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REVIEW

Effect of melatonin supplementation on sleep quality: a systematic review and meta-analysis of randomized controlled trials

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Abstract

Background The Present study was conducted to systematically review the effect of the melatonin on sleep quality. We summarized evidence from randomized clinical trials (RCTs) that investigated the effects of melatonin on sleep quality as assessed by the Pittsburgh Sleep Quality Index (PSQI) in adults with various diseases.

Methods The literature searches of English publications in MEDLINE and EMBASE databases were performed up June 2020. Results were summarized as mean differences (MD) with 95% confidence intervals (CI) using random effects model (DerSimonian–Laird method). Heterogeneity among studies was evaluated by the Cochrane Q test and I-squared (I2). To determine the predefined sources of heterogeneity, subgroup analysis was performed.

Results Of 2642 papers, 23 RCTs met inclusion criteria. Our results indicated that melatonin had significant effect on sleep quality as assessed by the Pittsburgh Sleep Quality Index (PSQI) (WMD: −1.24; 95% CI −1.77, −0.71, $p=0.000$). There was significant heterogeneity between studies ($I^2=80.7\%$, $p=0.000$). Subgroup analysis based on health status and kind of intervention were potential between-study heterogeneity. Subgroup analysis based on health status revealed melatonin intervention in subjects with Respiratory diseases (WMD: −2.20; 95% CI −2.97, −1.44, $p=0.000$), Metabolic disorders (WMD: −2.74; 95% CI −3.48, −2.00, $p=0.000$) and sleep disorders (WMD: −0.67; 95% CI −0.98, −0.37, $p=0.000$) has significant effect on sleep quality.

Conclusion We found that the treatment with exogenous melatonin has positive effects on sleep quality as assessed by the Pittsburgh Sleep Quality Index (PSQI) in adult. In adults with respiratory diseases, metabolic disorders, primary sleep disorders, not with mental disorders, neurodegenerative diseases and other diseases.

Keywords Melatonin · Sleep quality · PSQI · Meta-analysis

Introduction

Sleep as a physiological and behavioral process is essential for body regulation and quality of life at any age[1]. Nowadays, sleep quality is often declined, and sleep deprivation or restriction causes several physiological and behavioral changes.[2] Inadequate sleep, in terms of either quantity or quality, is a known risk factor for several diseases such as cardiovascular diseases, hypertension, vascular disorders, metabolic dysfunction and neurocognitive and leading to an increase in mortality and create a substantial burden on the health care system [3–6]. Also, the sleep disturbance causes clinically significant impairment in social, occupational, or other important areas of functioning [7]. Almost a third of the world's population suffers from sleep disorders, mainly insomnia, because of stressful working conditions and aging and these disorders are more common in women and the elderly [8]. Current medications have substantial adverse events, such as excessive daytime sleepiness, poor tolerance to the medication, cognitive impairment, dependency and withdrawal [9]. Due to these side effects, there has been an increased interest to find a new pharmaceutical with less side effects and non-pharmaceutical approach such as yoga, physical exercise, cognitive behavioral therapy, acupuncture, mindfulness,

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and nutritional therapy to promote better sleep quality [10]. Melatonin (N-acetyl-5-methoxytryptamine) is an endogenous indoleamine that is produced nocturnally by the pineal gland and released into the bloodstream exclusively at night following the circadian rhythm. Melatonin is a sleep regulator and signal of darkness in humans [11]. Some randomized, placebo-controlled trials indicated that melatonin intervention cannot improve quality of sleep [12, 13]. However, some of the recent findings published suggest that melatonin is a potent drug candidate for sleep disorders [14, 15]. To the best of our knowledge, there is no comprehensive review on the efficacy of melatonin intervention for the improvement of sleep quality as assessed by the PSQI in different disease. Thus, with accumulating evidence, we perform a systematic review and meta-analysis of randomized controlled trials (RCTs) to investigate the roles of exogenous melatonin, versus placebo, in the treatment of sleep quality sleep quality as assessed by the PSQI in adult with various disease.

Methods

The present meta-analysis was reported based on the Preferred Reporting Items of Systematic Reviews and Meta-Analysis (PRISMA) statement guideline [16]. The PICOS-model [17], where the acronym PICOS stands for population (all individuals except children under 18 years old and pregnant and lactating women), intervention (melatonin supplementation), comparison (studies which had control group), outcome (studies that reported. The Pittsburgh Sleep Quality Index) and study design that were randomized controlled trial (RCT) were used.

Search strategy

A throughout search was conducted in PubMed, Scopus, Embase and Google Scholar from inception to June 2020 with no time restriction. Only articles published in English were considered in this review. We used medical subject headings (MeSH) and text words to identify the potential interest studies. Search words included:

Melatonin OR "Melatonin supplementation" AND Sleep OR "Sleep Initiation and Maintenance Disorders" OR "Sleep Disorders, Intrinsic" OR "Sleep Wake Disorders" OR "Mental Health" OR sleep* OR "sleep quality" OR mental health" OR "Pittsburgh sleep quality index". We hand searched all reference lists of eligible articles, related reviews, and meta-analyses to prevent missing any relevant studies. Unpublished documents and grey literature like conference papers, theses, and patents were not included.

