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Neurocognitive effects of melatonin treatment in healthy adults and individuals with Alzheimer's disease and insomnia: A systematic review and meta-analysis of randomized controlled trials

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ABSTRACT

Endogenous melatonin levels are inversely associated with age and cognitive deficits. Although melatonin can improve psychopathological behavior disturbances in clinical trials, whether melatonin may also enhance cognitive function remains elusive. This study examined cognitive outcomes from randomized trials of melatonin treatment for Alzheimer's disease (AD), insomnia, and healthy-subjects. Twenty-two studies met the inclusion criteria (AD = 9, insomnia = 2, healthy-subjects = 11). AD patients receiving >12 weeks of melatonin treatment improved mini-mental state examination (MMSE) score [MD: 1.82 (1.01; 2.63) $p < 0.0001$]. Importantly, melatonin significantly improved MMSE score in mild stage of AD [MD: 1.89 (0.96; 2.82) $p < 0.0001$]. In healthy-subjects, although daytime melatonin treatment notably decreased in accuracy by correct responses [SMD: -0.74 (-1.03; -0.45) $p < 0.00001$], the reaction-time score on different stimuli ($p = 0.37$) did not increased. Additionally, by pooling of short-term, spatial, and visual memory scores, melatonin did not reduce memory function ($p = 0.08$). Meta-analysis of MMSE score suggested that melatonin is effective in treatment for mild stage of AD. Additionally, we propose that melatonin may be preferable to traditional hypnotics in management of insomnia.

1. Introduction

The global aging of the population is rapidly becoming a daunting healthcare challenge (Chang et al., 2019; He et al., 2016). Worldwide, there were approximately 617 million people aged ≥ 65 years in 2016, which is expected to increase to nearly 1.6 billion by 2050 (He et al., 2016). Therefore, understanding both the natural and pathological impacts of aging on cognitive changes will become increasingly important in the future (Bäckman et al., 2006; Harada et al., 2013; Helmchen and Reischies, 1998; Prinz et al., 1982; Raz and Rodrigue, 2006). Dementia is one of the most common syndromes in the elderly population, with almost 50 million people suffering from dementia worldwide, and roughly 82 million people projected to have dementia by 2030 (World Health Organization, 2019). Insomnia appears to be more prevalent in later life, and to be associated with increased risk of Alzheimer's disease (AD) (Osorio et al., 2011; Pallesen et al., 2014; Winsky-Sommerer et al., 2019). There is accumulating evidence that insomnia significantly alters attention and episodic memory (Fortier-Brochu and Morin, 2014; Grau-Rivera et al., 2020; Haimov, 2006; Lowe et al., 2017). The mechanism underlying the effect of insomnia in increasing the severity of AD has been suggested to involve increased beta-amyloid production and decreased beta-amyloid clearance by poor sleep patterns (Cordone et al., 2019; Xie et al., 2013; Zhong et al., 2019). In addition, elderly subjects with AD show significant sleep disturbance, including shortened sleep

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duration and fragmented sleep (Prinz et al., 1982; Spira et al., 2014; Vitiello et al., 1990), as well as misalignment of circadian rhythm (Juby et al., 1991; Uddin et al., 2020; Yesavage et al., 2004).

Melatonin is a naturally occurring hormone secreted by the pineal gland in the brain, and is thought to be beneficial in the management of insomnia (Ferracioli-Oda et al., 2013; Luthringer et al., 2009; Wade et al., 2011) and AD (Cardinali et al., 2002; Gehrman et al., 2009; Hossain et al., 2019; Luengo et al., 2019; Serfaty et al., 2002). The mechanisms underlying these effects may be associated with balancing circadian rhythmicity (Hossain et al., 2019; Myers and Badia, 1995; Webb and Puig-Domingo, 1995), regulation of the immune system (Maestroni, 1993), and antioxidant properties (Hardeland et al., 1993; Sumsuzzman et al., 2020). Misalignment of the circadian system and reduction of endogenous melatonin levels suggest that melatonin replacement therapy may be of considerable benefit for AD-type dementia (Cardinali et al., 2014; Skene et al., 1990; Ohashi et al., 1999). Although many studies have demonstrated that melatonin is effective in treating AD, the results were not consistent (Asayama et al., 2003; Dowling et al., 2008). Several meta-analyses have been performed regarding the use of melatonin to improve cognition in dementia (Jansen et al., 2006; Wang et al., 2017; Xu et al., 2015), but these studies did not address how the duration of melatonin intervention differentially impacts cognition or which severity classes of AD show the greatest benefit of melatonin treatment.

Benzodiazepines, a class of psychoactive drugs, are among the most widely prescribed medications for insomnia and circadian misalignment (Nowell et al., 1997; Scharf et al., 1990). Despite their crucial hypnotic effect, these medications also significantly decrease memory function (Bixler et al., 1991; Chowdhury et al., 2016; Kamboj and Curran, 2006) and have other serious adverse effects (Glass et al., 2005; Guina and Merrill, 2018; Holbrook et al., 2000). Many studies have suggested that melatonin may be more suitable than benzodiazepines in the management of circadian misalignment and sleep disorders because melatonin improves sleep without significant performance impairment (Clay et al., 2013; Ghaeli et al., 2018; Rogers et al., 2003, 1998). To date, there have been no systematic reviews on the effects of melatonin on cognitive function in adult participants with or without insomnia.

This systematic review was performed to determine how the duration of melatonin intervention differentially impacts cognition in AD, which classes of AD according to severity show the greatest benefit of melatonin treatment, to assess the clinical efficacy of melatonin intervention for cognitive function in insomnia, and to evaluate the clinical effectiveness of melatonin intervention for cognitive function in healthy subjects.

2. Methods

The performance and reporting of this systematic review and meta-analysis (SR-MA) were performed in accordance with PRISMA guidelines (Moher et al., 2009). This study also followed the recommendations of Wager et al. (Wager and Wiffen, 2011) for the ethical publication of SR-MA.

2.1. Search strategy

First, database searches were conducted in February 2020 using comprehensive search strings in PubMed, Embase, CINAHL, and Cochrane library. Search strings were formulated from the following term sets: 1) sleep, insomnia, AD-type dementia, 2) melatonin, and 3) study type. Citation retrieval was limited to human studies, English language, and age (18+). Second, the journals *Sleep*, *Sleep Medicine*, and *Journal of Pineal Research* were searched for additional pertinent studies. Third, we also screened the references of selected reports to identify further studies. The literature search was completed on February 19, 2020. The search strings used for each database are shown in **Appendix-A**. Finally, citation chasing was performed using Google Scholar after the results of the bibliographic database searches were screened, and a set of potentially eligible studies was identified.

2.2. Eligibility criteria

Based Melatonin; cognition; Alzheimer's disease; insomnia; healthy-subjects; systematic review; meta-analysis on the PICOS formula, the following selection criteria were used: Population: a) the included studies involved at least 50 % of participants with AD-type dementia diagnosed based on accepted criteria, such as Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV), DSM-V, and National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) (DSM-IV, 1994; DSM-V, 2013; McKhann et al., 1984) of any level of severity measured by MMSE (Perneczky et al., 2006); b) included studies involved participants with any type of typical insomnia features, including persistent sleep difficulty, sufficient sleep opportunity, and associated daytime dysfunction, diagnosed based on accepted criteria, such as DSM and self-reported sleep questionnaires (DSM-IV-TR, 2000; Krystal et al., 2019); c) healthy adults.

Intervention and comparison: the included trials assessed the effects of orally administered melatonin monotherapy compared with placebo.

Outcome: cognition.

Study design: randomized controlled trials (RCTs), both parallel and crossover RCTs, with freely accessible full text, were considered for inclusion.

We excluded the following: 1) other than AD-type dementia; 2) apnea syndrome; 3) current/past history of serious medical illness; 4) circadian rhythm disturbances (jetlag-type, shiftwork type, altered sleep phase-type); and 5) case reports, case studies, reviews, bulletins, commentaries, and conference abstracts.

2.3. Study selection

Reporting of the reference management software may enhance transparency, and reproducibility of systematic reviews. Therefore, we used Mendeley as reference management software to organize and manage large volumes of references. Mendeley was also applied to remove duplicate articles. The remaining unique articles were then entered into the web-based systematic review app, Rayyan, specifically designed to accelerate initial screening (Ouzzani et al., 2016). Two reviewers then independently performed eligibility assessment. Disagreements were resolved by discussion between the reviewers. During primary screening, the records were screened based on the title and abstract, and if a citation appeared eligible or ambiguous, its full text was considered. Any decision making after reading of the full text is referred to as secondary screening. Finally, we contacted the authors to retrieve any missing data.

2.4. Data extraction

Two investigators individually extracted the following information: author name and year of publication, location, study design, sample size, population characteristics, interventions, and measured outcomes. With regard to continuous data, the mean and standard deviation (SD) of change score from baseline and the total number of participants for each intervention group at each time point were extracted. Where changes in means and SDs from baseline to follow-up were not reported, the mean, SD, and number of participants for each intervention group at each endpoint were extracted if available.

