Efficacy of dietary supplements on improving sleep quality: a systematic review and meta-analysis

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Abstract

Purpose

Different dietary supplements aimed at improving sleep quality are available on the market, but there has not been a comprehensive review to evaluate the efficacy of these dietary supplements on subjective sleep quality. We aimed to summarize up-to-date research evidence and identify the types of dietary supplement that improve subjective sleep.

Methods

Multiple databases (Ovid Emcare, Ovid MEDLINE (R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and APA PsycInfo) were used for searching papers published until August 2020. The changes in sleep quality indices, intervention duration and sample size were extracted from every paper. To analyze the effect of dietary supplements on sleep quality, a random effects model with mean difference (MD) and 95% confidence interval was adopted. The heterogeneity across studies was measured by I^2 statistics. The quality of included studies was evaluated by Cochrane's risk of bias tool.

Results

Thirty-one randomized controlled trials of dietary supplements were included. Subjective sleep quality was significantly improved by supplementation of amino acids (MD: -1.27, 95% [confidence interval (CI): -2.35, -0.20; I^2=0%]), melatonin (MD: -1.21, 95% [confidence interval (CI): -2.17, -0.24; I^2=79%]) and vitamin D (MD: -1.63, 95% [confidence interval (CI): -3.15, -0.10; I^2=85%]). Although not all studies provided adequate data for meta-analysis, we also discussed how magnesium, zinc, resveratrol and nitrate supplementation may improve sleep quality.

Conclusions

Amino acids, vitamin D and melatonin supplements were significantly beneficial to improve sleep quality. However, high heterogenity and wide confidence levels were observed in vitamin D and melatonin. Further research for the effect of magnesium, zinc, resveratrol and nitrate supplementation on improving sleep quality is required.

Keywords

Dietary supplements, Sleep, Meta-analysis, Clinical trial, Systematic Review, Melatonin

INTRODUCTION

Sleep covers a significant part of human lifetime and adequate sleep is essential for good mental or physical health. Having poor sleep quality can lead to mental health problems, including daytime dysfunction and exhaustion, weakened intellectual functions, such as attention deficit and memory loss, and depression, anxiety and stress [(1)]. Furthermore, poor sleep quality can increase the risk of cardiometabolic diseases, including obesity, diabetes and hypertension [(1)].

Sleep quality is a collective measure of sleep parameters, including sleep duration and the presence of sleep problems. It can be measured objectively through polysomnography and actigraphy or subjectively through sleep diaries and self-reported questionnaires. Subjective sleep quality is a retrospective evaluation of sleep experience, and the most common and validated tool for assessment is the Pittsburgh Sleep Quality Index (PSQI). It includes seven components, namely subjective sleep quality, sleep latency, sleep duration, habitual sleep efficacy, sleep disturbances, use of medications for sleep and daytime dysfunction in the previous month [(1)], as recalled by Individuals. According to previous meta-analyses, poor sleepers as identified by PSQI have higher chances for hypertension, diabetes, obesity and metabolic syndrome [(2-5)].

Poor sleep quality has been common in multiple population, but the prevalence of poor sleepers was 36% for 9,284 individuals aged from 18-80 in Germany [(6)], 26.6% for 26,851 individuals aged ≥12 years in China [(7)], 50% for 8,481 individuals ≥18 years of age from Chile, Ethiopia, Peru and Thailand [(8)] and 30% for 2800 Japanese adults aged ≥20 years showed that they had poor sleep quality [(9)]. For studies conducted among middle-aged and older adults, cross-sectional study with 3289 subjects aged 50-70 years from Beijing and Shanghai showed that 47% of them had poor sleep quality [(10)]. The prevalence was 38.2% for 2,144 subjects aged 43-71 years in Spain [(11)].

Given the importance of sleep quality on mental and cardiometabolic health, it is necessary to identify strategies for improvement. Different types of dietary supplements are available on the market. For example, melatonin, a circadian hormone produced by the human brain at night, is found to have analgesic and antidepressive effect that can be used to treat sleep disturbance with little side effects [(12)]. Apart from this, vitamin D supplements have been used to treat sleep disorders [13]. L-theanine, an amino acid, was reported to have anti-stress effect and enhancing sleep quality [14].

However, there has not been a comprehensive review to evaluate the efficacy of dietary supplements on subjective sleep quality. We aimed to summarize up-to-date research evidence and to identify the types of supplementation that are beneficial to sleep health.

METHODS

Search strategy

In the present review, multiple databases were selected in the platform of Ovid, namely Ovid Emcare (1995 to 2020 Week 26), Ovid MEDLINE (R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations (1946 to June 26, 2020) and APA PsycInfo (1806 to June Week 4 2020). Keywords such as “supplement*” and “sleep quality” were used to search for relevant articles. A combination of search terms was used, including the keywords related to sleep quality (“sleep problem*”, “sleep disturb*”, “sleep difficult*”, “sleep efficien*”, “sleep laten*”, “sleep quality”, “sleep quality index”, “Pittsburg sleep quality index” and “PSQI”) and keywords related to randomized controlled trial (“randomized controlled trial”, “cluster randomized controlled trial”, “clinical trial”, “controlled clinical trial”, “crossover study”, “crossover design”, “crossover procedure”, “double blind procedure”, “double blind method”, “double blind study”, “single blind procedure”, “single blind method”, “single blind study”, “random allocation”, “random assignment” and “randomization”). All articles with English abstracts were assessed. The search strategy has been registered in PROSPERO (CRD42020196470).