Eligibility criteria

The included studies in this meta-analysis were as follows: (1) randomized control trials (RCT), (2) only executed on adult population (aged > 18 years) and (3) reported sleep quality as assessed by PSQI. Literature excluded if they met the following criteria: (1) they were study design except RCT (2) had studies the effects of melatonin along with other interventions (3) had lack of sufficient data for the outcomes of interest in individuals and (4) studies carried out with less than 2 weeks' follow-ups.

Data extraction

Two independent researchers (F. GH., N. R.) extracted the data for this meta-analysis, evaluated the quality of eligible studies, and performed double-checks. Any disagreements and differences were resolved by a third independent investigator (Kh-M), if necessary. The following data from the full text of selected studies were extracted: first author's name, year of publication, study location, study duration, gender, mean age and mean body mass index (BMI) of participants, study design, the health status of the study population, number of participants in each group, dose of melatonin supplementation and outcome results (means and standard deviations for PSQI before and after intervention).

Statistical analysis

The effect of melatonin on sleep quality as assessed by the Pittsburgh Sleep Quality Index (PSQI) was estimated by pooling mean and standard deviation (SD) values of the baseline and the end of the studies in both intervention and control groups. If the studies did not report mean and SD, we used the following formula to calculate missing SDs for changes: SD change = square root [(SD baseline2 + SD final2)—(2 × R × SD baseline × SD final)]. We considered a correlation coefficient of 0.9 as the R-value of the mentioned formula (18). Standard errors (SE) were converted to SD according to the formula of SE $\sqrt{}$ n. If a study provided medians (interquartile ranges), we converted them to means (SD) as described by Hozo and colleagues [19]. If the study results reported graphically, we used Get Data Graph Digitizer software to estimated mean (SD). At first, a fixed-effect model was performed to pool the data. The heterogeneity was substantially significant when the Cochrane Q test showed a p value < 0.1 and I^2 statistic provided the relative amount of variance of the summary effect. In case of heterogeneity, a random effects model by DerSimonian and Laird method [20] was applied. To evaluate the predefined sources of heterogeneity, subgroup analysis as performed

based on baseline BMI, dose of Melatonin, study duration, age, health status, kind of intervention and gender. Publication bias was evaluated using Egger's regression test and Begg's rank correlation tests [21, 22]. Meta-analysis was carried out using Stata software, version 14 (Stata Corp LP, College Station, TX, USA).

Results

Selected studies

The initial search identified 2642 publications through Scopus, PubMed, Embase and Google Scholar. Then, we identified 284 duplication records. After excluding duplicates, a total of 2358 studies were retrieved for title and abstract screening. After screening for title and abstract, 2324 articles were excluded and 34 papers were retrieved for full text review. Out of 34 retrieved papers, 11 articles were excluded due to report different unit [12, 23, 24], without sufficient data [13, 25], complex intervention [26–30] or overlapped by chosen studies [31]. Finally, 23 papers [32–54] were eligible for this systematic review and meta-analysis. The flow chart of literature search is shown in Fig. 1.

Quality assessment

We used Cochrane scoring system to assess the quality of the included studies. The risk of bias is assessed by seven criteria which are as follows: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other biases. Studies were stratified as low risk of bias, high risk of bias or unclear regarding each criterion.