2.5. Risk of bias analysis

For risk of bias (RoB) analysis, the Cochrane RoB tools (Higgins and Altman, 2008) were used to estimate performance, attrition, detection, selection, and reporting biases. The RoB evaluation items included

generating random sequence, allocation concealment, blinding of patients and outcome assessors, incomplete outcome data, and selective reporting. Two reviewers conducted the RoB assessment independently of each other and then crosschecked their findings.

2.6. Data synthesis and statistical analysis

Statistical analysis was performed using RevMan version 5.3 (Cochrane Collaboration). We enumerated the mean differences (MDs) where studies exercised the same scale for each outcome (Deeks et al., 2011a), and the standardized mean differences (SMDs) where trials used different scales (Deeks et al., 2011b). In parallel group studies, the mean change scores were retrieved from baseline to follow-up for melatonin and placebo treatment groups. Furthermore, in the case of multi-arm intervention trials, we divided the shared group into two groups of smaller sample size and included two comparisons (Higgins et al., 2011a), which reduced bias and overcame unit analysis error. If reporting was vague, such as missing SD (change from baseline), as this information was often not available from trial reports and has to be imputed (Higgins et al., 2011b), the corresponding authors of the studies were emailed to request the missing information. If the authors did not respond, we calculated the missing values from other similar trials included in the same meta-analysis. In this case, we first computed the correlation using the following formula:

$$\mathbf{Corr} = \mathbf{SD^2_{baseline}} + \mathbf{SD^2_{follow\text{-}up}} - \mathbf{SD^2_{change}}/2 \times \mathbf{SD_{baseline}} \times \mathbf{SD_{follow\text{-}up}}.$$

SDs of the changes from baseline were then calculated using the formula: (Higgins et al., 2011c).

$$\mathbf{SD_{change}} = \sqrt{\mathbf{SD^2_{baseline}} + \mathbf{SD^2_{follow\text{-}up}} - (2 \times \mathbf{Corr} \times \mathbf{SD_{baseline}} \times \mathbf{SD_{follow\text{-}up}})}$$

To avoid bias, we conducted sensitivity analyses by assuming correlation coefficients of 0.5 (low positive correlation) and 0.0 (negligible correlation) (Mukaka, 2012). In the AD population, we performed our pre-planned subgroup analysis to determine how the duration of melatonin intervention differentially impacte from other similar trials inc d cognition, and in which AD severity types melatonin treatment was most beneficial. In subgroup analysis, if the data of subgroups were independent, we used a fixed-effect inverse-variance weighted average method; otherwise, a random-effects model was used (Deeks et al., 2011c).

If there were no carry-over or period effects, the most appropriate analysis of continuous data for a crossover study is the paired *t*-test (Higgins et al., 2011d). However, not all studies clearly reported paired analyses. Therefore, for each study and each comparison, we calculated the SMD, the pooled SD, and the SE of the SMD (Higgins et al., 2011e). When the correlation coefficient could not be obtained from raw data, a conservative value of 0.5 was assumed (Follmann et al., 1992). In our meta-analysis, we did not amalgamate change scores and final values in any analysis of SMDs. To avoid bias, we also did not unify the data from parallel group and crossover trials. In addition, if the data could only be attained from figures, the data were extracted with GetData v 2.26 software (Graph Digitizer). We pooled the available data using the generic inverse variance approach, and applied a random-effects model (Deeks et al., 2011d). In the absence of clinical or statistical heterogeneity, we also applied a fixed-effect model for pooling. To assess statistical heterogeneity, we performed the chi^2 test and calculated the I^2 value (Deeks et al., 2011d). An estimate $\geq$ 50 % was taken to indicate moderate heterogeneity, and scores ranging from 75%–100% were taken to indicate substantial heterogeneity (Higgins et al., 2003). To explore the possible factors for statistical heterogeneity, we performed post hoc subgroup analysis based on several melatonin doses and time of day of melatonin administration. In all analyses, $p < 0.05$ was taken to indicate statistical significance.

3. Results

3.1. Search results

The electronic database search yielded 2642 articles, 881 of which were duplicates. After reviewing the titles and abstracts, 44 studies were included for full text evaluation. A total of 22 trials were selected in this systematic review after application of eligibility criteria (Fig. 1).

3.2. Characteristics of studies

Twenty-two RCTs met the inclusion criteria and investigated the impact of melatonin on cognition in AD, insomnia, and healthy subjects. Of these, nine trials in AD patients (Asayama et al., 2003; Gao et al., 2009; Gehrman et al., 2009; Morales-Delgado et al., 2018; Riemersma-van der Lek et al., 2008; Serfaty et al., 2002; Singer et al., 2003; Wade et al., 2014; Xu et al., 2020), two in insomnia patients (Jean-Louis et al., 1998; Luthringer et al., 2009), and 11 in healthy subjects (Atkinson et al., 2005; Dollins et al., 1993, 1994; Gorfine et al., 2007; Gorfine and Zisapel, 2007; Lieberman et al., 1984; Otmani et al., 2008; Paul et al., 2003; Rogers et al., 2003, 1998; Suhner et al., 1998) were identified by citation searching. Eight of nine AD trials had a parallel design (Asayama et al., 2003; Gao et al., 2009; Gehrman et al., 2009; Morales-Delgado et al., 2018; Riemersma-van der Lek et al., 2008; Singer et al., 2003; Wade et al., 2014; Xu et al., 2020) and the remaining trial was a crossover study (Serfaty et al., 2002). Two of the nine AD trials were excluded from the meta-analyses of cognitive outcomes as the SDs of the change scores were not available for each measurement time point reported in the studies (Gehrman et al., 2009; Serfaty et al., 2002). However, cognitive outcome data obtained with the MMSE were pooled from seven studies (Asayama et al., 2003; Gao et al., 2009; Morales-Delgado et al., 2018; Riemersma-van der Lek et al., 2008; Singer et al., 2003; Wade et al., 2014; Xu et al., 2020), and data obtained with ADAS-Cog were pooled from three studies (Asayama et al., 2003; Singer et al., 2003; Wade et al., 2014). Data from two studies (Gao et al., 2009; Riemersma-van der Lek et al., 2008) represented both short-term (< 12 weeks) and long-term (> 12 weeks) follow-up time points. Of these, one study (Riemersma-van der Lek et al., 2008) included two of four treatment and control arms studied with regard to the effects of bright light and melatonin on the cognitive and non-cognitive symptoms of AD. The data pertaining to the groups that received bright light and bright light plus melatonin were not included in the analysis. Another study also included more than one intervention group, i.e., one receiving melatonin at a dose of 2.5 mg and another with a dose of 10 mg (Singer et al., 2003). These two groups were included in the meta-analysis, and the placebo group was split by sample size. Based on the severity of AD, three trials (Gao et al., 2009; Wade et al., 2014; Xu et al., 2020) were classified as mild AD and four trials (Asayama et al., 2003; Morales-Delgado et al., 2018; Riemersma-van der Lek et al., 2008; Singer et al., 2003) as moderate AD. For insomnia patients, one of two was crossover trial (Jean-Louis et al., 1998) and the another (Luthringer et al., 2009) had a parallel design. Due to the review criteria and heterogeneous outcomes, these studies were not included in the meta-analysis. On the other hand, all of the studies in healthy subjects had a crossover design. Four of the eleven trials included were excluded from the meta-analyses of cognitive outcomes as the SDs of the baseline or change scores were not available for each measurement time point reported in the studies (Gorfine et al., 2007; Gorfine and Zisapel, 2007; Otmani et al., 2008; Paul et al., 2003). However, cognitive outcome data, obtained from the reaction time, were pooled from seven studies (Atkinson et al., 2005; Dollins et al., 1993, 1994; Lieberman et al., 1984; Rogers et al., 2003, 1998; Suhner et al., 1998), those regarding accuracy subdomain with the number of correct responses were pooled from three studies (Dollins et al., 1993, 1994; Suhner et al., 1998), and those regarding memory were pooled from three studies (Atkinson et al., 2005; Rogers et al., 2003; Suhner et al., 1998). Melatonin doses ranged