Study selection

After removing duplicated studies, initial screening on the titles and abstracts was independently conducted by two reviewers using the inclusion and exclusion criteria to remove irrelevant studies. After abstract screening, we evaluate the full texts of remaining articles. Any disagreement between the two independent researchers were resolved by discussion. We also identified two additional papers from the reference list of included studies.

Study inclusion criteria

1. All human participants.

2. Randomized controlled trials using dietary supplements.

3. Studies that examined subjective sleep quality with a self-reported questionnaire.

Study exclusion criteria

1. Observational studies, review papers, comment, letters, news, notes, protocols, papers or abstracts from conference proceedings.

2. Articles without an abstract or full text in English.

Outcome assessment

The outcome of this review was subjective sleep quality, which was self-reported using questionnaires. Any study entailing the use of self-reported sleep quality tools or predefined categories of sleep quality was included in the present review.

Data extraction and quality assessments

Data was extracted by two researchers and a spreadsheet was used for data collection. For each included study, the study characteristics were extracted, namely the first author, the country where the study was conducted, sample size, number of males, mean age, intervention and control used, methods to measure sleep quality, duration of the dietary intervention and target population. The scores and standard deviation of the Pittsburgh Sleep Quality Index were extracted from the articles. Studies without providing sufficient information for meta-analysis were presented narratively.

The methodological quality of the included studies was assessed by Cochrane Handbook for Systematic Reviews of Interventions [15]. This tool is used for assessing the possibility of bias in the design, conduct and analysis of included studies. Sequence generation (selection bias), allocation sequence concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias) and selective outcome reporting (reporting bias) are the approaches to evaluate study quality. The risk of bias is ranked as “low”, “high” or “unclear” when there is limited information or uncertainty for potential bias.

Statistical analysis

The means and standard deviations of the outcomes, which was the PSQI global score, were extracted from each study. Next, the mean differences between the intervention group and the control group for each outcome were computed and summarized using forest plots. A random effects model using inverse variance method was used to combine the mean difference (MD) from individual studies with 95% confidence interval (CI). Heterogeneity was examined using I^2 statistics, where I^2 greater than 50% suggested substantial heterogeneity. All analyses were conducted using the Review Manager software (RevMan, version 5.4).

Sensitivity analysis

We performed sensitivity analysis by excluding studies one at a time and generating an estimated pooled effect to identify individual study would significantly affect the result in terms of the magnitude of pooled mean differences and heterogeneity across studies in I^2.

RESULTS

Study selection

A total of 249 articles was identified through literature search, and we included 116 potentially relevant articles for further review. After full text evaluation, we selected 29 articles, and identified two additional papers from the biography of included studies, making a total of 31 articles. Fifteen of the included papers provided sufficient data for meta-analysis while the remaining sixteen studies were presented narratively. The detailed study selection is presented in Figure 1.

Characteristics of included studies

There were 2,575 subjects from 31 studies and 591 of them were males (23.0%). Studies were published from 2010 to 2020. One study was conducted in Malaysia (70 participants), ten in Iran (575 participants), two in England (80 participants), three in Australia (120 participants), one in Israel (94 participants), one in Turkey (80 participants), nine in America (1,322 participants), one in France (101 participants), two in Italy (103 participants) and one in Germany (30 participants). PSQI was adopted in most included studies to access sleep quality (29 of 31 articles). The details of study characteristics were presented in Table 1. Information on the risk of bias has been presented in Table 2.