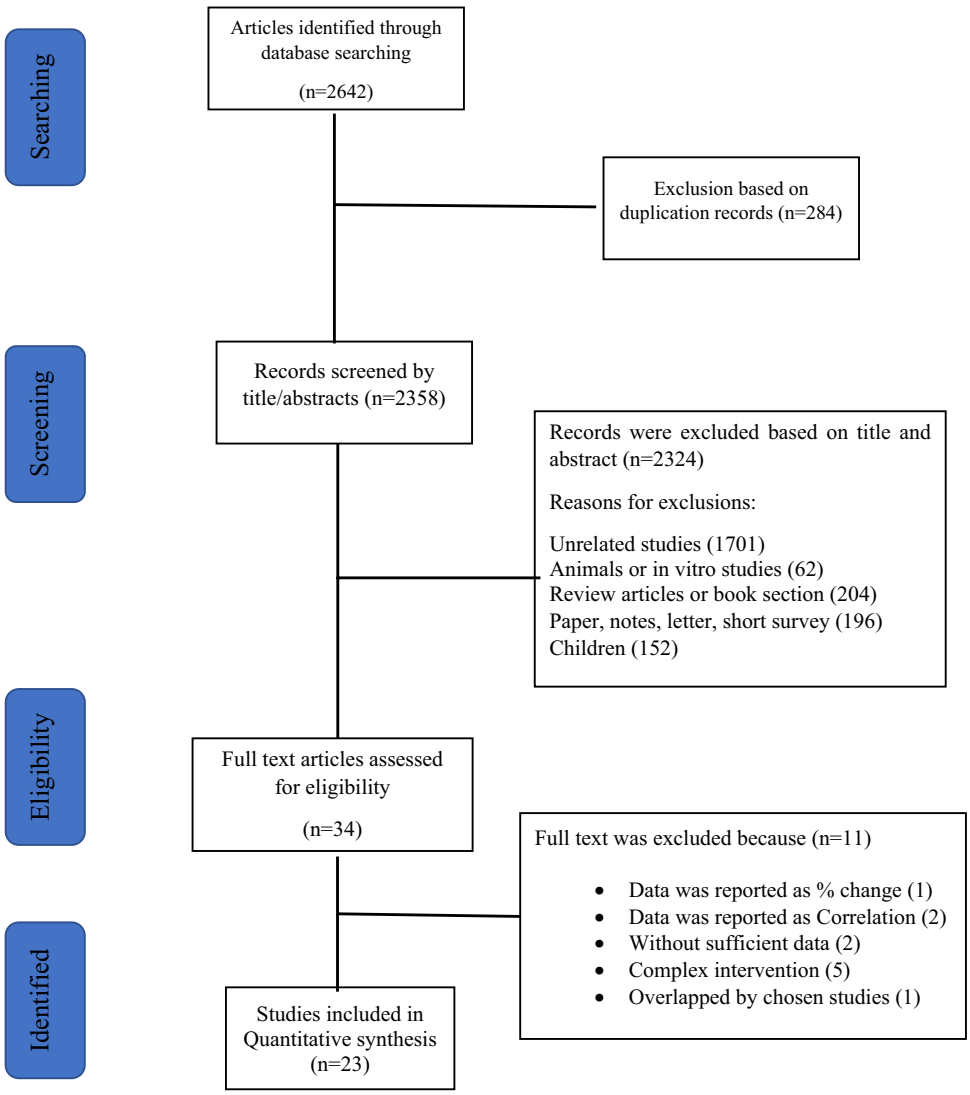

Fig. 1 Flow chart of the number of studies identified and selected into the meta-analysis

Ten studies reported a random allocation of participants [37, 41–43, 45, 47, 51–54], and the other 13 studies showed an unclear risk of bias [32–36, 38–40, 44, 47–50]. Allocation concealment reported in 21 trials [32–45, 47, 49–54] and the remainder showed an unclear risk of bias [46, 48]. Nineteen trials showed low risk of bias in terms of blinding of participants and personnel [32–39, 41–47, 51–54]. Seven publications had low risk of bias regarding blinding of outcome assessment [32–35, 41, 53, 54]. Selective reporting considered as low risk in 17 trials [33–36, 38–40, 42, 44–50, 53, 54] and high risk in 5 trials[37, 41, 43, 51, 52]. Except for two studies [38, 39], the rest of the studies showed low risk of bias based on incomplete outcome [32–37, 40–54]. 17 publications illustrated low risk of bias based on other potential threats to validity [32–38, 40–45, 47, 49, 53, 54]. Details of risk of bias assessment are described in Table 1.

Studies characteristics

Eventually, we identified 23 trials that assessed the effects of melatonin on sleep quality. Included studies carried out in various countries such as Iran [32, 36, 37, 41, 52, 53], USA [50, 51], Denmark [49], Brazil [34, 44, 46], Korea [39], UK [40, 43, 47, 48], Mexico [47], South Korea [45], Singapore [38], Sri Lanka [35], Canada [33], Norway [42], Australia [54]. Publication dates ranged from 2004 and 2020. The follow-up period ranged from 2 to 24 weeks. The sample size of the included studies ranged from 16 to 711 participants. Some studies enrolled only males [32, 41] and females [34, 42, 50–52] and the rest of included studies involved both genders [33, 35–40, 43–49, 53, 54]. Types of melatonin administration were melatonin [32–38, 41, 42, 44, 46, 47, 50–53] and Prolonged-release melatonin [39, 40, 43, 45, 48, 49, 54] among included studies. Study dose varied between 2 and 10 mg melatonin. 23 studies were conducted