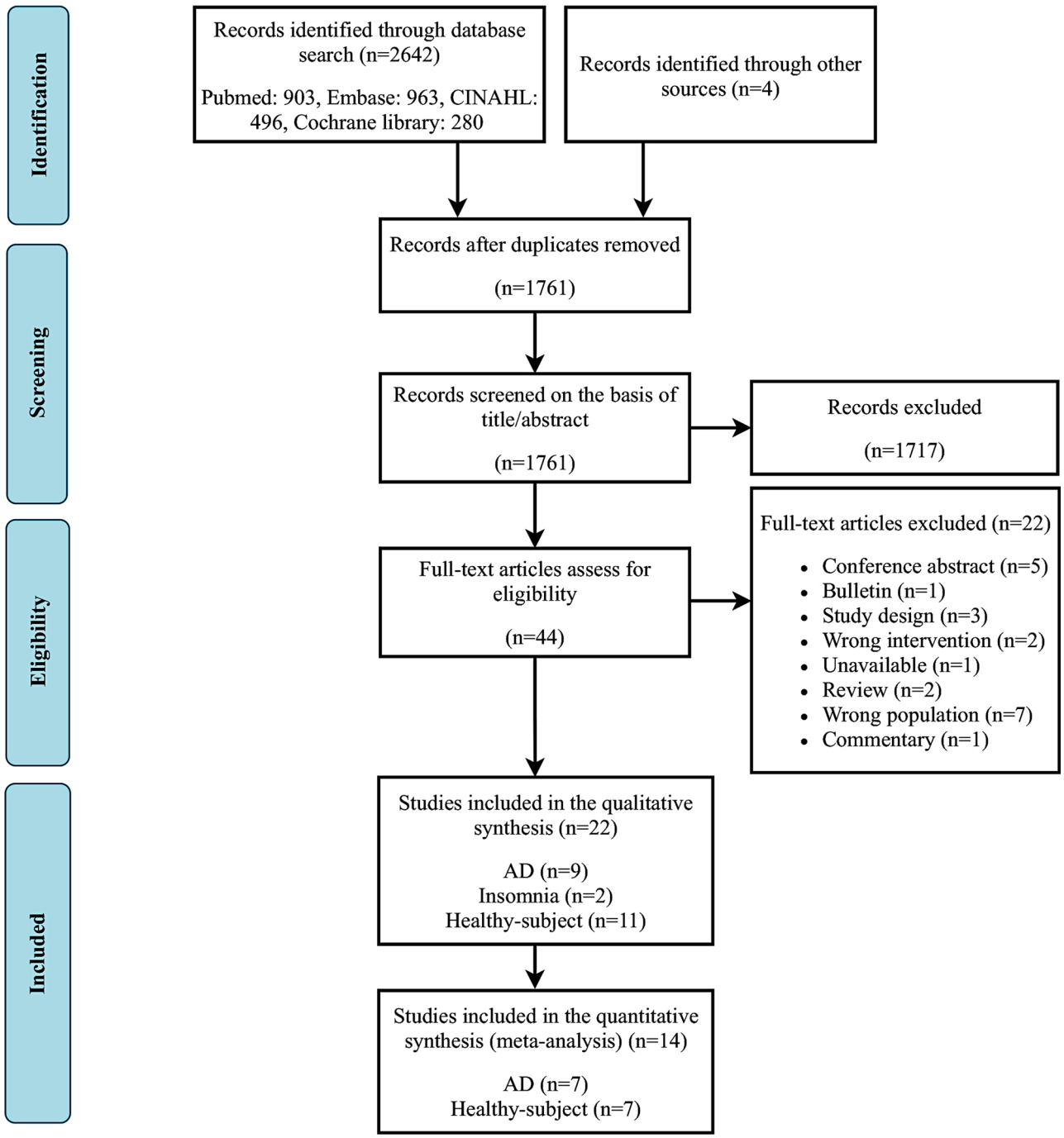

Fig. 1. Flow diagram of the systematic review and literature search results of the meta-analysis.

from 5 to 80 mg; four trials used 5 mg (Atkinson et al., 2005; Rogers et al., 2003, 1998; Suhner et al., 1998), two trials used 10 mg (Dollins et al., 1993, 1994), and one trial used > 10 mg (Lieberman et al., 1984). With regard to the time of day of melatonin administration in investigations of the effect on memory, melatonin was administered at noon (11:45, 12:00) in two trials (Atkinson et al., 2005; Rogers et al., 2003), and afternoon (16:30) in one trial (Suhner et al., 1998). A wide variety of outcome measures were used within these selected trials. We divided these different outcome measures into three cognitive domains (Table 1). The detailed characteristics of the selected trials are shown in Table 2.

3.3. Participant characteristics

The AD trials included in the analysis evaluated a total of 569 participants with a mean age of 78.95 years. Overall, 43.76 % of participants were male and 56.24 % were female. Several inventories were applied for diagnosis of AD patients (Table 2). The effects of melatonin on cognition were assessed in a total of 50 subjects with insomnia, with a mean age of 64.77 years. Overall, 56.00 % of the participants with insomnia were male and 44.00 % were female. In healthy subjects, the effects of melatonin on cognition were assessed in a total of 182 participants with a mean age of 29.14 years. Overall, 71.48 % of the healthy participants were male and 28.52 % were female.

Table 1
Cognitive domains and related tests.

Cognitive Domain	Test
Global cognitive function	Mini mental state examination
	Alzheimer's disease assessment scale-cog
Memory	Delayed recall
	Digit span
	Rivermead memory test
	Picture recognition task
	California verbal learning test
	Spatial memory task
	GEMAT test
Attention	Recognition Reaction Time
	Choice reaction time
	Wilkinson auditory vigilance task
	Vigilance test
	Digit vigilance task
	Power of attention
	Serial reaction time
	Serial subtraction task
	Multitask score
	Choice visual reaction time
	Logical reasoning task
	Beck-TENSOR
	Signal-detection
	Simple auditory reaction time
	Digit symbol substitution test
	Motor reaction time
Verbal function	Logical reasoning

3.4. Risk of bias

We separately appraised the RoB for parallel and crossover design trials; the abridged RoB assessment graph is shown in Fig. 2, and the individual RoB scores of each study are shown in Fig. 3. Four parallel design studies (Gao et al., 2009; Gehrman et al., 2009; Luthringer et al., 2009; Xu et al., 2020) inadequately reported methods for generating random sequences, and two trial (Gao et al., 2009; Xu et al., 2020) provided insufficient details about the allocation concealment, and were considered unclear risks of selection bias (Fig. 2A, Fig. 3A). Based on adequate information pertaining to the blinding of participants and outcome assessment, we rated almost all trials as low risk of performance as well as detection bias, with the exception of one study (Gao et al., 2009) with unclear RoB. We considered the risk of attrition bias to be unclear in one study (Gehrman et al., 2009), and one study (Gehrman et al., 2009) apprised as unclear risk of selective reporting bias owing to lack of information about completion of study by all the participants. We considered one study (Gehrman et al., 2009) to have unclear risk of other bias due to lack of information about study funding or potential conflicts of interest of the investigators/authors; two studies (Luthringer et al., 2009; Wade et al., 2014) were at high RoB as the authors reported having received financial support from a pharmaceutical company and the sponsor/funder had directly engaged with the design, collection, management, analysis, and interpretation of the data; and one study was at low risk of other bias due to insufficient information about study funding or potential conflicts of interest of the investigators/authors.

All except one of the crossover studies had inappropriate descriptions of the methods used for generating random sequences, allocating concealment, or blinding of participants and assessors; the one exception was a study that reported low risk of bias (Serfaty et al., 2002) (Fig. 2B, Fig. 3B). Although the majority of studies had a low risk of attrition bias, three trials (Dollins et al., 1994; Lieberman et al., 1984; Suhner et al., 1998) reported high risk of attrition bias due to handling of incomplete outcome data, and one study (Serfaty et al., 2002) had low risk of attrition bias. Most of the trials had a low risk of reporting bias, while the risk of reporting bias was unclear for five studies (Atkinson et al., 2005; Dollins et al., 1994, 1993; Jean-Louis et al., 1998; Lieberman et al., 1984) due to insufficient information.

3.5. Effects of melatonin intervention on AD

Long-term (> 12 weeks) melatonin treatment was more effective than short-term (< 12 weeks) melatonin treatment as determined using the MMSE scale. Taken together, four studies (Gao et al., 2009; Riemersma-van der Lek et al., 2008; Wade et al., 2014; Xu et al., 2020) (220 participants) that used MMSE to measure cognitive function showed that long-term melatonin treatment significantly improved global cognitive function (MD = 1.82; 95 % CI: [1.01, 2.63]; $p < 0.0001$, $I^2 = 40$ %) (Fig. 4). However, short-term melatonin treatment in five studies (Asayama et al., 2003; Gao et al., 2009; Morales-Delgado et al., 2018; Riemersma-van der Lek et al., 2008; Singer et al., 2003) (319 participants) did not improve global cognitive function (MD = 0.30; 95 % CI: [−0.30, 0.90]; $p = 0.33$, $I^2 = 0\%$) (Fig. 4).

Based on the severity of AD, melatonin treatment significantly improved MMSE score in mild level AD (MMSE ≥ 20), while moderate AD (MMSE = 10–20) remained unchanged. Pooling the results of three studies (Gao et al., 2009; Wade et al., 2014; Xu et al., 2020) (171 participants) using MMSE to measure cognitive function in participants with mild AD showed that melatonin treatment significantly improved global cognitive function (MD = 1.89; 95 % CI: [0.96, 2.82]; $p < 0.0001$, $I^2 = 55$ %) (Fig. 5). In four studies in participants with moderate AD (Asayama et al., 2003; Morales-Delgado et al., 2018; Riemersma-van der Lek et al., 2008; Singer et al., 2003) (288 participants), melatonin treatment did not improve global cognitive function (MD = −0.01; 95 % CI: [−0.80, 0.79]; $p = 0.98$, $I^2 = 0\%$) (Fig. 5).

We calculated the correlation coefficients from the study by Wade et al. (Wade et al., 2014) to ascertain missing SDs. As sensitivity analysis, we applied correlation coefficients of 0.5 and 0.0. Using a correlation coefficient of 0.5 (> 12 weeks, $p <$ 0.00001; mild AD, $p < 0.0001$) (Table 3, **Supplementary Fig. 1&2**), as well as 0.0 (> 12 weeks, $p =$ 0.0001; mild AD, $p =$ 0.0001) (Table 3, **Supplementary Fig. 3&4**), the pooled difference between treatment and placebo remained statistically significant.