Table 1. Characteristics of included studies

Authors, year	Country	Sample size	BMI (kg/m²)	Age range or mean ± SD, year	Target population	Sleep quality measurement	Male, No. (%)	Intervention duration	Intervention used	Control used
Altiparmak et al (2019) [12]	Turkey	80	Not reported	Intervention: 49.28±13.73; Control: 47.15±12.77	Patients suffering from neuropathic pain	PSQI	41 (51%)	30 days	Melatonin 3mg and gabapentin 900mg	Placebo and gabapentin 900mg
Bigelman et al (2011) [16]	United States	58	Not reported	Intervention: 22±5.1; Control: 20.3±1.6	Healthy, moderately trained men and women	PSQI	44 (76%)	6 weeks	250 mg quercetin, 100 mg isoquercetin, 100 mg omega-3 fatty acids, 30 mg EGCG, a vitamin mixture, and sucrose	Placebo contained no quercetin, isoquercetin, EPA, DHA, EGCG, and vitamin mixture
Chee and Ong (2019) [1]	Malaysia	70	Not reported	Intervention: 30.40±7.51; Control: 31.17±7.33	Adults with sleep disorders	PSQI	12 (25%)	4 weeks	150 mg alpha-s1-casein tryptic hydrolysate and 50 mg L-theanine	Placebo (150 mg skimmed milk powder)
Chen et al (2014) [17]	United States	95	Intervention: 25.7; Control: 25.0	Intervention: 48-80; Control: 38-71	Postmenopausal women with history of primary breast cancer and had completed all active cancer treatment at least 60 days	PSQI	0 (0%)	4 months	3 mg oral melatonin	Placebo
Cornu et al (2010) [18]	France	101	Not reported	Intervention: 25.1-64.7; Control: 24.9-64.8	Adult patients with a chronic primary insomnia	LSEQ	32 (32%)	1 month	260 mg Soya oil (Glycine max), 173 mg Cade oil (Cannabis sativa), 50 mg Houblon (Humulus Lupulus), 6 mg Soya lecithin	Placebo (olive oil)
Daneshvar et al (2020) [19]	Iran	60	Intervention: 25.1±2.1; Control: 25.1±3.0	Intervention: 64.4±8; Control: 66.3±9	People with Parkinson's disease	PSQI	32 (63%)	12 weeks	10 mg melatonin	Placebo
Dretsch et al (2014) [20]	United States	78	Not reported	Intervention: 30.8±6.8; Control: 32.1±8.1	United States Army Soldiers	PSQI	72 (92%)	60 days	2.5 g of EPA+DHA ethyl esters	Corn oil ethyl esters
Ghaderi et al (2019) [21]	Iran	54	Intervention: 25.0±4.1; Control: 24.8±4.3	Intervention: 42.5±8.0; Control: 42.7±9.9	Patients under MMT	PSQI	54 (100%)	12 weeks	10 mg melatonin	Placebo
Ghaderi et al (2017) [22]	Iran	68	Intervention: 25.5±4.4; Control: 24.6±4.4	Intervention: 40.1±9; Control: 42.5±8	MMT patients	PSQI	/	12 weeks	50,000 IU vitamin D supplements	Placebo
Gholipour et al (2017) [23]	Iran	54	Intervention: 25.7±3.89; Control: 24.99±2.6	Intervention: 30.93±5.48; Control: 31.5±5.46	ICU nurses of two academic hospitals	PSQI	4 (8%)	1 month	220 mg of zinc sulfate	Placebo
Grima et al (2018) [24]	Australia	33	Intervention: 26.1±4.1; Control: 25.5±3.7	Intervention: 35±11; Control: 38±11;	Patients with TBI	PSQI	22 (67%)	4 weeks	2 mg melatonin	106 mg mannitol, 11 mg acacia and 106 mg pure icing sugar
Guthrie et al (2018) [25]	United States	355	27.3±4.3	54.4±3.8	Peri- and postmenopausal women	PSQI	0 (0%)	12 weeks	1.8 g omega-3 fatty acids supplement with 425mg ethyl EPA, 100 mg DHA, and 90mg of other omega-3s	Placebo
Hidese et al (2019) [14]	Germany	30	22.5±3.9	48.3±11.9	Participants with no major psychiatric illness	PSQI	9 (30%)	4 weeks	L-theanine (200 mg)	Placebo
Kotlarczyk et al (2012) [26]	United States	18	Intervention: 21.7±3.5; Control: 25.7±3.7	Intervention: 50.3±3.0; Control: 47.5±2.0	Perimenopausal women	PSQI	0 (0%)	6 months	3-mg melatonin in lactose	Lactose only
Majid et al (2018) [13]	Iran	89	Intervention: 26.3±6.5; Control: 25.76±4.85	Intervention: 37.9±9.50; Control: 35.5±10.00	People with sleep disorders	PSQI	21 (24%)	8 weeks	4 edible pearls, each 50 000 IU vitamin D	Placebo
Mason et al (2016) [27]	United States	218	Not reported	59.6 ± 5.1	Overweight postmenopausal women	PSQI	0 (0%)	12 months	2000 IU/day vitamin D3 + a lifestyle-based weight-loss program	Placebo + a lifestyle-based weight-loss program

Table 1. Characteristics of included studies *(continued)*

Authors, year	Country	Sample size	BMI (kg/m²)	Age range or mean ± SD, year	Target population	Sleep quality measurement	Male, No. (%)	Intervention duration	Intervention used	Control used
Mirzaei et al (2018) (28)	Iran	74	Not reported	Intervention: 42.1±10; Control: 41±10	Patients with FMS	PSQI	/	8 weeks	Trazodone 25 mg at bedtime + vitamin D 50 000 IU weekly	Trazodone 25 mg at bedtime + placebo
Nielsen et al (2010) (29)	United States	100	Not reported	59.2 ± 0.8	Adults with poor sleep quality	PSQI	22 (22%)	8 weeks	20 mg/day magnesium citrate	Sodium citrate
Ostadmohammad et al (2020) (30)	Iran	60	Intervention: 26.4±4.7; Control: 26.4±5.9	Intervention: 65.6±13.1; Control: 64.1±8.2	Diabetic hemodialysis patients	PSQI	38 (72%)	12 weeks	10 mg melatonin	Placebo
Pennisi et al (2017) (31)	Italy	60	Intervention: 25.4±3.6; Control: 25.8±3.4	Intervention: 46.4±4.1; Control: 46.8±4.4	Patients with chronic hepatitis C treated with Peg-IFN-α and RBV	PSQI	35 (58%)	12 months	1.5 mg/kg Peg-IFNα2b, 100 mg RBV/month and 19.8 mg/day Resveratrol	1.5 mg/kg Peg-IFNα2b, 100 mg RBV and placebo
Reed et al (2014) (32)	United States	355	Intervention: 26.8±4.4; Control: 27.1±4.3	Intervention: 54.4±3.6; Control: 55.0±3.8	Peri- and postmenopausal women	PSQI	0 (0%)	12 weeks	425 mg ethyl EPA,100 mg DHA, 90 mg of other omega-3s, natural lemon oil, rosemary extract, and vitamin E	Placebo (olive oil, natural lemon oil, rosemary extract, and vitamin E)
Roguin et al (2017) (33)	Israel	94	Not reported	Intervention: 63.1±12.4; Control: 66.7±9.3	Participants with NLC	PSQI	37 (39%)	4 weeks	Magnesium oxide and magnesium oxide monohydrate 865 mg	Placebo
Rondanelli et al (2011) (34)	Italy	43	Intervention: 23.1±2.4; Control: 21.9±2.3	Intervention: 78.6±4.1; Control: 78.1±3.8	Participants with primary insomnia	PSQI	16 (37%)	8 weeks	0.5 g of protein, 14 g of carbohydrates, 0.2 g of fat, 5 mg of melatonin, 225mg of magnesium, and 11.25 mg of zinc in 100g pear pulp	100g pear pulp
Shabani et al (2019) (35)	Iran	58	Intervention: 27.1±4.6; Control: 27.8±4.7	Intervention: 26.5±3.5; Control: 26.0±3.3	Women suffering from PCOS	PSQI	0 (0%)	12 weeks	10 mg melatonin	Placebo
Shamloo et al (2019) (36)	Iran	30	Not reported	20.7±3.7	Male athletes	PSQI	30 (100%)	1 week	Beetroot contain 300 mg of nitrate per 100 cc	100 cc sour cherry drink and rose water
Simper et al (2019) (37)	England	20	Not reported	21.0±1.0	Undergraduate university students	PSQI	11 (55%)	4 weeks	13 g of protein, 0.5 g carbohydrate, 1000 mg of Cherry active and 200 mg of magnesium	50 µL artificial cherry flavoring, 15 g of glucose powder, 0.65 g sucralose and 0.06 g of salt
Spong et al (2013) (38)	Australia	5	Not reported	26-68	Patients with complete tetraplegia and poor sleep	BNSQ	5 (100%)	2 weeks	3 mg melatonin	Without supplementation
Sweazea et al (2018) (39)	United States	45	Intervention: 25.6±3.5; Control: 25.2±3.5	Intervention: 24.0±4.3; Control: 24.4±34.4	Healthy normotensive men	PSQI	45 (100%)	2 weeks	7880 mg of a proprietary blend of nitrate-rich extracts	Prune juice
Taheri et al (2018) (40)	Iran	28	Not reported	Intervention: 63.1±2.2; Control: 62.9±1.9	Prediabetes women	PSQI	0 (0%)	8 weeks	Aerobic training with Omega-3 supplement	Aerobic training
Wightman et al (2015) (41)	United Kingdom	60	Not reported	18-30	Healthy adults	PSQI	9 (15%)	28 days	500 mg of pure trans-resveratrol with 10 mg of piperine	Placebo (methyl cellulose)
Wong et al (2017) (42)	Australia	80	Intervention: 26.7±0.8; Control: 26.4±0.9	Intervention: 30.93±5.48; Control: 31.5±5.46	Healthy postmenopausal women	PSQI	0 (0%)	14 weeks	75 mg of trans-resveratrol	75 mg calcium, hydrogen phosphate, microcrystalline cellulose, ProSolv 50, and hydrated magnesium silicate

BMI, Body Mass Index; PSQI, Pittsburgh Sleep Quality Index; EGCG, epigallocatechin gallate; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; MMT, methadone maintenance treatment; ICU, Intensive Care Unit; LSEQ, Leeds Sleep Evaluation Questionnaire; TBI, traumatic brain injury; FMS, fibromyalgia syndrome; NLC, Nocturnal Leg Cramps; PCOS, polycystic ovary syndrome; BNSQ, Basic Nordic Sleep Questionnaire.

Table 2. Risk of bias for each included study

Study, year	Random sequence generation	Allocation concealment	Selective reporting	Blinding (participants and personnel)	Blinding (outcome assessment)	Incomplete outcome data
Altiparmak et al (2019) [12]	Low	Low	Low	Low	Low	Low
Bigelman et al (2011) [16]	Unclear	Low	Unclear	Low	Low	Low
Chee and Ong (2019) [1]	Unclear	Low	Unclear	Low	Low	Low
Chen et al (2014) [17]	Unclear	Low	Unclear	Low	Low	Low
Cornu et al (2010) [18]	Low	Low	Unclear	Unclear	Low	Low
Daneshvar et al (2020) [19]	Low	Low	Low	Low	Low	Low
Dretsch et al (2014) [20]	Low	Low	Unclear	Low	Low	Low
Ghaderi et al (2019) [21]	Low	Low	Low	Low	Low	Low
Ghaderi et al (2017) [22]	Low	Low	Low	Low	Low	Low
Gholipour et al (2017) [23]	Low	Low	Unclear	Low	Low	Low
Grima et al (2018) [24]	Low	Low	Unclear	Low	Low	Low
Guthrie et al (2018) [25]	Unclear	Low	Unclear	Low	Low	Unclear
Hidese et al (2019) [14]	Low	Low	Low	Low	Unclear	Low
Kotlarczyk et al (2012) [26]	Low	Low	Unclear	Low	Low	Low
Majid et al (2018) [13]	Low	Low	Unclear	Low	Low	Low
Mason et al (2016) [27]	Unclear	Low	High	Low	Low	Low
Mirzaei et al (2018) [28]	Low	Low	Low	Low	Low	Low
Nielsen et al (2010) [29]	Unclear	Low	Unclear	Low	Low	Low
Ostadmohammad et al (2020) [30]	Low	Low	Unclear	Low	Low	Low
Pennisi et al (2017) [31]	Low	Low	Unclear	Low	Low	Low
Reed et al (2014) [32]	Low	Low	Unclear	Low	Low	Low
Roguin et al (2017) [33]	Low	Low	Low	Low	Low	Low
Rondanelli et al (2011) [34]	Unclear	Low	Unclear	Low	Low	Low
Shabani et al (2019) [35]	Low	Low	Low	Low	Low	Low
Shamloo et al (2019) [36]	Unclear	Low	Unclear	Unclear	Low	Unclear
Simper et al (2019) [37]	Unclear	Low	Unclear	Low	High	Low
Spong et al (2013) [38]	Unclear	High	Low	Unclear	Unclear	Low
Sweazea et al (2018) [39]	Unclear	Low	Unclear	Low	Low	Low
Taheri et al (2018) [40]	Unclear	High	Unclear	High	High	Low
Wightman et al (2015) [41]	Unclear	Low	Unclear	Low	Low	Low
Wong et al (2017) [42]	Unclear	Low	Low	Low	Low	Low

Results from meta-analyses

For two included studies that provided amino acid supplements [1, 14], the pooled mean difference between the intervention and control groups was -1.27 with 95% [confidence interval (CI): -2.35, -0.2; I^2=0%] (Figure 2).

For seven included studies that provided melatonin supplements [12, 17, 19, 21, 26, 30, 35], five of these studies [12, 19, 21, 30, 35] showed significantly lower PSQI for the intervention group. The pooled mean difference between the intervention and control groups was -1.21 with 95% [confidence interval (CI): -2.17, -0.24; I^2=79%] (Figure 3). A substantial heterogeneity has been found among the studies.

Both included studies [16, 20] that provided omega-3 supplements did not show significant difference in PSQI for intervention and control groups. The pooled mean difference between the intervention and control groups was 0.13 with 95% [confidence interval (CI): -0.84, 1.09; I^2=0%] (Figure 4).

Of four included studies that provided vitamin D supplements [13, 22, 27, 28], three studies [13, 22, 28] showed significantly lower PSQI for the intervention group. The pooled mean difference between the intervention and control groups was -1.63 with 95% [confidence interval (CI): -3.15, -0.10; I^2=85%] (Figure 5). A substantial heterogeneity has been found among the studies.

Studies not included in meta-analyses

Studies were not included in meta-analysis for the reasons below. Two studies used indices Leeds Sleep Evaluation Questionnaire (LSEQ) and Basic Nordic Sleep Questionnaire (BNSQ) to access sleep quality [18, 38], six studies did not have comparable studies for meta-analysis [23, 31, 33, 34, 37, 39], five studies described the overall finding without providing relevant data [24, 29, 32, 41, 42]. Two studies presented the result graphically [36, 40], and one study only mentioned mean reduction in PSQI [25].

Magnesium

Nielsen and others studied the effect of magnesium supplements on sleep quality in 100 individuals with poor sleep quality in the United States (29). The intervention group was given magnesium supplements while the control group was given placebo. There was a significant reduction in PSQI values in both group and there was no significant difference between two groups. Roguin et al. investigated the effect of magnesium supplements on sleep quality in 94 individuals experiencing nocturnal leg cramps in Israel (33). The intervention group was given magnesium supplements while the control group was given placebo. There was no statistically significant difference between two groups.

Melatonin

Spong and researchers assessed sleep quality in five patients with complete tetraplegia and poor sleep using Basic Nordic Sleep Questionnaire (BNSQ) (38) . The intervention group with 5 individuals was given melatonin capsules while the control group was not given any supplementation. Participants in intervention showed improvement in sleep quality but the magnitude was not statistically significant. Grima et al. evaluated the effect of melatonin supplements on sleep quality in 33 patients from Australia with traumatic brain injury (24). The intervention group was given melatonin capsules while the control group was given placebo capsules. There was a significant reduction in PSQI scores from 10 to 7.68 in the intervention group when compared to the placebo group.

Nitrate

Sweazea and others studied the effect of nitrate supplementation on sleep quality in 45 healthy normotensive men in America (39). The intervention group was given nitrate-rich extracts while the control group was given prune juice. PSQI scores decreased in both groups and sleep quality did not vary significantly between the intervention and control group. Shamloo and colleagues investigated the effect of nitrate on sleep quality in 30 male athletes in Iran (36). The intervention group was given nitrate-containing beetroot juice while the control group was given a sour cherry drink. The results suggested that the intervention group had a significant improvement in sleep quality compared to placebo group. Results from two trials were not meta-analyzed because Shamloo et al only presented the results graphically.

Omega-3

Three out of six included studies using omega-3 supplementation were not meta-analyzed because the findings were presented graphically, or only mean values were provided. Cornu and colleagues assessed sleep quality in 101 adult patients with a chronic primary insomnia in France using a self-reported instrument, namely Leeds Sleep Evaluation Questionnaire (LSEQ) [18]. The intervention group was given omega-3 capsules while the control group was given placebo capsules. Marked improvement in the quality of sleep was observed in both groups but did not differ significantly by intervention. Reed and others investigated the effect of omega-3 supplements on sleep quality in 355 women in the United States [32]. The intervention group was given omega-3 supplements while the control group was given placebo. There was no significant improvement in sleep quality of intervention group compared to the control group. Taheri studied the effect of omega-3 supplementation on sleep quality in 28 older women with obesity and prediabetes in Iran [40]. The intervention group was given omega-3 supplements along with aerobic training while the control group was only given aerobic training. Sleep quality was improved in both groups, but no significant difference was found between the two groups. Guthrie et al. investigated the effect of omega-3 supplementation on sleep quality in 355 peri- and postmenopausal American women [25]. The intervention group was given omega-3 capsules while the control group was given identical placebo capsules. Omega-3 intervention showed little effect on the PSQI as there was a mean reduction of PSQI scores from 1.2 to 1.6 relative to control.

Resveratrol

The results for reveratrol trials were not meta-analyzed because two studies only presented the findings with average values of sleep quality. Pennisi et al. studied the effect of resveratrol on sleep quality in 60 patients with chronic hepatitis C in Italy [31]. The intervention group was given resveratrol supplements while the control group was given placebo. Intervention group has significatnly improved sleep quality when comparing with control group. Wightman and colleagues investigated the effect of resveratrol on sleep quality in 60 healthy, young humans in the United Kindgom [41]. The intervention group was given resveratrol capsules while the control group was given placebo. There was no significant differences in sleep quality observed between intervention and control group. Wong and other researchers investigated the effect of resveratrol supplementation on sleep quality in 80 healthy postmenopausal women in Australia [42]. The intervention group was given resveratrol capsules while the control group was given placebo. There was a significant improvement in sleep quality observed in the intervention group.

Zinc

Baradari and associates investigated the effect of zinc supplementation on sleep quality (PSQI) in 54 Intensive Care Unit nurses in Iran [23]. The intervention group was given zinc sulfate capsules while the control group was given placebo. The results showed that there was a significant improvement in sleep quality in the intervention group than the placebo group.

Co-supplementation

Simper et al. investigated the effect of amino acids and magnesium on sleep quality (PSQI) in 20 undergraduate university students in England [37]. The intervention group was given supplements with protein and magnesium while the control group was given placebo. There was no statistically significant difference in sleep quality between intervention and control group. Rondanelli and coworkers applied co-supplementation, including melatonin, magnesium and zinc to investigate the effect of them on sleep quality in 43 participants with primary insomnia in Italy [34]. The intervention group was given co-supplements while the control group was given placebo. There was a significantly improved overall PSQI score in the intervention group but not in the placebo group.

Sensitivity analysis of included studies

We performed sensitivity analysis for each meta-analysis to identify the individual study that can affect heterogenity across studies. However, this was not applicable for amino acids and omega-3 as there were only two included studies. For melatonin, the heterogeneity in I^2 values and the statistical significance of pooled mean difference were similar regardless of study being excluded. For vitamin D, after excluding one included study [27] , the heterogenity in I^2 decreased from 85% to 0%, while the I^2 after excluding the remaining three studies [13, 22, 28] were similar. The pooled mean difference changed to insignificant when each of the three studies were removed [13, 22, 28], but remained significant when the study published by Mason and colleagues [27] was excluded.

DISCUSSION

Summary of Main findings

In the present review, we found that the supplementation of amino acids, melatonin and vitamin D can improve subjective sleep quality. However, for trials using melatonin and vitamin D, heterogenous findings were observed despite significant intervention effects. More randomized controlled trials should be performed to verify on the effects of melatonin and vitamin D in multiple population. Although not all studies provided adequate data for meta-analysis, we also discussed how zinc, resveratrol, magnesium and nitrate supplementation may improve sleep quality.

Interaction between melatonin and nutrients on sleep regulation

Melatonin is a hormone that involved in regulating sleep cycle and has strong antioxidative effect. While poor sleep quality may be attributed by increased oxidative stress [43], melatonin increases the superoxide dismutase (SOD) activity that prevents damages to cell membrance under oxidative stress [44]. Given the roles of melatonin in sleep regulation, it is not surprising to see its impact on better sleep quality. Morover, omega-3 with melatonin can provide antioxidant effect by increasing superoxide dismutase (SOD) activity remarkably in human body [45]. Amino acid tryptophan can regulate sleep and circadian rhythms as it increases melatonin level by being a precursor for endogenous melatonin synthesis [46]. Magnesium can enhance the activity of serotonin N-acetyltransferase, which is an enzyme required for melatonin synthesis [47] .

On the other hand, epidemiological studies suggest how vitamin D deficiency can lead to poor sleep quality. A meta-analysis including six cross-sectional studies, two case-control studies and one cohort study, which mainly used 20 ng/ml as the vitamin D deficiency cut-off value, reported that vitamin D deficiency had an inverse relationship with increased risk of sleep disorder [48].

Vitamin D receptors were found in brain areas of sleep regulation, such as the anterior and posterior hypothalamus, where pacemaker cells essential in maintaining sleep were present. Furthermore, vitamin D can stimulate tryptophan hydroxylase-2 (TPH-2) which expresses a vitamin D response element at the gene level. Vitamin D can thus regulate trytophan convertion to serotonin to produce melatonin [48, 49].

Magnesium can influence the concentrations of cytochrome P450 (CYP) enzymes, which involve in the activation (i.e. 25-hydroxylase and 1α-hydroxylase) and deactivation (i.e. 24-hydroxylase) of vitamin D. Both 1α-hydroxylase and 24-hydroxylase are magnesium dependent, therefore, magnesium influences vitamin D concentration by affecting biomarkers of vitamin D synthesis and metabolism [50].

Strengths and limitations of the study

The major strength of our meta-analysis is to comprehensively evaluate the efficacy of dietary supplements in improving sleep quality across various populations. PSQI has been the consistent tool to access subjective sleep quality, which increases the comparability of findings. In addition, we only included randomized controlled trials for review, which provided higher quality of evidence.

Nonetheless, several limitations should be noted. First, the present study included only articles written in English, therefore we may miss eligible studies in other languages. Furthermore, some studies were not meta-analyzed because relevant data was not provided. Also, some included studies only had small sample size. Two studies in narrative review [37, 38] involved five and twenty participants respectively, while one study in meta-analysis [26] included only eighteen individuals. In addition, there is a large variation in the duration of dietary intervention, ranging from one week to twelve months. The dose of supplements being used also varies, for example, the dosage of vitamin D supplementation ranged from 2000 IU to 50 000 IU. It is possible that for those which showed no effect on improving sleep quality, a significant intervention effect will be observed if the dose is increased. Last, the heterogeneity of studies using melatonin and vitamin D supplements was high, despite the use of consistent methods for subjective sleep quality measurement.

Implications for further research

Although we found a significant improvement in sleep quality by dietary supplementation, RCTs with longer duration and larger sample size should be conducted to verify our findings.

Furthermore, dose-response effect of different supplements on sleep quality have not yet be evaluated. Further research on the synergistic effects of nutrients on sleep quality is also necessary.

CONCLUSION

Supplementation of amino acids, vitamin D and melatonin have shown significant benefit on subjective sleep quality, but the findings are hetergeoneous. Further research for the effect of melatonin, magnesium, nitrate, resveratrol, vitmain D and zinc supplementation on improving sleep quality is required.

Main Messages

- This systematic review and meta-analysis evaluate the efficacy of dietary supplements in sleep quality.
- Amino acids, vitamin D and melatonin supplements may improve sleep quality.
- Further research on the efficacy of nitrate, magnesium, resveratrol and zinc supplements on sleep quality is required.

Current research questions

- What are the effects of dietary supplements on improving sleep quality?
- Will the effect of dietary supplements vary between different populations (i.e. male vs female)?
- Are nutrient deficiencies associated poor sleep quality?

What is already known on the subject

- Poor sleep quality has been common in multiple population.
- Poor sleep quality can increase the risk of cardiometabolic diseases, including obesity, diabetes, and hypertension.

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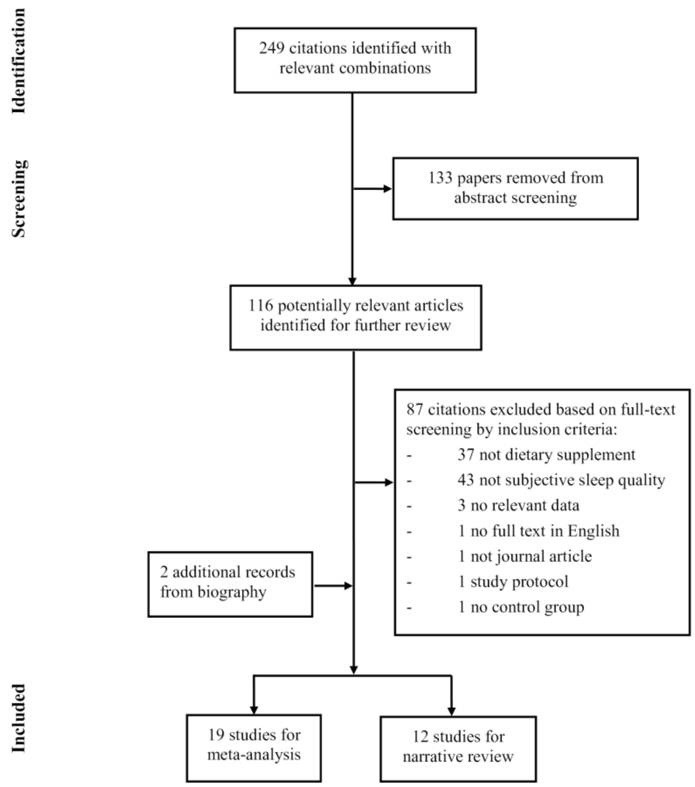


Figure 1. Flow chart of literature search and screening process

1

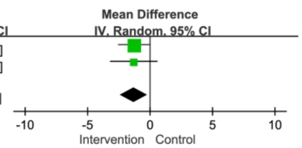
Flow chart of literature search and screening process

210x297mm (300 x 300 DPI)

	Intervention			Control				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Chee, 2019	4.52	2.65	25	5.78	1.93	23	67.9%	-1.26 [-2.56, 0.04]
Hidese, 2019	8.3	2.45	15	9.6	2.84	15	32.1%	-1.30 [-3.20, 0.60]
Total (95% CI)			**40**			**38**	**100.0%**	**-1.27 [-2.35, -0.20]**

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.00$, df = 1 (P = 0.97); $I^2 = 0\%$

Test for overall effect: Z = 2.32 (P = 0.02)

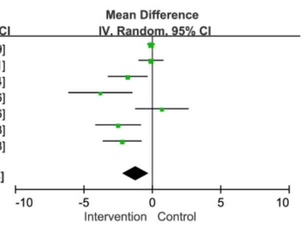


Forest plot on effects of amino acids supplementation and subjective sleep quality

209x279mm (300 x 300 DPI)

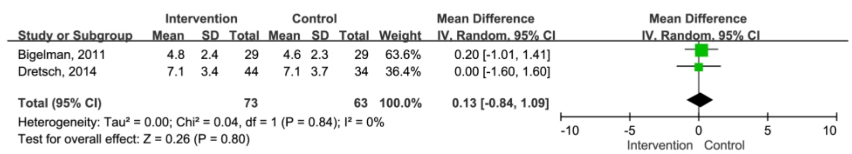
	Intervention			Control				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Altiparmak, 2019	3.2	0.52	40	3.3	0.76	40	20.5%	-0.10 [-0.39, 0.19]
Chen, 2014	5.3	2.4	46	5.4	2	44	17.6%	-0.10 [-1.01, 0.81]
Daneshvar, 2020	6.7	2.7	25	8.5	2.6	26	14.1%	-1.80 [-3.26, -0.34]
Ghaderi, 2019	6.2	4.8	26	10	3.9	28	9.3%	-3.80 [-6.14, -1.46]
Kotlarczyk, 2012	4.7	2.8	13	4	1.4	5	11.2%	0.70 [-1.26, 2.66]
Ostadmohammad, 2019	7.4	2.8	26	9.9	3.4	27	12.8%	-2.50 [-4.17, -0.83]
Shabani, 2019	4.7	2.1	29	6.9	3.3	29	14.3%	-2.20 [-3.62, -0.78]
Total (95% CI)			**205**			**199**	**100.0%**	**-1.21 [-2.17, -0.24]**

Heterogeneity: $Tau^2 = 1.16$; $Chi^2 = 29.20$, $df = 6$ ($P < 0.0001$); $I^2 = 79\%$
Test for overall effect: $Z = 2.45$ ($P = 0.01$)



Forest plot on effects of melatonin supplementation and subjective sleep quality

209x279mm (300 x 300 DPI)

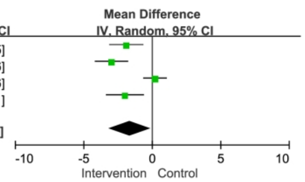


Forest plot on effects of omega-3 supplementation and subjective sleep quality

209x279mm (300 x 300 DPI)

	Intervention			Control				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Ghaderi, 2017	4.5	2.2	34	6.4	3	34	24.6%	-1.90 [-3.15, -0.65]
Majid, 2018	6.75	2.97	46	9.73	3.04	47	24.8%	-2.98 [-4.20, -1.76]
Mason, 2016	7.6	2.9	83	7.4	2.8	84	26.9%	0.20 [-0.66, 1.06]
Mirzaei, 2018	6.2	2.2	37	8.2	3.7	37	23.7%	-2.00 [-3.39, -0.61]
Total (95% CI)			**200**			**202**	**100.0%**	**-1.63 [-3.15, -0.10]**

Heterogeneity: $Tau^2 = 2.05$; $Chi^2 = 20.67$, df = 3 ($P = 0.0001$); $I^2 = 85\%$
Test for overall effect: $Z = 2.09$ ($P = 0.04$)



Forest plot on effects of vitamin D supplementation and subjective sleep quality

209x279mm (300 x 300 DPI)