Table 1 Cochrane risk of bias assessment

Study	Random Sequence Generation	Allocation Concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective outcome reporting	Other sources of bias	Overall quality
Mousavi et al	U	L	L	L	L	U	L	Good
Gendy et al	U	L	L	L	L	L	L	Good
Campos et al	U	L	L	L	L	L	L	Good
De Silva et al	U	L	L	L	L	L	L	Good
Halvani et al	U	L	L	U	L	L	L	Good
Ostadmohammadi et al	L	L	L	U	L	H	L	Good
Song et al	U	L	L	U	U	L	L	Good
Jun et al	U	L	L	U	U	L	U	Fair
Wade et al. (2007)	U	L	H	U	L	L	L	Good
Ghaderi et al	L	L	L	L	L	H	L	Good
Alstadhaug et al	L	L	L	U	L	L	L	Good
Wade et al. (2014)	L	L	L	U	L	H	L	Good
Nunes et al	U	L	L	U	L	L	L	Good
Ahn et al	L	L	L	U	L	L	L	Good
Medeiros et al	U	U	L	U	L	L	U	Fair
Morales-Delgado et al	L	L	L	U	L	L	L	Good
Wade et al. (2011)	U	U	H	U	L	L	U	Fair
Baandrup et al	U	L	U	U	L	L	L	Good
Chen et al	U	L	U	U	L	L	U	Fair
Kotlarczyk et al	L	L	L	U	L	H	U	Good
Shabani et al	L	L	L	U	L	H	U	Good
Grima et al	L	L	L	L	L	L	L	Good
Daneshvar Kakhakia et al	L	L	L	L	L	L	L	Good

Abbreviations: L, low risk of bias; H, high risk of bias; U, unclear risk of bias

on Alzheimer patients [43], perimenopausal women [51], subjects diagnosed with alcohol use disorder [33], patient with asthma [34], IBS patients [38], patient with insomnia [40, 48], patients with RBD [39], COPD patients [36, 44], diabetic patients [37], patients under MMT [41], postmenopausal women with breast cancer [50], Parkinson's disease patients [45, 46, 53], women with PCOS [52], patients with migraine [42], patients with early-stage cirrhosis [35], SM-injured patients [32], patients with dementia [47], patients with schizophrenia or bipolar disorder [49] and patient with brain injury [54]. The studies performed in subjects with different baseline BMI; six studies carried out in subjects under 25 kg/m^2 [34, 36, 39, 41, 44, 45], nine studies over than 25 kg/m^2 [32, 37, 40, 42, 48, 51–54] and nine studies did not report BMI [33, 35, 38, 43, 46, 47, 49, 50]. 20 studies were parallel randomized clinical trial and three studies were cross over randomized clinical trial. The summary of the main features of the included studies is shown in Table 2.

Meta-analysis

Effect of melatonin on sleep quality

Overall, 23 clinical trials evaluated the effect of melatonin on PSQI. Pooled effect size from random effect model showed a significant lowering effect of melatonin on PSQI (WMD: −1.24; 95% CI −1.77, −0.71, $p=0.000$). There was significant heterogeneity between studies ($I^2=80.7\%$, $p=0.000$) (Fig. 2).

We observed that subgroup analysis based on health status could explain potential between study heterogeneity. Also, we observed that subgroup analysis based on kind of intervention (melatonin vs prolonged-release melatonin) were another source of heterogeneity, because heterogeneity decreased below 50%. Both of intervention improved sleep quality significantly [melatonin: (WMD: −1.52; 95% CI −2.34, −0.70, $p=0.000$) and prolonged-release melatonin (WMD: −0.71; 95% CI −1.21, −0.21 $p=0.006$)]. Subgroup analysis based on baseline BMI, dose of melatonin, study duration, age, and gender showed no significant differences between subgroups (Table 3). Subgroup analysis based on health status revealed that subjects with respiratory diseases (WMD: −2.20; 95% CI −2.97, −1.44, $p=0.000$), metabolic disorders (WMD: −2.74; 95% CI −3.48, − 2.00, $p=0.000$) and sleep disorders (WMD: −0.67; 95% CI −0.98, −0.37, $p=0.000$) without significant heterogeneity and score of PSQI significantly decreased following melatonin supplementation; but there was not any significant effect in mental disorders ($p=0.648$), neurodegenerative diseases ($p=0.132$), and other disease ($p=0.224$). Also, subgroup analysis revealed that both doses (≤3 mg and > 3 mg) decreased score of PSQI significantly [≤3 mg (WMD: −0.87; 95% CI −1.38, −0.35, $p=0.005$) and > 3 mg (WMD: −2.03; 95% CI −3.11, -0.96, $p=0.001$].

Publication bias and sensitivity analysis

The sensitivity analysis indicated that removing any of the studies could not substantially change the effect of melatonin on PSQI (Fig. 3). Assessment of publication bias by visual inspection of funnel plot indicated no evidence of publication bias in the meta-analysis of melatonin intervention on sleep quality (Fig. 4). Egger's weighted regression tests also were performed to explore the publication bias. There was no evidence of publication bias for studies examining the effect of melatonin on PSQI ($p=0.293$, Egger's test, and $p=0.882$, Begg's test).