In terms of ADAS-Cog, both < 12 weeks and moderate AD subgroups had the same number and identical studies, likewise both > 12 weeks and mild AD subgroups. The meta-analysis results from all subgroup trials using ADAS-Cog to measure cognitive impairment showed that melatonin did not improve global cognition with treatment for < 12 weeks/moderate AD (MD = −1.86; 95 % CI: [−4.14, 0.43]; $p = 0.11$, $I^2 = 53$ %) (Fig. 6) or > 12 weeks/mild AD (MD = 0.26; 95 % CI: [−2.76, 3.28]; $p = 0.87$) (Fig. 6).

3.6. Effects of melatonin on healthy subjects

3.6.1. Effects of melatonin on attention domain

Fig. 7 summarizes the results related to the attention domain. We divided the attention domain into two subdomains, i.e., 1) reaction time (higher score indicates poor outcome) and 2) accuracy (lower score indicates poor outcome). Seven crossover trials (Atkinson et al., 2005; Dollins et al., 1993, 1994; Lieberman et al., 1984; Rogers et al., 2003, 1998; Suhner et al., 1998) (118 patients) investigated the effects of melatonin on reaction time using different assessment tools. The following outcome measures were identified from these studies and pooled: 1) Choice reaction time (CRT), 2) Choice visual reaction time (CVRT), 3) Vigilance tasks, and 4) Beck tensor analysis. The results obtained by pooling of seven studies (Atkinson et al., 2005; Dollins et al., 1993, 1994; Lieberman et al., 1984; Rogers et al., 2003, 1998; Suhner et al., 1998) showed that melatonin did not increase the reaction time scores (SMD = 0.29; 95 % CI: [−0.34, 0.92]; $p = 0.37$, $I^2 = 89$ %) (Fig. 7A). We imputed a correlation coefficient of 0.5 for all crossover trials. Our conclusions did not change when the melatonin and placebo results were substituted as sensitivity analysis with correlation coefficients of 0.8 (SMD = 0.30; 95 % CI: [−0.33, 0.93]; $p = 0.35$, $I^2 = 96$ %) (Table 3, Supplementary Fig. 5) and 0.0 (SMD = 0.27; 95 % CI: [−0.36, 0.91]; $p = 0.40$, $I^2 = 78$ %) (Table 3, **Supplementary** Fig. 8).

Table 2
Characteristics of the studies.

Author, Year (Location)	Study design	Participants	Diagnosis criteria	Intervention (Time)	Control	Cognitive outcomes
AD						
Serfaty et al., 2002 (UK)	Cross-over	Total: n = 25 (16 male, 9 female); 84.2 ± 7.6 y Total: n = 20 (3 male, 17 female); 79.2 ± 6.4 y	DSM-IV	MT-6 mg/day for 2 wk (Before bed)	PLA	MMSE
Asayama et al., 2003 (Japan)	Parallel-group	1. MT group: n = 11 (78.9 ± 7.3 y) 2. PLA group: n = 9 (79.4 ± 5.3 y)	NINCDS-ADRDA, DSM-IV	MT-3 mg/day for 4 wk (Before bed)	PLA	MMSE, ADAScog
Singer et al., 2003 (USA)	Parallel-group	Total: n = 157 (69 male, 88 female); 77.4 ± 8.9 y 1. MT group (2.5 mg): n = 54 2. MT group (10 mg): n = 51 2. PLA group: n = 52	NINCDS-ADRDA	1. MT-2.5 mg/day for 8 wks 2. MT-10 mg/day for 8 wks (Before bed)	PLA	MMSE, ADAScog
Riemersma-van der Lek et al., 2008 (Netherlands)	Parallel-group	Total: n = 91 (13 male, 78 female); 85.5 ± 5 y 1. MT group: n = 46 (86 ± 5 y) 2. PLA group: n = 45 (85 ± 5 y)	NINCDS-ADRDA, DSM-IV	MT-2.5 mg/day for 6 wks-3.5 y (Before bed)	PLA	MMSE
Gao et al., 2009 (China)	Parallel-group	Total: n = 36 (All male); 77.0 ± 2.9 y 1. MT group: n = 15 2. PLA group: n = 16	NINCDS-ADRDA	MT-2.9 mg/day for 24 wks (Before bed)	PLA	MMSE
Gehrman et al., 2009 (USA)	Parallel-group	Total: n = 41 (13 male, female 28); 82.9 ± 7.0 y 1. MT group: n = 24 2. PLA group: n = 17	NINCDS-ADRDA	MT-10 mg (8.5 mg IR + 1.5 mg SR)/day for 10 days (Before bed)	PLA	MMSE
Wade et al., 2014 (U.S.A and U.K)	Parallel-group	Total: n = 80 (41 male, 39 female); 75.3 y 1. MT group: n = 39 2. PLA group: n = 34	MMSE score ≥ 15	MT-2 mg/day for 24 wks (Before bed)	PLA	MMSE, ADAScog
Morales Delgado et al., 2018 (Mexico)	Parallel-group	Total: n = 40 (16 male, 24 female); 82.65 y 1. MT group: n = 21 (82.2 ± 5.8 y) 2. PLA group: n = 19 (83.1 ± 7.4 y)	DSM-V, CDR = 1–2	MT-5 mg/day for 8 wks (Before bed)	PLA	MMSE
Xu et al., 2020 (China)	Parallel-group	Total: n = 79 (42 male, 37 female); 66.40 y 1. MT group: n = 40 (66.3 ± 8.8 y) 2. PLA group: n = 39 (66.5 ± 8.3 y)	DSM-IV	MT-0.15 mg/day for 24 wks (Before bed)	PLA	MMSE
Insomnia						
Jean-Louis et al., 1998 (U.S.A)	Cross-over	Total: n = 10 (4 male, 6 female); 68.8 ± 15.8 y	Self-reported sleep-wake disturbances: (1) difficulty initiating sleep, and (2) frequent nocturnal awakenings	MT-6 mg/day for 10 days (Before bed)	PLA	Delayed recall
Luthringer et al., 2009 (Israel)	Parallel-group	Total: n = 40 (24 male, 16 female) 1. MT group: n = 20 (59.6 ± 2.9 y) 2. PLA group: n = 20 (61.9 ± 4.8 y)	DSM-IV criteria for primary insomnia	MT-2 mg/day for 3 wk (Before bed)	PLA	MRT, RRT
Healthy-subject						
Atkinson et al., 2005 (U.K)	Cross-over	Total: n = 12 (all male); 25.2 ± 5.0 y	Healthy-subject	MT-5 mg single dose (11:45)	PLA	Digit span, CRT
Dollins et al., 1993 (U.S.A)	Cross-over	Total: n = 20 (all male); 25 y	Healthy-subject	MT-10, 20, 40, 80 mg single dose (11:45)	PLA	WAV, CRT
Dollins et al., 1994 (U.S.A)	Cross-over	Total: n = 20 (all male); 23.05 y	Healthy-subject	MT- 0.1, 0.3, 1.0, 10 mg single dose (11:45)	PLA	WAV, CRT
Gorfine et al., 2007 (Israel)	Cross-over	Total: n = 13 (7 male, 6 female); 25.7 ± 3 y	Healthy-subject	MT-2 mg single dose (12:30–14:00)	PLA	fMRI
Gorfine and Zisapel, 2007 (Israel)	Cross-over	Total: n = 12 (7 male, 5 female); 26 ± 3.7 y	Healthy-subject	MT-2 mg single dose (16:00)	PLA	fMRI
			Healthy-subject	MT-2 mg for 2 days (20:00)	PLA	DVT, POA, PRT, RMT

(*continued on next page*)

Table 2 (*continued*)

Author, Year (Location)	Study design	Participants	Diagnosis criteria	Intervention (Time)	Control	Cognitive outcomes
Otmani et al., 2008 (Israel)	Cross-over	Total: n = 16 (12 male, 4 female); 59.4 ± 3.2 y				
Paul et al., 2003 (Canada)	Cross-over	Total: n = 23 (9 male and 14 female); 29.9 ± 10.3 y	Healthy-subject	MT-6 mg single dose (09:45)	PLA	SRT, LRT, SST, multitask score
Rogers et al., 1998 (Australia)	Cross-over	Total: n = 16 (10 male and 6 female), 22.4 y	Healthy-subject	MT-5 mg single dose (12:30)	PLA	CVRT
Rogers et al., 2003 (Australia)	Cross-over	Total: n = 16 (6 male and 10 female), 21.4 y	Healthy-subject	MT-5 mg single dose (12:00)	PLA	Spatial memory, vigilance test, logical reasoning
Suhner et al., 1998 (Switzerland)	Cross-over	Total: n = 20 (12 male and 8 female); 31 y	Healthy-subject	MT-5 mg single dose (16:30)	PLA	GEMAT test, signal-detection, Beck-TENSOR
Lieberman et al., 1984 (U. S.A)	Cross-over	Total n = 14 (all male); 31.5 y	Healthy-subject	MT-80 mg 3 times 2 h period (12:00–14:00)	PLA	CRT

Age data are mean ± standard deviation.

AD, Alzheimer's disease; n, Number; y, Years; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders-IV; MT, Melatonin; wk, Week; PLA, Placebo; MMSE, Mini-Mental State Examination; NINCDS-ADRDA, National institute of neurological and communicative disorders and stroke and the Alzheimer's disease and related disorders association; ADAS-cog, Alzheimer's disease assessment scale-cog; MRT, Motor reaction time; RRT, Recognition reaction time; CRT, Choice reaction time; CLVT, California verbal learning test; WAV, Wilkinson auditory vigilance task; fMRI, functional magnetic resonance imaging; DVT, Digit vigilance task; POA, Power of attention; PRT, Picture recognition task; RMT, Rivermead memory test; SRT, Serial reaction time; LRT, Logical reasoning task; SST, Serial subtraction task; CVRT, Choice visual reaction time.

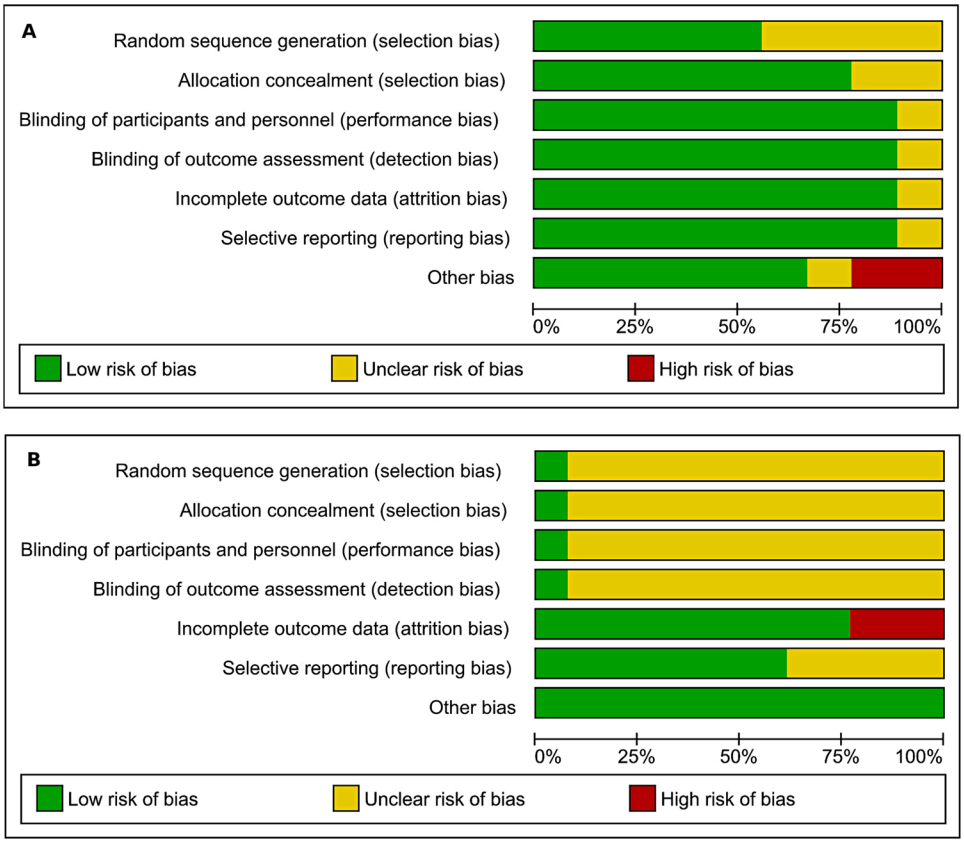

Fig. 2. Risk of bias graph. (A) Parallel studies, (B) Crossover studies.

On the other hand, three crossover trials (Dollins et al., 1993, 1994; Suhner et al., 1998) (60 patients), investigated the effects of melatonin on accuracy using different assessment tools. The following outcome measures were identified from these studies and pooled: 1) Wilkinson auditory vigilance (WAV) task and 2) signal detection. The results from pooling of these three studies (Dollins et al., 1993, 1994; Suhner et al., 1998) showed that melatonin significantly decreased accuracy (SMD = −0.74; 95 % CI: [−1.03, −0.45]; $p < 0.00001$, $I^2 = 19$ %) (Fig. 7B). We imputed a correlation coefficient of 0.5 for all crossover trials. Our conclusions did not change when the melatonin and placebo results were substituted as sensitivity analysis with correlation coefficients of 0.8 (SMD = −0.77; 95 % CI: [−1.10, −0.44]; $p < 0.00001$, $I^2 = 69$ %) (Table 3, **Supplementary** Fig. 6), and 0.0 (SMD = −0.74; 95 % CI: [−1.15, −0.33]; $p = 0.0004$, $I^2 = 0$%) (Table 3, **Supplementary** Fig. 9). However, the heterogeneity increased with a correlation coefficient of 0.8 and heterogeneity decreased with a correlation coefficient of 0.0.

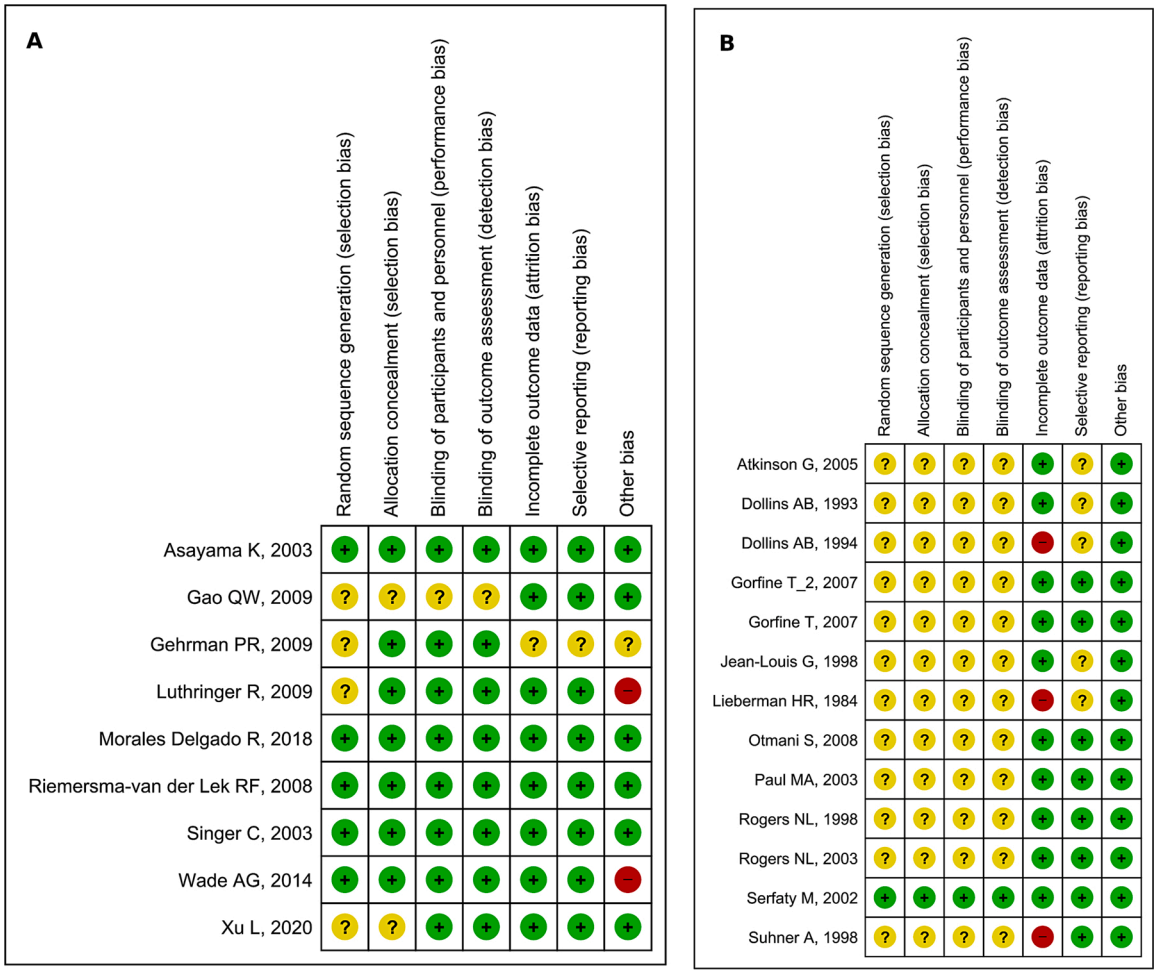

Fig. 3. Risk of bias summary. (A) Parallel studies, (B) Crossover studies.

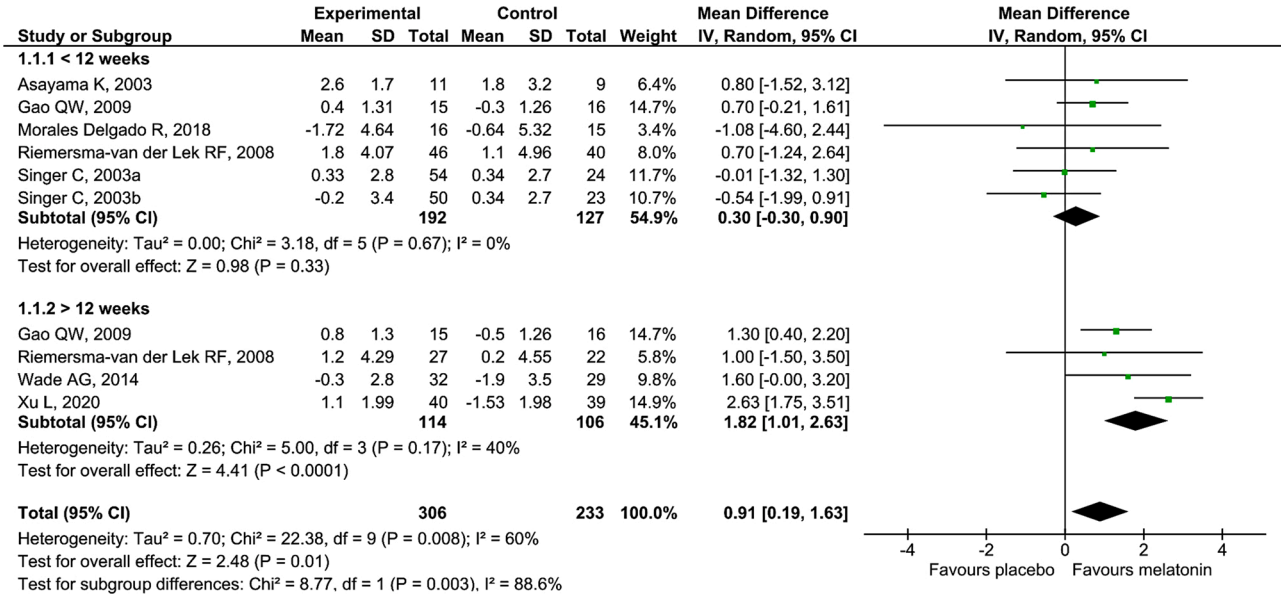

Fig. 4. Forest plot comparing the changes in the MMSE scale score between melatonin and placebo groups with short-term (< 12 weeks) and long-term (> 12 weeks) treatment in AD. MMSE, mini-mental state examination; AD, Alzheimer's disease; CI, confidence interval; SD, standard deviation; IV, independent variable.

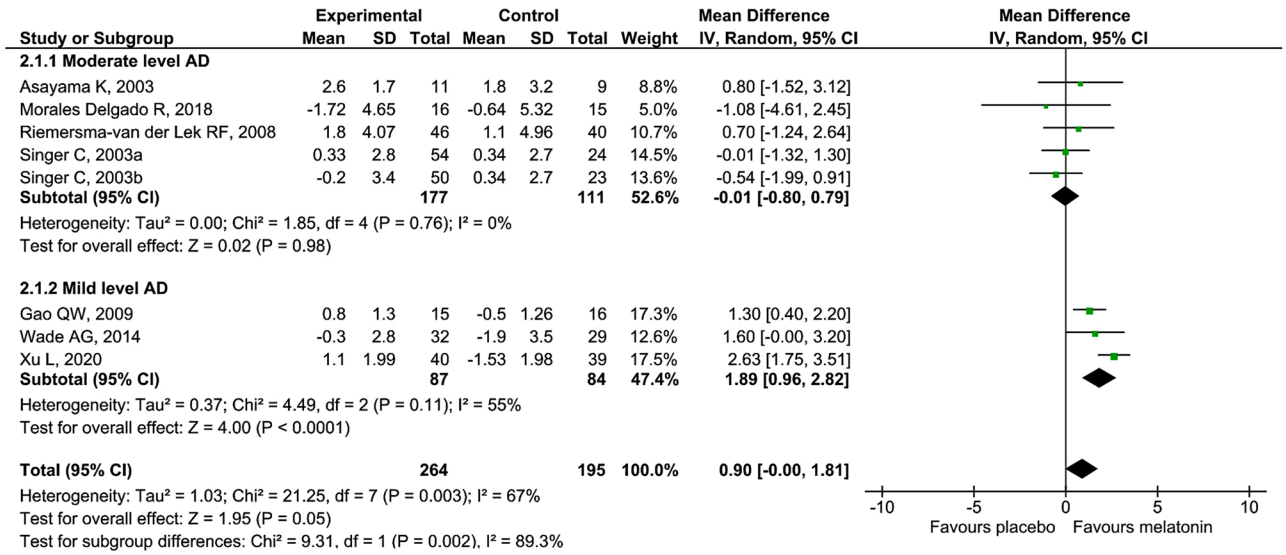

Fig. 5. Forest plot comparing the changes in the MMSE scale score between melatonin and placebo groups according to different severity of AD. MMSE, mini-mental state examination; AD, Alzheimer's disease; CI, confidence interval; SD, standard deviation; IV, independent variable.

Table 3
Summary of sensitivity analysis.

Outcome measures	Correlation coefficient 0.80				Correlation coefficient 0.00			
	Trials (n)	Effect size (95 %CI)	*p*-value	I^2	Trials (n)	Effect size (95 %CI)	*p*-value	I^2
Reaction time	**7**	SMD 0.30 [-0.33, 0.93]	0.35	96 %	**7**	SMD 0.27 [-0.36, 0.91]	0.40	78 %
Accuracy	3	SMD -0.77 [-1.10, -0.44]	<0.00001	69 %	3	SMD -0.74 [-1.15, -0.33]	0.0004	0%
Memory	3	SMD -0.82 [-1.72, 0.08]	0.07	94 %	3	SMD -0.76 [-1.67, 0.14]	0.10	71 %
MMSE (<12 weeks)	5	MD 0.18 [-0.53, 0.88]*	0.62	0%	5	MD 0.07 [-0.71, 0.86]	0.85	0%
MMSE (>12 weeks)	4	MD 1.88 [1.13, 2.63]*	<0.00001	0%	4	MD 1.84 [0.89, 2.79]	0.0001	0%
MMSE (moderate level AD)	4	MD -0.05 [-0.89, 0.80]*	0.91	0%	4	MD -0.06 [-0.93, 0.80]	0.88	0%
MMSE (mild level AD)	3	MD 1.91 [1.06, 2.75]*	<0.0001	17%	3	MD 1.87 [0.91, 2.84]	0.0001	0%

SMD = standardized mean difference; CI = confidence interval, MMSE = mini mental state examination, AD = Alzheimer's disease; MD = mean difference.
* Correlation coefficient 0.50.

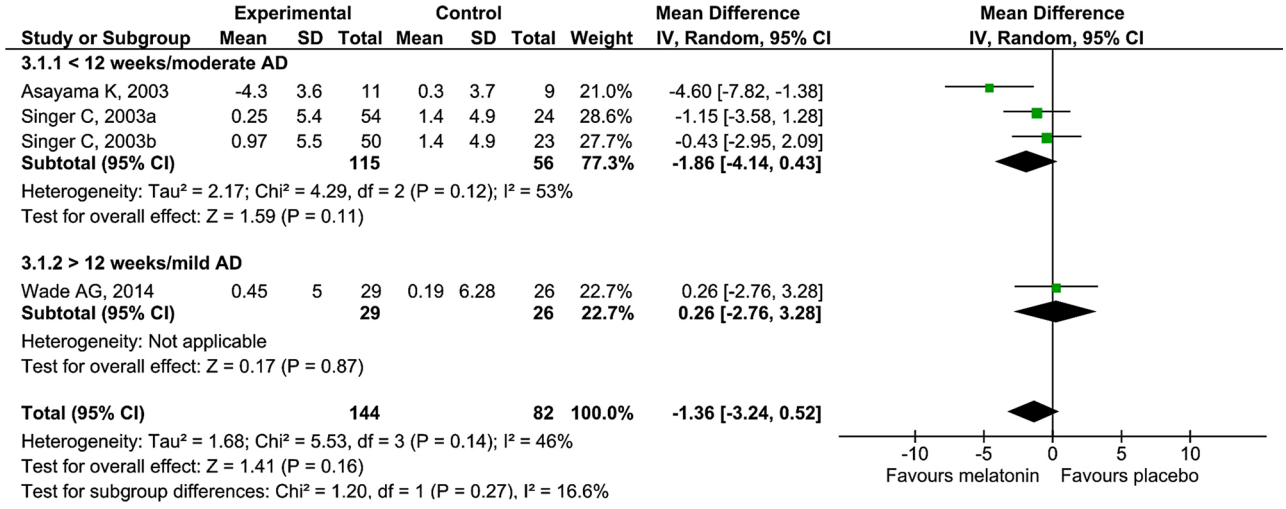

Fig. 6. Forest plot comparing the changes in the ADAS-Cog scale score between melatonin and placebo groups based on the duration of treatment and severity of AD. ADAS-Cog, Alzheimer's Disease Assessment Scale cognitive subscale; AD, Alzheimer's disease; CI, confidence interval; SD, standard deviation; IV, independent variable.

3.6.2. Effects of melatonin on memory domain

Fig. 8 summarizes the results of the memory domain. Three crossover trials (Atkinson et al., 2005; Rogers et al., 2003; Suhner et al., 1998) (48 patients) investigated the effects of melatonin on memory using different assessment tools. The following outcome measures were identified from these studies and pooled: 1) short-term memory by digit span test, 2) spatial memory test, and 3) visual memory by GEMAT test. The results of pooling of these three studies (Atkinson et al., 2005;

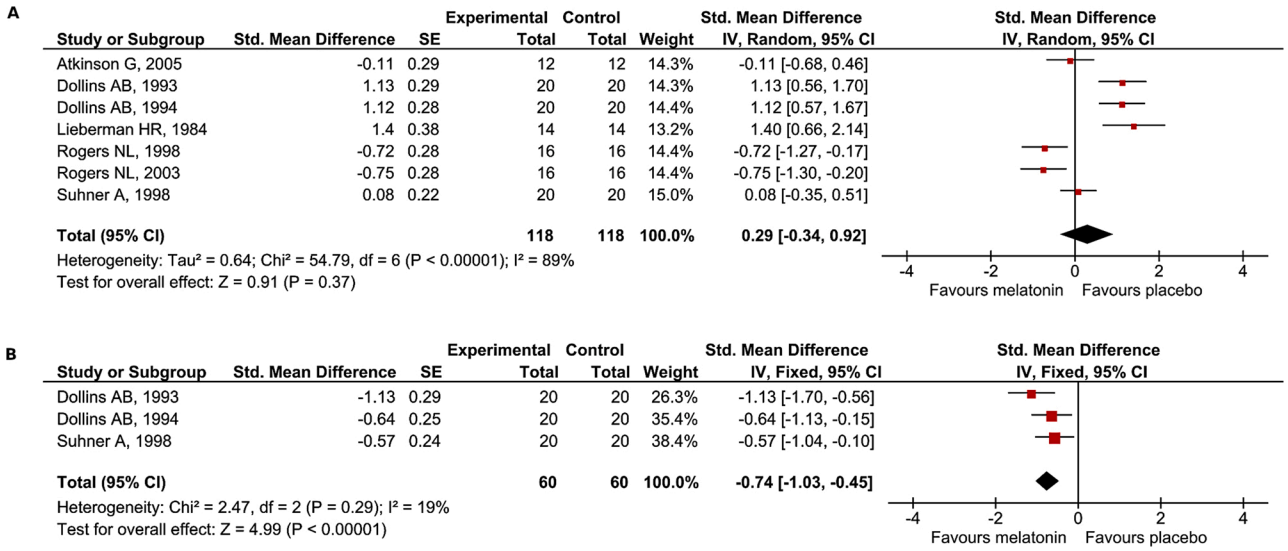

Fig. 7. Forest plot comparing the changes in attention between melatonin and placebo groups in healthy subjects. (A) Reaction time. (B) Accuracy. CI, confidence interval; SD, standard deviation; IV, independent variable.

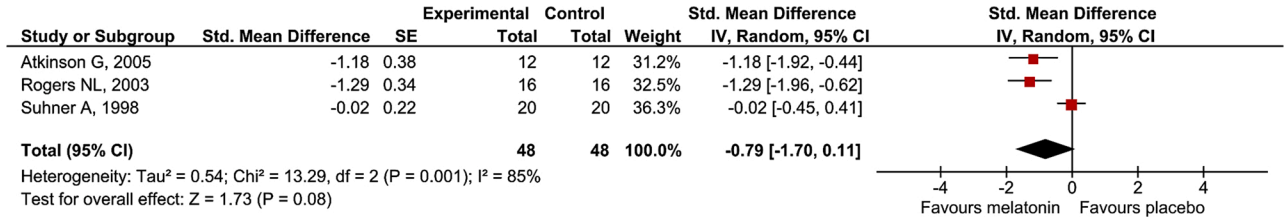

Fig. 8. Forest plot comparing the changes in memory function between melatonin and placebo groups in healthy subjects. CI, confidence interval; SD, standard deviation; IV, independent variable.

Rogers et al., 2003; Suhner et al., 1998) showed that melatonin did not reduce memory domain (SMD = −0.79; 95 % CI: [−1.70, 0.11]; p = 0.08, I^2 = 85 %) (Fig. 8). We imputed a correlation coefficient 0.5 for all crossover trials. Our conclusions did not change when the melatonin and placebo results were substituted as sensitivity analysis with correlation coefficients of 0.8 (SMD = −0.82; 95 % CI: [−1.72, 0.08]; p = 0.07, I^2 = 94 %) (Table 3, **Supplementary** Fig. 7), and 0.0 (SMD = −0.76; 95 % CI: [−1.67, 0.14]; p = 0.10, I^2 = 71 %) (Table 3, **Supplementary**

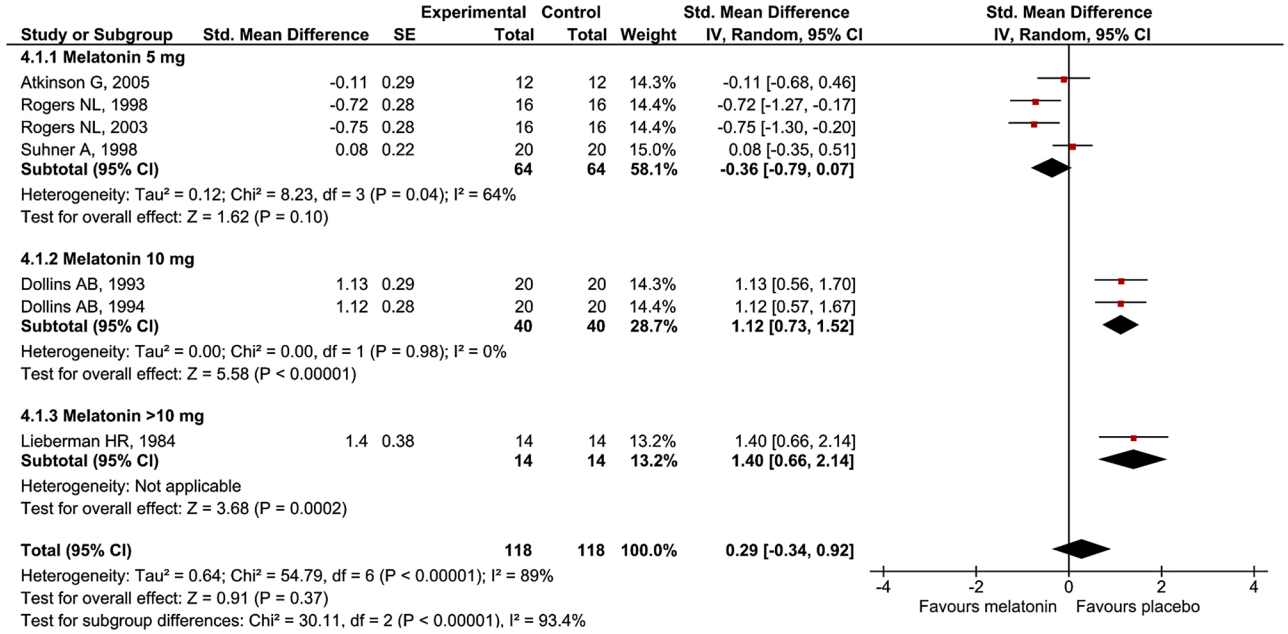

Fig. 9. Forest plot comparing the changes in reaction time among several doses of melatonin and placebo groups in healthy subjects. CI, confidence interval; SD, standard deviation; IV, independent variable.

Fig. 10).

3.6.3. Subgroup analysis

We performed subgroup analysis to examine heterogeneity. According to the reaction time, we found $I^2 = 89$ %, which indicated considerable heterogeneity, and therefore performed post hoc subgroup analysis based on different melatonin doses. Four trials (Atkinson et al., 2005; Rogers et al., 2003, 1998; Suhner et al., 1998) assessed the effectiveness of a melatonin dose of 5 mg compared with placebo according to reaction time. The meta-analysis demonstrated that melatonin did not increase the reaction time scores (SMD = −0.36; 95 % CI: [−0.79, 0.07]; $p = 0.10$, $I^2 = 64$ %) (Fig. 9). The heterogeneity among the trials was low ($I^2 = 64$ %, $p = 0.10$) (Fig. 9). Two trials (Dollins et al., 1993, 1994) assessed the effectiveness of a melatonin dose of 10 mg compared with placebo according to reaction time. The meta-analysis demonstrated that melatonin significantly increases the reaction time scores (SMD = 1.12; 95 % CI: [0.73, 1.52]; $p < 0.00001$, $I^2 = 0$%) (Fig. 9). There was no statistical heterogeneity among the trials ($I^2 = 0$%, $p < 0.00001$) (Fig. 7). Only one trial (Lieberman et al., 1984) assessed the effectiveness of a melatonin dose > 10 mg compared with placebo according to reaction time. The meta-analysis demonstrated that melatonin significantly increases the reaction time scores (SMD = 1.40; 95 % CI: [0.66, 2.14]; $p < 0.00001$) (Fig. 9).

For the memory domain, $I^2 = 85$ % indicated considerable heterogeneity. Therefore, we performed post hoc subgroup analysis based on time of day of melatonin administration. Two trials (Atkinson et al., 2005; Rogers et al., 2003) assessed the effectiveness of melatonin administered at noon according to the memory domain. The meta-analysis demonstrated that melatonin significantly decreased memory (short-term and spatial memory) (SMD = −1.24; 95 % CI: [−1.74, −0.74]; $p < 0.00001$, $I^2 = 0$%) (Fig. 10). There was no statistical heterogeneity among the trials ($I^2 = 0$%, $p < 0.00001$). Only one trial (Suhner et al., 1998) assessed the effectiveness of melatonin administered in the afternoon according to the memory domain. The meta-analysis demonstrated that melatonin did not decrease memory (visual memory) (SMD = −0.02; 95 % CI: [−0.45, 0.41]; $p = 0.93$) (Fig. 10).

3.7. Effects of melatonin on subjects with insomnia

Although there have been few studies of cognitive outcomes in insomnia patients, our literature search identified two studies (Jean-Louis et al., 1998; Luthringer et al., 2009) that assessed several cognitive outcomes after melatonin treatment in subjects with insomnia. Although we could not combine the data due to the differences in study design and outcomes measured, we descriptively analyzed the effects of melatonin in insomnia patients based on these studies. One of the two studies reported that chronic nighttime melatonin treatment improved memory without any detrimental effects (Jean-Louis et al., 1998). This study suggested that prolonged melatonin treatment might yield better results with regard to cognition and non-cognition behavior because melatonin can improve sleep quality, which further might be involved in cognition and non-cognition behavior improvement. The remaining one study showed that daytime cognitive performance was not impaired by melatonin and consistently improved cognition compared with placebo.

4. Discussion

This systematic review summarized the available evidence regarding the effects of melatonin on cognitive function in AD, insomnia, and healthy subjects. Our meta-analysis suggested that patients with AD could eventually show benefits with regard to increased MMSE scores ($p < 0.0001$) after 12 weeks of melatonin therapy, while the ADAS-Cog scale remained unchanged. Furthermore, melatonin treatment may be more effective in mild than moderate AD ($p < 0.0001$). However, inconsistent effects of melatonin have appeared on the ADAS-Cog scale. One possible explanation for this discrepancy is that the ADAS-Cog scale is not subtle enough to record and monitor variance in the mildest stages of AD (Hobart et al., 2013; Kueper et al., 2018). Further work is required to modify the ADAS-Cog scale or develop a new test. Previous meta-analyses had many limitations. First, they only investigated the overall effects of melatonin intervention, and all of the studies reported that cognitive function did not change significantly with melatonin therapy (Jansen et al., 2006; Wang et al., 2017; Xu et al., 2015). These three meta-analyses did not clarify how the duration of melatonin intervention differentially impacted cognition, and which types of AD with regard to severity showed the greatest benefit after melatonin treatment (Jansen et al., 2006; Wang et al., 2017; Xu et al., 2015). Next, it is generally accepted that analysis based on changes from the baseline are more reliable than studies based on the final values (Deeks et al., 2011e). We calculated the change score in our meta-analysis, while Wang et al. (Wang et al., 2017) used final values. Although Xu et al. (Xu et al., 2015) calculated the change score in their meta-analysis, they did not split the placebo group with smaller sample size from one study (Singer et al., 2003), which increased unit-of-analysis error (Higgins et al., 2011a). To address this issue, we divided the placebo group into smaller sample sizes for independent comparison, which was therefore free of unit analysis error. Overall, our study not only solved the above limitations, but also added more citations than previous meta-analyses. Therefore, this study was more valuable than previous similar studies.

There is accumulating evidence that melatonin restores the sleep/wake cycle, enhances sleep quality and daytime activity, and sustains

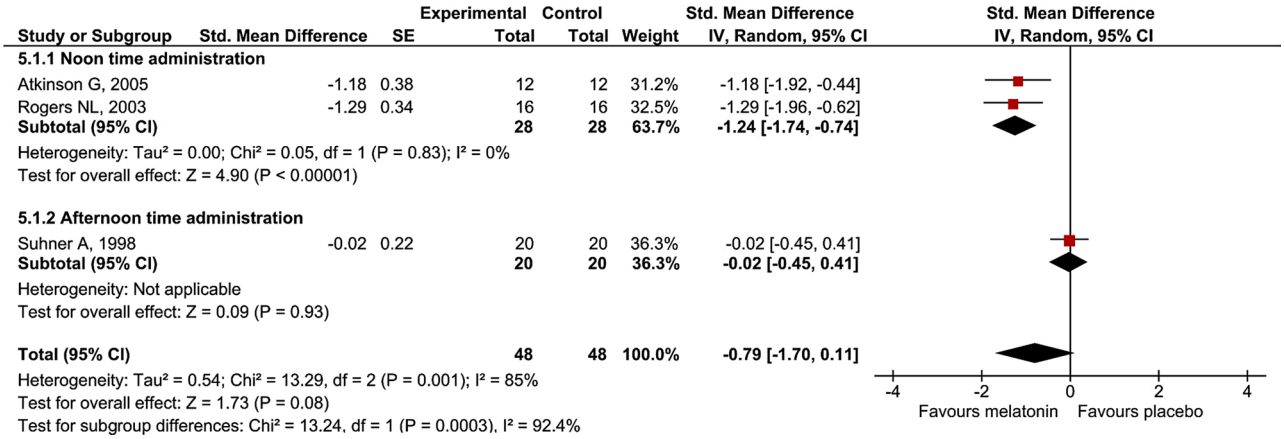

Fig. 10. Forest plot comparing the changes in memory function between ingestion of melatonin at noon and afternoon and placebo groups in healthy subjects. CI, confidence interval; SD, standard deviation; IV, independent variable.

the physiological sleep structure in insomnia patients (Lemoine and Zisapel, 2012; Wade et al., 2007, 2011). This may explain why melatonin showed a greater beneficial effect on cognition in mild to moderate AD patients with insomnia as a comorbidity (Wade et al., 2014). Importantly, the management of sleep complaints with long-established hypnotics may not be advantageous and even detrimental in healthy middle-aged and elderly subjects due to the loss of cognitive function associated with these drugs (Chavant et al., 2011; Leufkens et al., 2009; Otmani et al., 2008). In addition, long-term ingestion of benzodiazepine has been linked to an increased risk of dementia (Ettcheto et al., 2020; Gray et al., 2016; He et al., 2019; Wu et al., 2009). Our systematic review showed that chronic nighttime melatonin treatment improved cognition without any detrimental effects, and daytime cognitive performance was not impaired by melatonin and consistently improve cognition with melatonin treatment when compared with placebo. As melatonin improves sleep without any significant risk of memory or cognitive decline, the improvement of sleep can also contribute to improvement of cognition by melatonin in AD and/or insomnia patients, as suggested in the present systematic review and meta-analysis. A recent review of published results on the use of melatonin in mild cognitive impairment yielded 12 reports (2 open-label retrospective study, 1 cohort study, 9 randomized controlled trials) that supported melatonin administration improves cognitive performance and sleep quality (Cardinali, 2019).

In healthy subjects, the present meta-analysis showed that daytime melatonin administration did not impair memory function ($p = 0.08$, $I^2 = 85$ %) or reaction time ($p = 0.37$, $I^2 = 89$ %), although melatonin significantly decreased accuracy subdomain with the number of correct responses ($p < 0.00001$, $I^2 = 19$ %). We performed subgroup analyses due to the high degree of heterogeneity between memory and reaction time outcomes. Based on the time of day of melatonin administration in the memory domain, the subgroup analysis demonstrated that treatment with melatonin at noon significantly reduced memory function ($p < 0.00001$, $I^2 = 0\%$), while administration in the afternoon did not ($p = 0.93$). Although these two timepoints assess different types of memory, this finding is important as several studies reported that melatonin had beneficial effects when administered in the afternoon compared with other times of the day (Claustrat et al., 1992; Crowley and Eastman, 2013; Eastman and Burgess, 2009; Nickelsen et al., 1989). In addition, the results of this study indicated that memory function was decreased following ingestion of melatonin at noon, but was unchanged by melatonin administered in the afternoon, which also supported the results of a previous study (Suhner et al., 1998). Furthermore, subgroup analysis demonstrated that a melatonin dose of 5 mg administered during the day did not negatively correlate with reaction time score ($p = 0.10$, $I^2 = 64$ %); however, doses of 10 mg ($p < 0.00001$, $I^2 = 0\%$) and ≥ 10 mg ($p = 0.0002$) adversely correlate with reaction time score. These findings interpret that a low dose of melatonin did not negatively induce neurobehavioral performance; however, a higher dose of melatonin shows the opposite effect. In human trials, acute melatonin treatment may increase subjective feelings of fatigue and cause a reduction in performance. The previous literatures demonstrated that a large acute dose of melatonin ingested at noon increases reaction time and induces drowsiness and sometimes sleep (Lieberman et al., 1982; Nickelsen et al., 1989). Furthermore, many studies reported that ingestion of ≥ 10 mg of melatonin at midday was associated not only with a significant reduction in oral temperature, feelings of vigor, and decrease working-memory, but also increases feeling of sleepiness, fatigue, confusion, and reaction time (Dollins et al., 1993; Lieberman et al., 1982; Nickelsen et al., 1989). Interestingly, administration of 5 mg of melatonin at the same time of day had no negative association with reaction time score (Atkinson et al., 2005; Lok et al., 2019; Suhner et al., 1998). