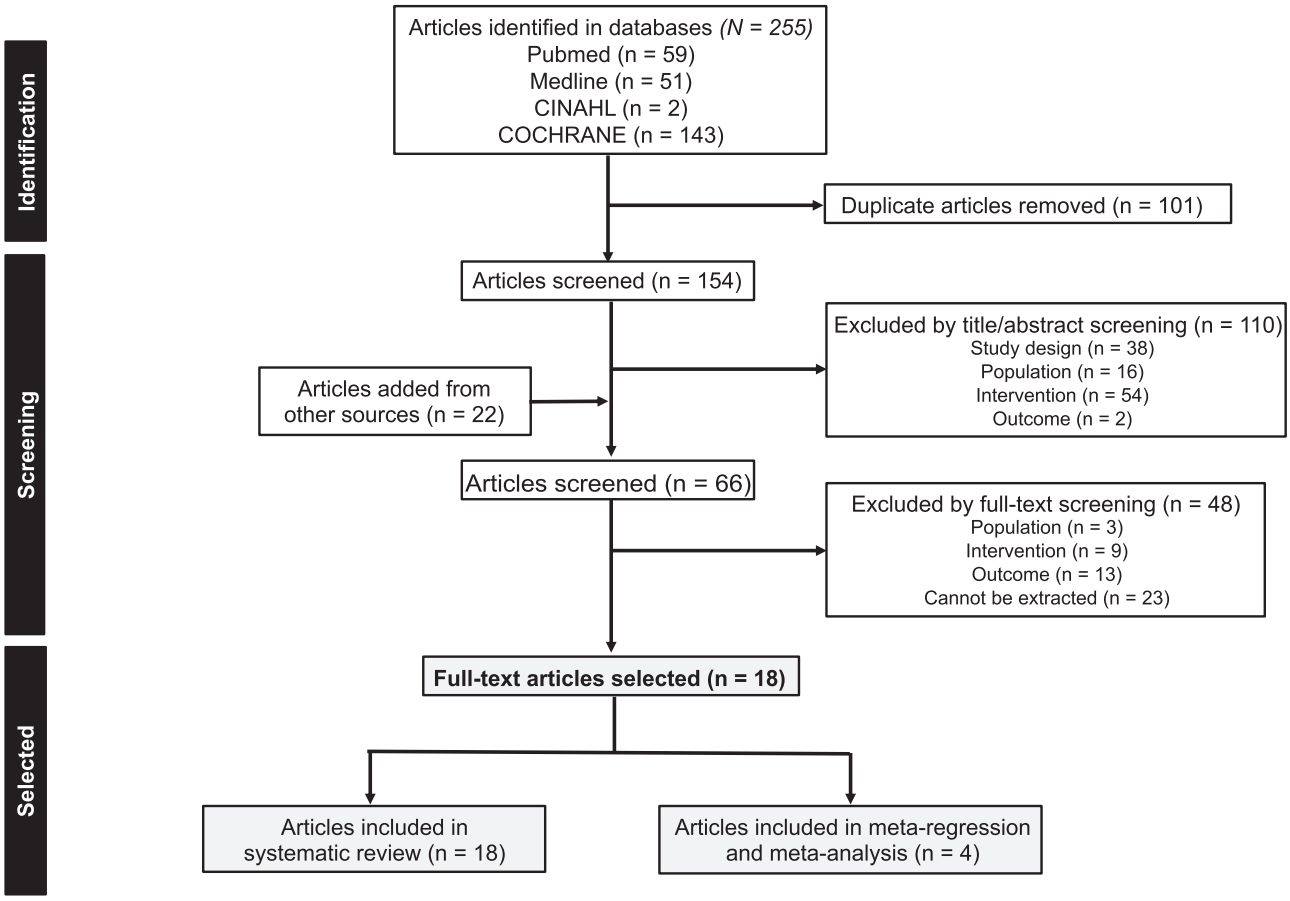

Figure 1 **Flow diagram of the literature search and screening process**

high, or unclear. RCTs were considered to have a high risk of selection bias when there was evidence of lack and/or insufficient randomization and allocation concealment within the individual RCT. RCTs were categorized as unclear if there was insufficient information to determine these statuses and as low when there was sufficient randomization and allocation concealment. In addition, studies were classified as at high risk of performance bias and detection bias when there was evidence of unblinding of participants and/or study investigators and outcome assessor. They were also considered at high risk when there was evidence of unblinding during the study. Similarly, an unclear status was assigned when insufficient information was provided to judge. In contrast, RCTs were classified as at low risk of performance and detection biases if the authors reported blinding of participants, study investigators, and outcome assessor.

Statistical analysis

A random-effects meta-analysis was performed to evaluate the effect of Trp supplementation on TST (h), WASO (min), SL (min), and SE (%). Data were reported as standardized mean difference (SMD) with their 95%CI. The SMDs were calculated from the mean change values between the sleep outcomes of the control and intervention groups. If these values

were not available, these change values were calculated, and the standard deviation of mean difference values (SD_{diff}) was estimated using an imputed correlation coefficient obtained from a selected study.[28] The following equation was used to obtain the correlation coefficient (Corr) for SD_{diff} estimation[30]:

$$\text{Corr} = \frac{SD_{post}^2 + SD_{pre}^2 - SD_{diff}^2}{2 \times SD_{post} \times SD_{pre}}$$

Where SD_{post} is the standard deviation of postintervention valuesand SD_{pre} is the standard deviation of preintervention (baseline) values.

Crossover trials were treated as parallel studies with the full number of study participants to represent the population for both the Trp supplementation and control groups.[30] Following this, a sensitivity analysis was conducted to assess the robustness of the meta-analysis results. This was done by omission of single-comparison sets of study data and repeating the meta-analysis.

A meta-regression analysis was also conducted with the mean difference and the standard error of the mean to examine the dose-dependent relationship between the Trp dose used in the intervention and the change values of TST, WASO, SL, and SE. The mean difference was obtained by calculating the mean changes of the sleep outcome values observed from the intervention and baseline. A random-effects model was applied when performing this meta-regression analysis.

To further investigate the dose-dependent efficacy of daily Trp supplementation on sleep qualities within intervention groups, an independent *t* test was also applied to determine the difference in postintervention sleep outcomes between 2 Trp dose groups: <1 g and ≥1 g. All the statistical analyses were performed using Stata/IC (StataCorp LP, College Station, TX, USA).

RESULTS

Study characteristics and quality assessment

The selected 18 articles reported on a total of 21 RCTs; characteristics of these RCTs are tabulated in Table 2. Of the 21 RCTs[7,12,14–29], 15 were crossover and 6 were parallel in study design. The Trp doses allotted in the RCTs ranged from 0.25 g to 15 g and the studies had an average intervention period of 5.5 days. For some of the RCTs, the study participants' exposure to the same intervention was replicated multiple times with a 1–2 week washout period.[14,16,17] Trp doses were mostly administered 20–30 minutes before the participants' bedtime. From these RCTs, sleep data that were reported and extracted were TST (n = 15), WASO (n = 9), SL (n = 16), SE (n = 7), total REM sleep (n = 11), and total NREM sleep (n = 5).

Figure 2 illustrates the risk-of-bias assessment of the 21 RCTs selected for this review and a detailed risk assignment of the individual RCTs is listed Table S2 in the Supporting Information online.[7,12,14–29] In Figure 2, it is shown that 52% (n = 11) and 81% (n = 17) of RCTs were categorized as of relatively low risk in detection bias and performance bias, respectively. On the other hand, although 48% (n = 10) of the RCTs had sufficient randomization, the risk of selection bias of most of the RCTs remained unclear.

Meta-analysis and meta-regression

Using a random-effects model, the meta-analysis results on the effect of Trp supplementation with TST, WASO, SL, and SE are shown in Figures 3[12,24,28], 4 [12,28], 5[24,26,28]and 6[12,28], respectively. Trp supplementation decreased the WASO (SMD, −1.08 min; 95%CI, −1.89 to −0.28). However, the favorable effect of Trp supplementation on TST, SL, and SE was not statistically significant. The SMDs were as follows: TST, 0.29 h (95%CI, −0.54 to 1.12); SL, −0.46 min (95%CI, −1.09 to 0.18); and SE, 1.04% (95%CI, −0.11 to 2.18). A sensitivity analysis (Table S3[12,24,26,28] in the Supporting Information online) revealed that the results of the meta-analysis seemed to be dependent on the data of Mohajeri et al.[28] Omission of their data resulted a significant meta-analysis result for WASO (SMD, −1.49 min; 95%CI, −2.04, −0.93), SL (−0.83 min; 95%CI, −1.53 to −0.12), and SE (SMD = 1.56%; 95%CI, 0.82% to 2.30%).

The dose-dependent relationship between Trp (g) with TST (h), WASO (min), SL (min), and SE (%) was assessed by random-effects meta-regression analysis. The dose-dependent regression coefficients are summarized in Table 3. The meta-regression correlation figures of Trp with TST, WASO, SL, and SE can also be seen in Figures S1–S4, respectively, in the Supporting Information online. There was an inverse association between the amount of Trp administered with change value of WASO (−81.03 min/g; $P = 0.017$); no association was observed with other sleep-quality outcomes.

Dose-response comparison of tryptophan and sleep

The dose-dependent efficacy of daily Trp supplementation (<1 g vs ≥1 g) on sleep-quality outcomes was examined and results are summarized in Table 4. The group given the >1 g dose of Trp had a more favorable sleep quality than the group given <1 g of Trp, as

Table 2 **Study design and characteristic of selected randomized controlled trials**

Reference	Study design	No.	Mean age/ age range (y)	Control		Intervention		Sleep-quality outcome					
				Trp dose (g)	Duration, no. of night (s)	Trp dose (g)	Duration, no. of night (s)	TST (h)	WASO (min)	SL (min)	SE (%)	Total REM sleep (h)	Total NREM sleep (h)
Hartmann (1967)[14]	Crossover	8	18–31	0	1 (10×)[a]	5–9	1 (10×)[a]	✓				✓	
Wyatt et al (1970)[15]	Crossover	5	18–21	0	10	7.5	10	✓				✓	
		7	–	0	5–10	7.5	5–10	✓	✓	✓		✓	✓
		3	–	0	3–6	7.5	3–6	✓				✓	✓
Hartmann et al (1971)[16]	Crossover	10	18–31	0	1 (10×)[a]	5–9	1 (10×)[a]			✓			✓
		24	42	0	4	2–5	4 (2×)[a]	✓	✓	✓	✓		
Griffiths et al (1972)[17]	Crossover	13	21–26	0	3	7.5	1 (2×)[a]			✓		✓	
		8	21–28	0	3	12	1 (2×)[a]			✓		✓	
Hartmann et al (1974)[18]	Crossover	10	21–35	0	3	1–15	1	✓	✓	✓		✓	✓
Murphy et al (1974)[19]	Crossover	34	–	0	5	9.6	20	✓					
Hartmann and Elion (1977)[20]	Parallel	42	19–23	0	1	1–3	1	✓	✓	✓		✓	
Adam and Oswald (1979)[21]	Crossover	12	54	0	2	1	2			✓			
Nicholson and Stone (1979)[22]	Crossover	6	20–30	0	1	2–6	1	✓		✓	✓	✓	
Hartmann and Spinweber (1979)[23]	Crossover	15	21–35	0	2	0.25–1	1	✓	✓	✓	✓	✓	✓
Moldofsky and Lue (1980)[24,b]	Crossover	7	–	0	1	5	4	✓		✓		✓	
Hartmann et al (1983)[25]	Parallel	52	–	0	7	1	6			✓			
Spinweber (1986)[26,b]	Parallel	20	20	0	3	3	6			✓			
Levitan et al (2000)[27]	Parallel	30	–	0	56	1–4	56			✓			
Hudson et al (2005)[12,b]	Parallel	49	–	0	7	0.25	7	✓	✓		✓		
Mohajeri et al (2015)[28b]	Parallel	59	54	0	19	0.7	19	✓	✓	✓	✓		
Ong et al (2017)[7]	Crossover	10	27	0.28	2	0.96	2	✓	✓	✓	✓		
van Dalfsen and Markus (2019)[29]	Crossover	98	22	0	7	1	7	✓	✓	✓	✓		

[a]There was a 1–2 week washout period between multiple intervention repeats.
[b]Studies used in meta-analysis and meta-regression.
Abbreviations: NREM, non-rapid eye movement; REM, rapid eye movement; SE, sleep efficiency; SL, sleep latency; Trp, tryptophan; TST, total sleep time.

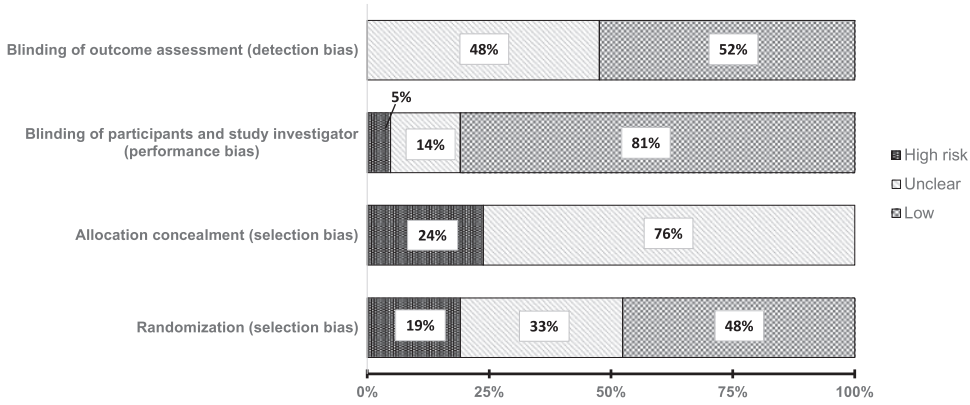

Figure 2 **Quality assessment evaluating the risk of bias within the randomized controlled trials selected for this systematic review, meta-analysis, and meta-regression**. Risk assessments are presented as percentages across all the qualified studies

evidenced by a significantly shorter WASO (Trp <1 g vs Trp ≥1 g: 56.55 vs 28.91 minutes; $P = 0.001$).

DISCUSSION

Multiple studies have reported the significant role of sufficient and restorative sleep on both physical and psychological health. Sleep disturbances have been suggested to be a predictor of various illnesses and are associated with decreased quality of life. In a cross-sectional study, Lund et al[31] found that individuals with poor sleep quality were more likely to use drugs to help regulate their sleep and wakefulness. Pharmaceutical hypnotics have also been used as the first primary pharmacotherapy to treat chronic insomnias. However, the use of sleep-regulating drugs may have unwanted side effects, such as dependency, and are mostly endorsed for short-term use.[5] Therefore, using physiological agents that are naturally used by the body to regulate sleep, such as Trp, may be a safer treatment alternative for sleep disturbances.[6]

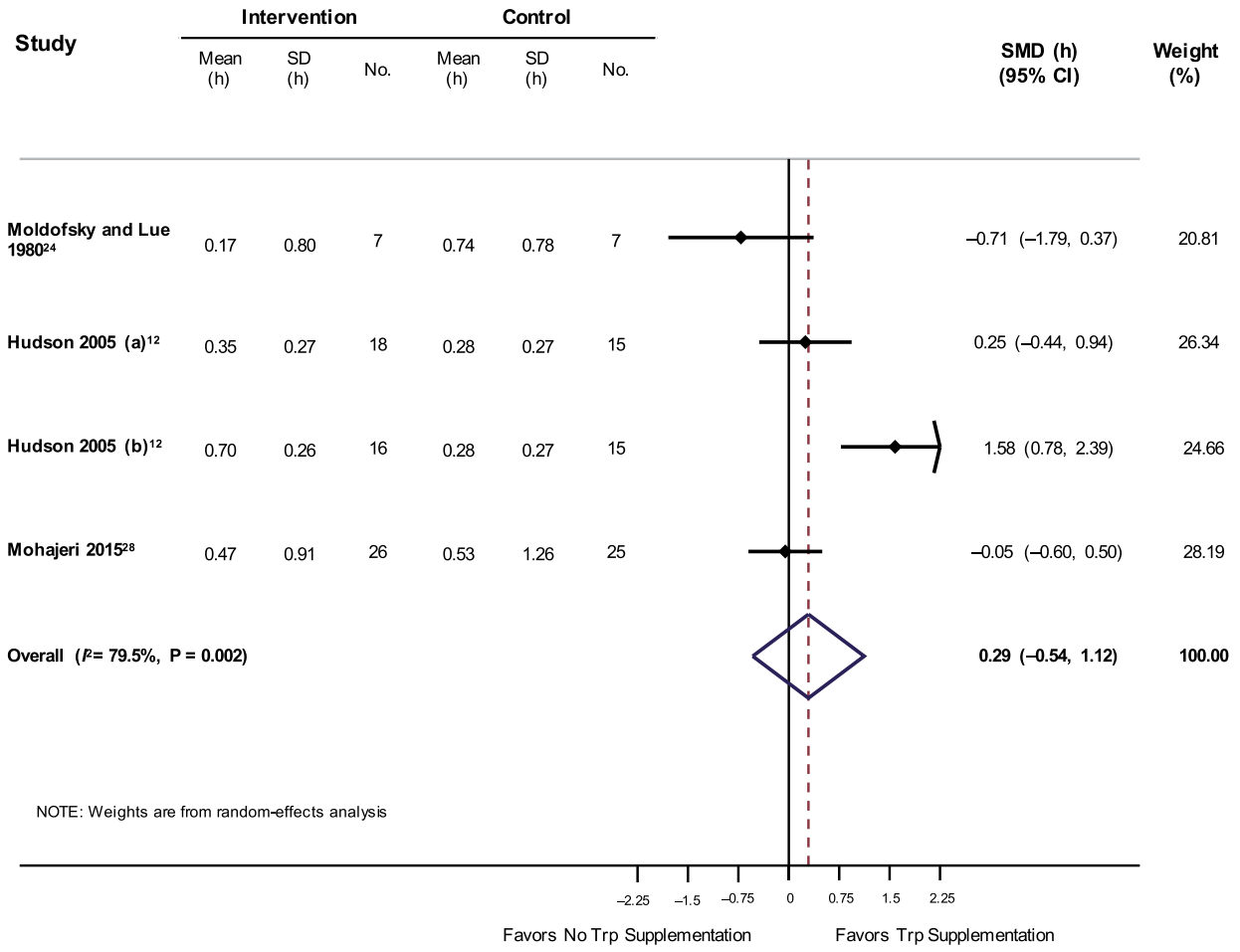

Figure 3 **Random-effects model meta-analysis comparing the standardized mean difference (SMD) in total sleep time (h) after tryptophan (Trp) supplementation**

Trp and sleep

The use of Trp has been documented to have sleep-inducing effects.[29] The findings of this systematic review, meta-analysis, and meta-regression, revealed that Trp supplementation favorably influences sleep maintenance parameters, such as WASO and SE. This was also observed by Lindseth et al,[32] who reported that consumption of high-protein diet containing high levels of Trp resulted in a shorter WASO than did a control diet lower in protein. In addition, Bravo et al[33] reported that consumption of Trp-enriched cereal resulted in increased SE in older adults as compared with placebo cereal.

Metabolically, the exact mechanism of the sedating effect of Trp has not been fully elucidated.[27,29] But as the precursor of serotonin (5-Hydroxytryptamine; 5-HT), it is believed that Trp's somnolent effect may be mediated by the serotonergic pathway.[27,34] When consumed, Trp is transported into the brain and converted to the sleep-regulating neurotransmitter 5-HT via the serotonergic pathway.[35] Under normal conditions, Trp hydroxylase, the rate-limiting enzyme involved in converting Trp to 5-hydroxytryptophan is not fully saturated. By saturating this enzyme with Trp, brain Trp levels can be increased and 5-HT synthesis enhanced. This process, in turn, has been claimed to induce sedation.[28] However, the precise nature of how 5-HT regulates sleep is not fully understood. Depending on factors such as the type of receptor and brain location, 5-HT can influence different physiological responses. In addition, 5-HT is also a positive modulator of the sleep-signaling hormone melatonin, which is secreted by the body to signal night time.[33] The activity of arakylamine *N*-acetyltransferase, the rate-limiting enzyme responsible for converting melatonin from 5-HT, is inhibited by light. Hence, in the absence of light, the pineal gland starts secreting melatonin.[36] One of the physiological effects of melatonin is stimulating peripheral vasodilation, which, in turn, decreases body core temperature. This lowering in central temperature facilitates the onset of sleep.[37] However, similar to 5-HT, the exact

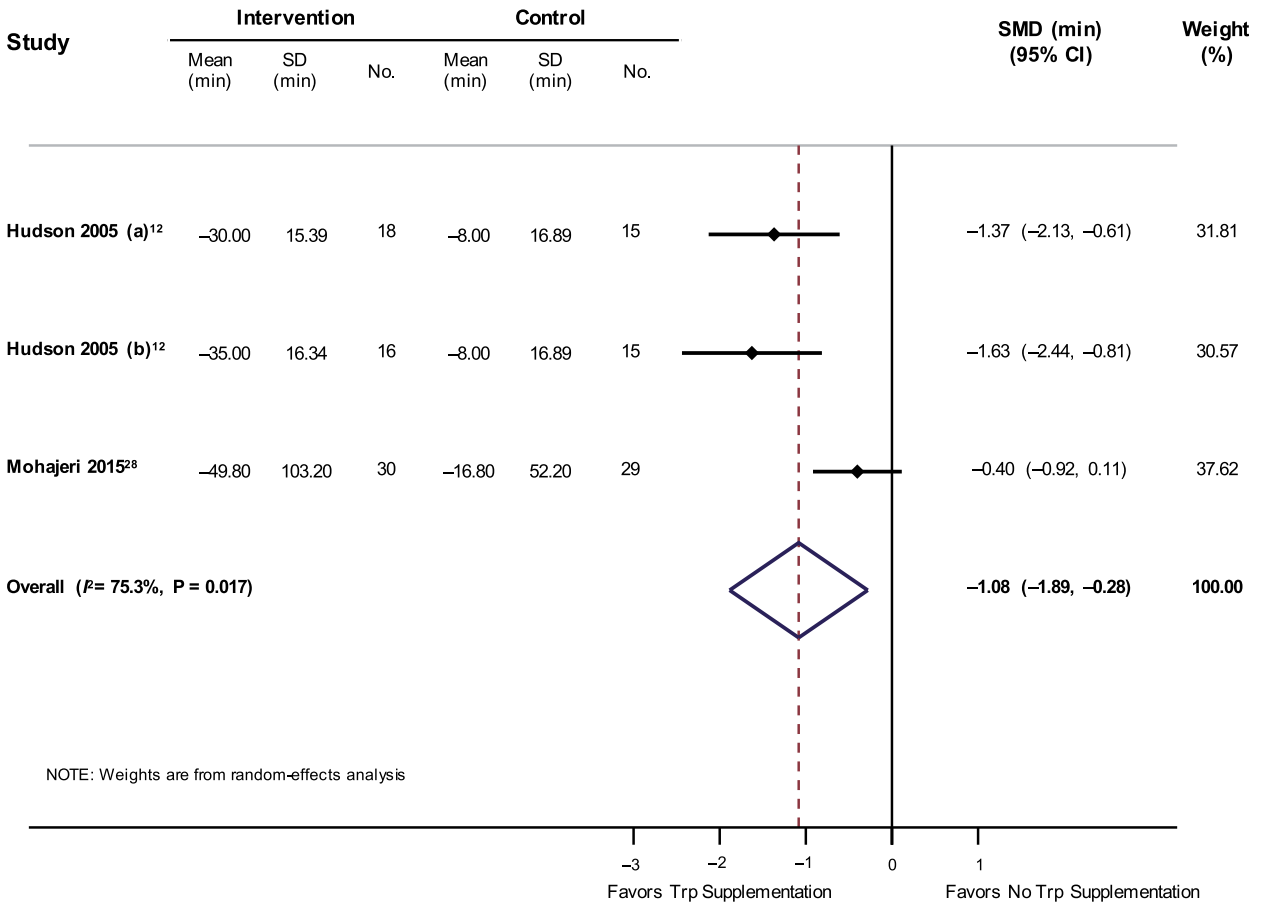

Figure 4 **Random-effects model meta-analysis comparing the standardized mean difference (SMD) in wake after sleep onset (min) after tryptophan (Trp) supplementation**

mechanisms and area where melatonin act to induce sleep are not known.[38] Therefore, more research is still needed in this area.

Sensitivity analysis of the meta-analysis results suggested that the results may have depended on data from the Mohajeri et al report.[28] When the data from this study were removed, the favorable effect of the Trp supplementation was statistically significant for the sleep-quality components WASO, SL, and SE.[28] This may be because the study was conducted with a population that did not have insomnia. The removal of data from the Mohajeri et al study allowed most of the weight to shift to data obtained from the insomnia population.[12,26] This finding suggests that sleep status of the population (insomnia vs no insomnia) may play a role in the effectiveness of Trp supplementation. This was also supported by previous studies in which authors reported that most of the beneficial effects of Trp on sleep-related outcomes were more consistently observed in individuals with mild to moderate insomnia as compared with those who were healthy.[5,12,34] There are few reasons that may explain these observations. The first is the "ceiling phenomenon."[27] Healthy people who do not have insomnia may have an SL value of 10 min and almost no WASO during the baseline. This condition may not provide an additional improvement in sleep quality when Trp is administered. Second, the effect of Trp loading may depend on the initial state of the population's serotonergic system.[8] Innate factors (e.g., genetics, sex) and environmental factors (e.g., stress, drugs) can modulate the serotonergic system to create a hyposerotonergic state. These factors can determine and increase the risk of development of serotonergic-activity related disorders. These serotonergic-vulnerable populations can include, but are not limited to, people with depression.[8]

There is a strong link between insomnia and depression, which are believed to be related to low 5-HT levels.[39] If a person who is already in a hyposerotonergic state prior to the Trp loading, the administration of Trp may be able to shift the 5-HT to its optimal level. Hence, the desirable effect of Trp loading is more prominently observed. However, for healthy people who may already be at their optimal serotonergic status,

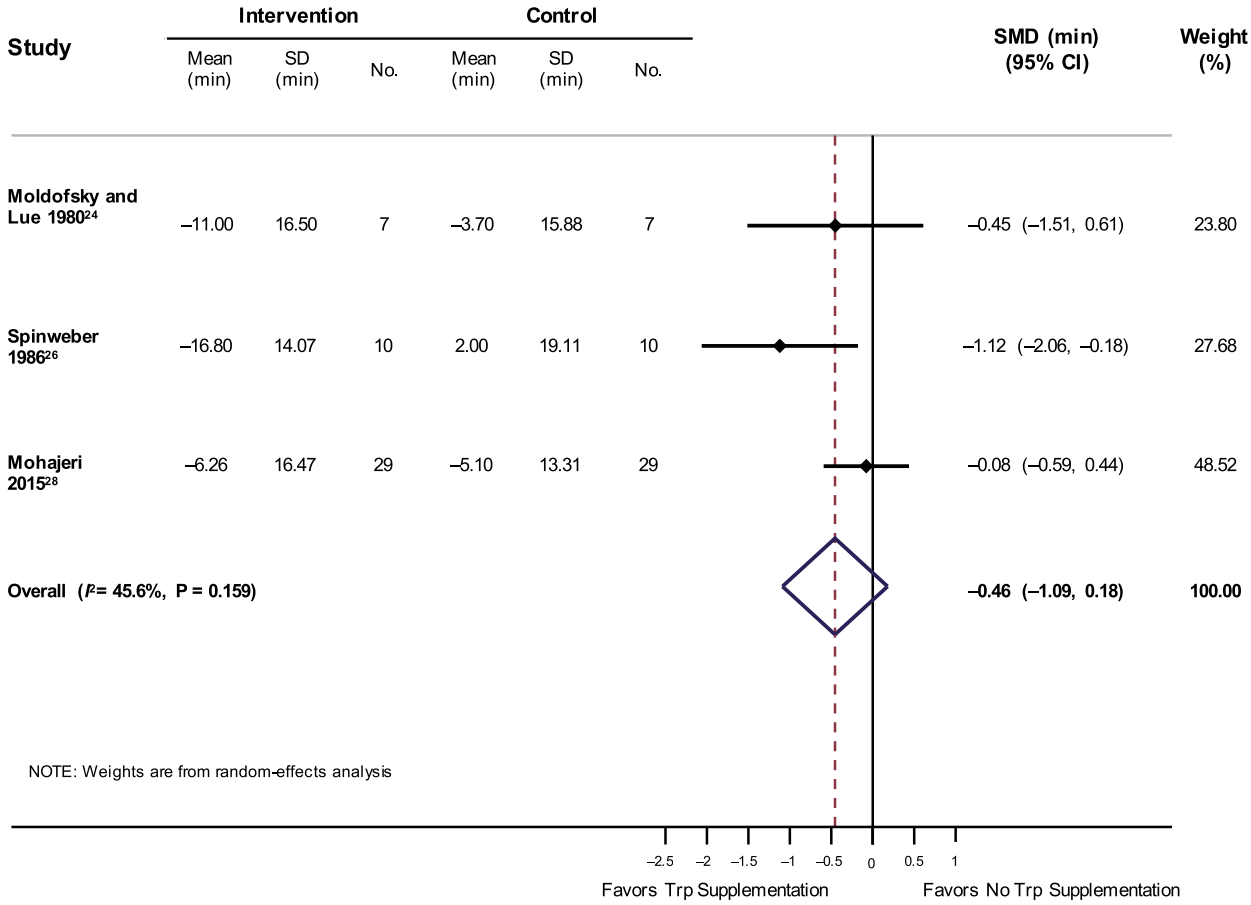

Figure 5 **Random-effects model meta-analysis comparing the standardized mean difference (SMD) in sleep latency (min) after tryptophan (Trp) supplementation**

the Trp loading can move beyond the ideal 5-HT level. Thus, no effect or the opposite effect was observed instead.[8] Nevertheless, more data are needed to confirm this hypothesis. Investigating how the underlying sleep status of a population (insomnia vs no insomnia) may affect the efficacy of Trp supplementation as a sleep aid could be an insightful research direction.

Tryptophan doses and sleep quality

The daily dose of Trp administered seems to play an important role in sleep quality. It has been suggested that using <1 g of Trp has a negative or unclear effects.[40] From the results (Table 4), the group taking ≥1 g of Trp supplementationhad improved WASO than the group taking <1 g of Trp supplementation.[7,12,15,16,18,20,23,28,29] Moreover, ≥1 g of Trp supplementation in people with insomnia further improved TST and SE values than did <1 g of Trp supplementation. These findings support that ≥1 g of Trp may be sufficient for improving sleep quality in people with insomnia, and this result is in line with evidence from previous studies. Trp hydroxylase is the rate-limiting enzyme that converts Trp to 5-HT and is normally not saturated by Trp.[8] A Trp dose of ≥1 g may be needed to effectively increase brain Trp levels for this rate-limiting conversion.[8,28] When the enzyme is sufficiently saturated, this, in turn, may increase melatonin synthesis and facilitate a sedation effect.[28] However, current evidence has shown that Trp is more effective in chronic insomnia,[6] and its optimum dose has not been well established. Therefore, more clinical studies are needed to investigate and determine with more certainty which groups with insomnia would benefit from Trp supplementation and at what dose.

Tryptophan and sleep architecture

Sleep consists of 2 types of architecture: REM and NREM sleep. These 2 types of sleep alternate cyclically with one another throughout the night, where REM and NREM take up 75% and 25% of total sleep, respectively.[41] On an electroencephalogram, REM sleep is characterized by beta waves, which are similar to the

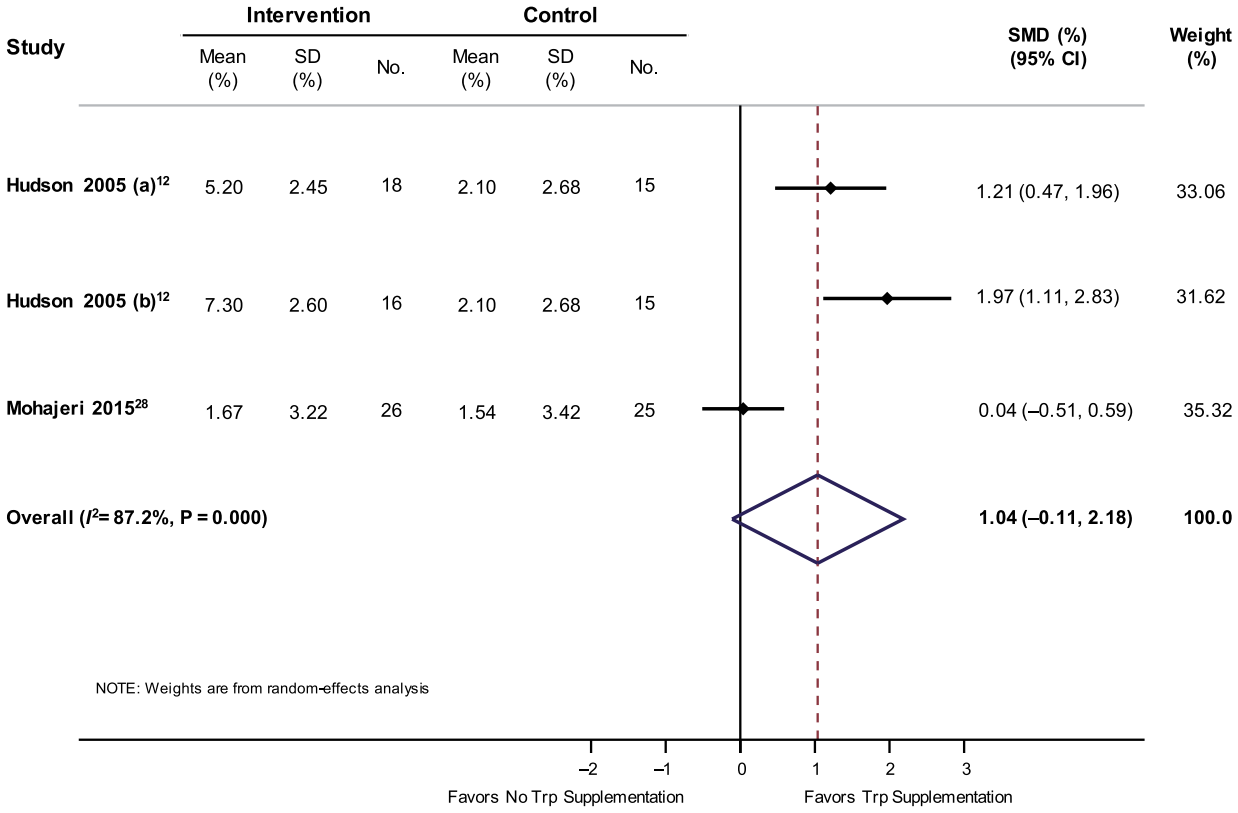

Figure 6 **Random-effects model meta-analysis comparing the standardized mean difference (SMD) in wake after sleep efficiency (%) after tryptophan (Trp) supplementation**

Table 3 **Summary of meta-regression results on the association between tryptophan dose (g) and sleep quality**

Sleep-quality outcome	No. of experimental arms[a]	Meta-regression coefficient	95%CI		*P*
TST (h)	7	−0.058	−0.248	0.132	0.471
WASO (min)	5	−81.03[b]	−135.0	−27.0	0.017
SL (min)	6	−2.46	−5.498	0.574	0.087
SE (%)	5	0.039	−16.49	16.57	0.995

[a]Combined number of experimental arms (control and interventions) from selected articles used to extract sleep-quality outcomes.
[b]Statistically significant ($P < 0.05$).
Abbreviations: SE, sleep efficiency; SL, sleep latency; TST, total sleep time; WASO, wake after sleep onset.

Table 4 **Comparison of postintervention mean of sleep-quality outcomes between tryptophan supplementation of <1 g and ≥1 g**

Sleep-quality outcome	Postintervention, mean (SD)		*P*
	Trp <1g	Trp ≥1g	
TST (h)	6.57 (0.98)	6.76 (0.92)	0.438
WASO (min)	56.55 (34.90)	28.91 (10.82)	0.001[a]
SL (min)	29.86 (20.46)	29.11 (22.28)	0.892
SE (%)	85.12 (9.53)	83.19 (6.28)	0.536
REM (h)	1.48 (0.37)	1.34 (0.42)	0.316
NREM (h)	2.77 (1.86)	2.39 (1.88)	0.681

[a]Statistically significant ($P < 0.05$).
Abbreviations: NREM, non-rapid eye movement; REM, rapid eye movement; SE, sleep efficiency; SL, sleep latency; Trp, tryptophan; TST, total sleep time; WASO, wake after sleep onset.

brain wave of an alert and awake person. On the other hand, NREM sleep is primarily characterized by delta waves.[41] Changes in sleep architecture have been associated with abnormalities in sleep-wake maintenance.[42] In the aging population, who often display a decrease in NREM sleep, reduced SE and increased numbers of arousal also have been reported.[43] NREM is also known as slow-wave sleep or deep sleep, and has restorative properties[9,41]; thus, an increased proportion of NREM sleep may suggest a better quality of sleep. Therefore, monitoring this sleep architecture is one of the objective measures commonly used to assess sleep quality.[9] This may also give an insight to the observations made from external measures of sleep quality, such as WASO and SE.

There is an evidence that Trp intake can modulate sleep architecture and aid in restoring NREM sleep.[12] Because of the lack of data, meta-analysis of sleep architecture could not be conducted. However, the difference between the <1 g and ≥1 g Trp groups was assessed and no impact of Trp dose was observed. This is possibly explained by the lower cutoff dose being compared. Changes in sleep architecture were more consistently observed at doses between 5 and 12 g.[44] To better evaluate the effect of Trp supplementation on sleep architecture, a 5 g cutoff may be needed, because prior studies observed changes in sleep architecture at Trp doses >5 g.[8]

Strengths and weaknesses

Most of the understanding about sleep has been based on association studies of sleep duration.[2] However, sleep duration is not the only contributor of optimal sleep quality, and sleep is a multidimensional concept made up of different components.[2] As a strength, in this systematic review, meta-regression, and meta-analysis, we assessed the impact of Trp supplementation on not only on quantity of sleep (TST) but also on different dimensions of sleep, including WASO, SL, SE, total NREM sleep, and total REM sleep. This approach may provide a comprehensive understanding of how Trp supplementation affects sleep health. In addition, the efficacy of Trp at different doses as a hypnotic agent was also examined.

However, this review still has a number of weaknesses. One of the main weaknesses is the inclusion of a limited number of studies in the quantitative analysis. This is especially important for both the meta-analysis and meta-regression analysis, and because of this, the statistical analysis performed may not generate enough power and should be interpreted with caution. In addition, most of the articles selected for this review were published from the 1960s to 1980s, and a good portion of the risk-of-bias evaluation of these papers cannot be determined. More recent studies, in which the method of Trp administration and sleep outcome measurement are standardized, would be required. Such studies would enable a more rigorous meta-analysis and meta-regression analysis to be performed. This is particularly important to confirm the results observed in this study. Another possible source of diversity between the RCTs was the food intake of the research participants. In a majority of the studies, the authors did not report dietary-sourced Trp in their population, which may also influence sleep-quality outcomes. To assess the effect of Trp supplementation on sleep, results should be adjusted for dietary Trp intake. An additional research opportunity to be explored is the mechanistic testing of Trp on sleep. Assessment of Trp level in the plasma and cerebrospinal fluid may also allow a better understanding of the mechanisms involved.[45]

CONCLUSION

Trp supplementation, especially at ≥1 g, can help improve sleep quality.

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SUPPORTING INFORMATION

The following Supporting Information is available through the online version of this article at the publisher's website:

Table S1 **Search terms and results for the systematic review assessing the effects of tryptophan**
Table S2 **Quality assessment of the randomized controlled studies (RCTs) selected for this review**
Table S3 **Sensitivity analysis following the removal of single groups or randomized controlled trials to assess the robustness of meta-analyses results studying tryptophan supplementation on sleep-quality components**
Figure S1 **Meta-regression correlation between tryptophan dose (g) and total sleep time (hours)**
Figure S2 **Meta-regression correlation between tryptophan dose (g) and wake after sleep onset (minutes)**
Figure S3 **Meta-regression correlation between tryptophan dose (g) and overall sleep latency (minutes)**

Figure S4 **Meta-regression correlation between tryptophan dose (g) and sleep efficiency (%)**

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