Discussion

In the current study, we proved a significant improvement in sleep quality as assessed by the Pittsburgh Sleep Quality Index (PSQI) by melatonin supplementation based on the random-effects model in adult populations. Some previous meta-analyses assess the effect of melatonin on sleep quality in special disease such as primary sleep disorders, secondary sleep disorder, chronic kidney diseases. Sleep disturbance (SD), unsatisfactory sleep, and altered sleep patterns are common among patients with various diseases which may result in decreasing quality of life. To the best of our knowledge, this study is the first meta-analysis that investigated the effect of melatonin on sleep quality as measured by the PSQI in adults with various diseases. However, there was evidence of between-study heterogeneity in this regard. We found participants' health status was the potential source of heterogeneity. Based on subgroup analysis, there were significant effects of melatonin supplementation on sleep quality in subjects with respiratory diseases, metabolic disorders, and sleep disorders, but in subjects with mental disorders, neurodegenerative diseases, other diseases such as breast cancer, migraine, patients under MMT, alcohol use disorder, cirrhosis, IBS, brain injury, did not show any significant effect. Besides, we observed that subgroup analysis based on the type of intervention was another source of heterogeneity however, both interventions improved sleep quality significantly. Also, we found that both doses (≤3 mg and > 3 mg) increased sleep quality significantly.

Melatonin is an important endogenous indoleamine that is synthesized and secreted into the systemic circulation and cerebrospinal fluid by the pineal gland. It has a substantial role to regulate the circadian rhythm and sleep during the night. It has also been suggested that melatonin may act to facilitate sleep by inhibiting the circadian drive for waking that comes from the suprachiasmatic nucleus [55].

Table 2 Characteristics of included studies

Author	Country	Year	Study design	Population	Gender	Sample size (intervention/control)		Mean age (intervention/control)		Intervention	Duration (weeks)	Daily dose (mg)	Study result
Chen et al	US	2014	Parallel	Breast cancer	Woman	39	41	59	59	Melatonin	16	3	There was not Significant reduction in PSQI score
Kotlarczyk et al	US	2012	Parallel	Perimenopausal women	Woman	13	5	50.3	47.5	Melatonin	24	3	There was not Significant reduction in PSQI score
Gendy et al	Canada	2020	Parallel	Alcohol use disorder	Mix	30	30	_	_	Melatonin	4	5	There was not Significant reduction in PSQI score
Campos et al	Brazil	2004	Parallel	Asthma	Woman	11	10	27	32.4	Melatonin	4	3	Significant reduction was observed in PSQI score
De Silva et al	Sri Lanka	2020	Cross-over	Cirrhosis	Mix	37	34	63.6	60.1	Melatonin	4	3	Significant reduction was observed in PSQI score
Halvani et al	Iran	2013	Parallel	COPD	Mix	23	25	65.7	66.85	Melatonin	4	3	Significant reduction was observed in PSQI score
Ostadmohammadi et al	Iran	2019	Parallel	Diabetic HD	Mix	26	27	65.6	64.1	Melatonin	12	10	Significant reduction was observed in PSQI score
Song et al	Singapore	2005	Parallel	IBS	Mix	20	20	27.15	27.7	Melatonin	2	3	There was not Significant reduction in PSQI score
Nunes et al	Brazil	2008	Parallel	COPD	Mix	12	13	64.17	67.38	Melatonin	3	3	Significant reduction was observed in PSQI score
Baandrup et al	Denmark	2016	Parallel	Schizophrenia or bipolar disorder	Mix	28	27	48.8	49.1	PRM	24	2	Significant reduction was observed in PSQI score
Shabania et al	Iran	2018	Parallel	PCOS	Woman	29	29	26.5	26	Melatonin	12	10	Significant reduction was observed in PSQI score
Mousavia et al	Iran	2016	Parallel	SM-injured patient	Man	15	15	51.46	51.66	Melatonin	8	3	Significant reduction was observed in PSQI score
Jun et al	Korea	2018	Parallel	RBD	Mix	7	9	68.1	66.4	PRM	4	2	There was not Significant reduction in PSQI score
Jun et al	Korea	2018	Parallel	RBD	Mix	9	9	64.7	66.4	PRM	4	6	There was not Significant reduction in PSQI score
Wade et al	UK	2007	Parallel	Insomnia	Mix	169	165	66.1	65.3	PRM	3	2	There was not Significant reduction in PSQI score
Ghaderi et al	Iran	2018	Parallel	Patients under MMT	Man	26	28	42.5	42.7	melatonin	12	10	Significant reduction was observed in PSQI score
Wade et al	UK, USA	2014	Parallel	Alzheimer	Mix	31	29	75.3	75.3	PRM	24	2	There was not Significant reduction in PSQI score
Medeiros et al	Brazil	2006	Parallel	Parkinson	Mix	8	10	62.9	60.7	Melatonin	4	3	Significant reduction was observed in PSQI score

Table 2 (continued)

Author	Country	Year	Study design	Population	Gender	Sample size (intervention/control)		Mean age (intervention/control)		Intervention	Duration (weeks)	Daily dose (mg)	Study result
Morales-Delgado et al	Mexico	2018	Parallel	Dementia	Mix	16	15	82.2	83.1	Melatonin	8	5	There was not Significant reduction in PSQI score
Wade et al	UK	2011	Parallel	Primary insomnia	Mix	358	353	61.9	61.5	PRM	3	2	Significant reduction was observed in PSQI score
Alstadhaug et al	Norway	2010	Cross-over	Migraine	Woman	22	24	42.3	42.3	Melatonin	16	2	There was not Significant reduction in PSQI score
Ahn et al	South Korea	2019	Parallel	Parkinson	Mix	16	18	66	64.6	PRM	4	2	Significant reduction was observed in PSQI score
Grima et al	Australia	2018	Cross-over	Brain injury	Mix	18	15	35	38	PRM	4 weeks	2	Significant reduction was observed in PSQI score
Daneshvar Kakhakia et al	Iran	2019	Parallel	Parkinson	Mix	25	26	64.4	66.3	Melatonin	12 weeks	10	Significant reduction was observed in PSQI score

COPD chronic obstructive pulmonary disease, *MMT* methadone maintenance treatment, *RBD* rapid eye movement sleep behavior disorder, *SM-injured* sulfur mustard lung injuries, *HD* hemodialysis, *PCOS* polycystic ovary syndrome, *PRM* prolonged-release melatonin

Melatonin levels decrease with age, so older adults are more prone to suffer from inadequate melatonin levels [56]. Therefore, the incidences of sleep disturbance increase with age.

The Pittsburgh Sleep Quality Index (PSQI) is an efficient tool for measuring the quality and patterns of sleep. It has been recommended as the main measure for global sleep and insomnia symptoms in recent expert consensus recommendations for a standard set of research assessments in insomnia [57]. This questionnaire has seven components to measure sleep quality and it differentiates "poor" from "good" sleep: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction over the last month [58]. That should be noted that a higher PSQI score indicates a lower sleep quality.

This review has focused on the effects of melatonin on sleep quality using the PSQI questionnaire in adult patients and showed that melatonin intervention can improve sleep quality. In line with our findings, Auld et al. [59] conducted a similar meta-analysis of randomized, placebo-controlled trials of melatonin in adult with primary sleep disorders. Although our analysis focused on subjects with any sleep disorders, Auld et al. revealed that exogenous melatonin reduces sleep onset latency in primary insomnia and DSPS and regulates the sleep–wake patterns in blind patients.

In another meta-analysis, Li et al. investigated the roles of melatonin supplementation for the treatment of secondary sleep disorders. Li et al.[14] demonstrated that melatonin improves sleep quality concerning sleep onset latency and total sleep time. However, Li et al. showed melatonin has no actions on the sleep efficiency of patients with secondary sleep disorders. Also, Zhang et al.[60] conducted a meta-analysis that investigated melatonin for sleep disorders in neurodegenerative disease and found melatonin improved sleep quality significantly, which is consistent with our results, but no significant effects were detected for objective sleep outcomes (total nocturnal sleep time (TNST), sleep efficiency, and the number of night-time awakenings).

In contrast, a meta-analysis by Buscemi et al.[61] reported that melatonin supplementation in people who had sleep disorders with sleep restriction is not effective on sleep onset latency and found that melatonin has no effect in reliving sleep problems. Additionally, some randomized, placebo-controlled trials indicated that melatonin intervention cannot improve the quality of sleep [12, 13].

In the current meta-analysis, we used one questioner to measure sleep quality, so, it can enhance the reliability of our results. Our study in subgroup analysis found that health status was the main source of heterogeneity. We found that melatonin was effective in respiratory diseases, metabolic disorders and primary sleep disorders, not in mental disorders, neurodegenerative disorders, and other diseases. It might be explained by different levels of sleep disturbances

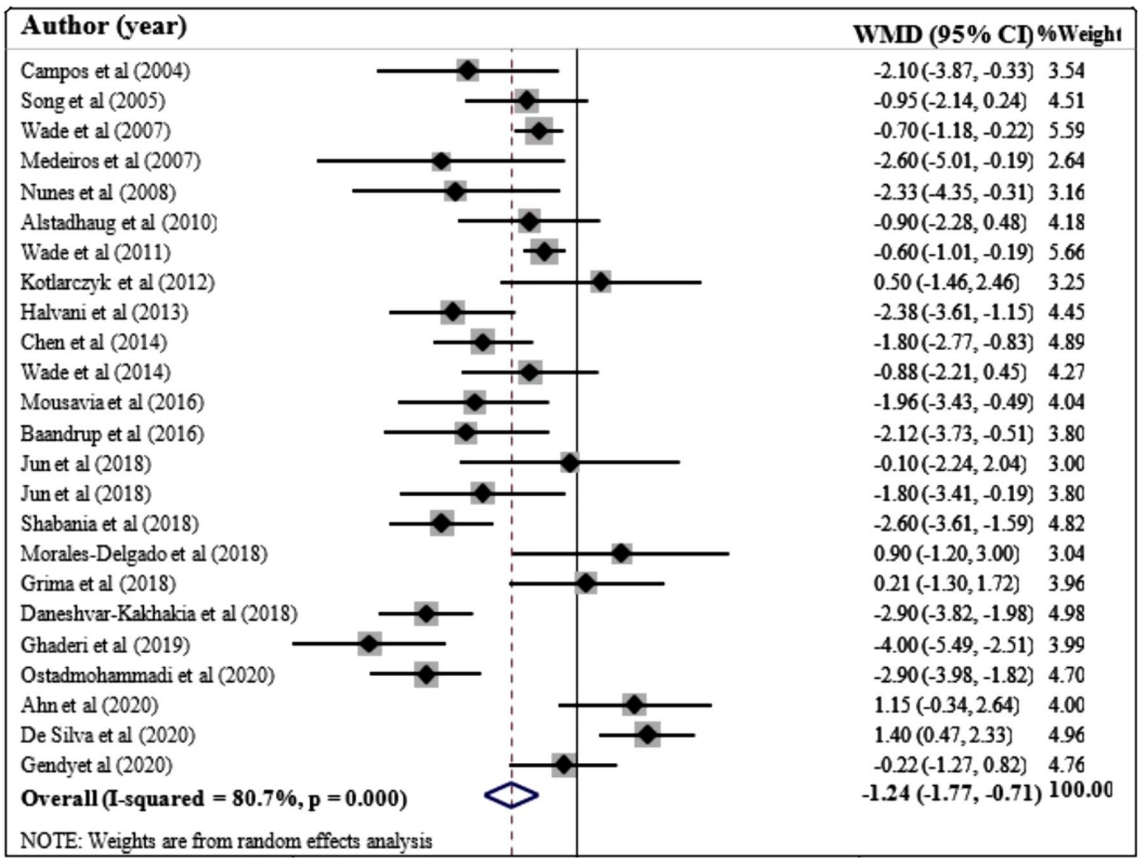

Fig. 2 Forest plot detailing weighted mean difference and 95% confidence intervals (CIs) for the effect of melatonin on PSQI

in these patients who may have a better response to melatonin. Also, some of the enrolled participants in two RCTs have already been experiencing _good_ sleep and some patients in these studies did not have insomnia, therefore, participants had heterogeneous symptoms of sleep disorders. However, an improvement in sleep quality was found in most of them. The etiology of sleep disorders is complex, involving multiple molecular mechanisms, so melatonin may be improving some aspect of sleep and it could be another reason for the lack of significant effect of melatonin in these subjects.

Furthermore, some RCTs included in these subgroups had only a few participants, which may not be representative of the large population afflicted by these sleep disorders. Besides, we observed that subgroup analysis based on kind of intervention (melatonin vs prolonged-release melatonin) could be another source of heterogeneity. Moreover, both melatonin and prolonged-release melatonin had a significant effect on sleep quality. Melatonin is tolerated well, unlike other sleeping medication melatonin has not high potential for dependence [62]. There is little evidence of substantial adverse events from long-term use of melatonin, and it can take many years for symptoms of toxicity to develop [63]. Using 20–100 mg/day melatonin orally in healthy subjects has no significant side effects with no important alterations to any physiological or biochemical measures [64]. Some studies demonstrated that long-term use of melatonin is well tolerated, without any crucial side effect [31, 48, 65]. However, there are concerns about chronic use of melatonin, in large doses it may interact with other medications [66].

Limitations

The current study has some limitations. Most analyses had high levels of heterogeneity, but this is expected because included studies had participants with different health conditions or doses and duration. Additionally, there were not enough studies to evaluate sleep problems in some diseases. Moreover, our search was limited to published English studies. Also, in this study, we used the PSQI global score to assess sleep quality, it seems that it is better to evaluate PSQI components separately.

Table 3 Subgroup analysis to assess the effect of melatonin on sleep quality

	NO	WMD (95% CI)	P within group	P heterogeneity	I^2
Subgroup analyses of melatonin supplementation on sleep quality					
Overall effect	24	− 1.24 (− 1.77, − 0.71)	0.000	0.000	80.7%
Age					
≤ 65	15	− 1.45 (− 2.18, − 0.72)	0.000	0.000	83.5%
> 65	8	− 1.00 (− 1.95, − 0.04)	0.041	0.000	77.9%
Trial duration (week)					
≤ 12	16	− 0.89 (− 1.50, − 0.29)	0.009	0.000	79.0%
> 12	8	− 1.93 (− 2.75, − 1.11)	0.000	0.002	68.8%
Melatonin Dose (mg)					
> 3	7	− 2.03 (− 3.11, − 0.96)	0.001	0.000	81.4%
≤ 3	17	− 0.87 (− 1.38, − 0.35)	0.005	0.001	70.5%
Kind of intervention					
Melatonin	15	− 1.52 (− 2.34, − 0.70)	0.000	0.000	84.1%
Prolonged-release melatonin	9	− 0.71 (− 1.21, − 0.21)	0.006	0.056	47.2%
Health status					
Mental disorders	2	− 0.69 (− 3.64, 2.27)	0.648	0.025	80.0%
Respiratory diseases	4	− 2.20 (− 2.97, − 1.44)	0.000	0.975	0.0%
Metabolic disorders	2	− 2.74 (− 3.48, − 2.00)	0.000	0.692	0.0%
Neurodegenerative diseases	4	− 1.19 (− 2.74, 0.36)	0.132	0.000	86.4%
Sleep disorders	4	− 0.67 (− 0.98, − 0.37)	0.000	0.513	0.0%
Other	8	− 0.74 (− 1.94, 0.45)	0.224	0.000	83.6%
Sex					
Mixed	17	− 0.97 (− 1.58, − 0.37)	0.002	0.000	81.0%
Men	2	− 2.98 (− 4.97, − 0.98)	0.004	0.056	72.6%
Women	5	− 1.55 (− 2.47, − 0.64)	0.001	0.052	57.4%
BMI					
> 25	9	− 1.40 (− 2.14, − 0.65)	0.000	0.000	83.7%
≤ 25	6	− 1.68 (− 2.99, − 0.37)	0.012	0.000	77.8%

CI confidence interval, *WMD* weighted mean differences

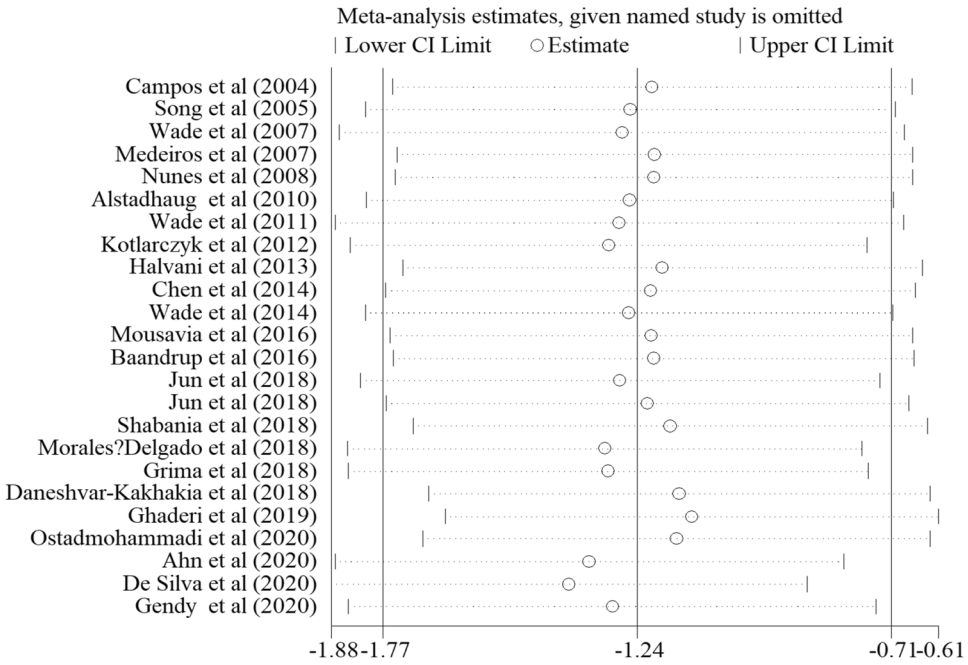

Fig. 3 Leave-one-out sensitivity analysis of the effect of melatonin on PSQI

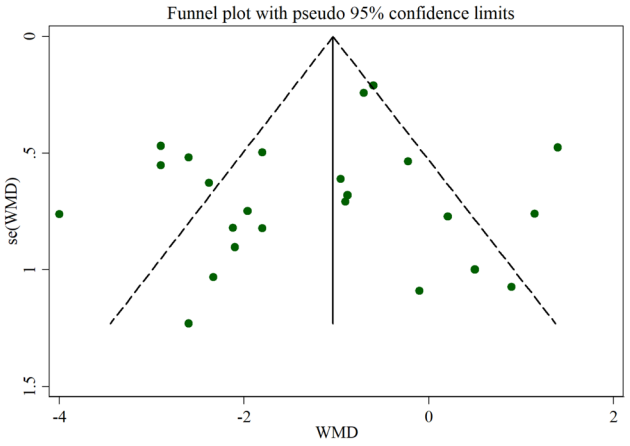

Fig. 4 Funnel plot for evaluating publication bias in the studies reporting the effect of melatonin on PSQI

Conclusion

In conclusion, combined data from interventional studies revealed a significant improvement in sleep quality after melatonin intervention. This significant effect was also seen in subjects with respiratory diseases, metabolic disorders, and primary sleep disorders, but there was not any significant effect on mental disorders, neurodegenerative diseases, and other diseases.

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Compliance with ethical standards

Conflicts of interest The authors declare no potential conflict of interest.

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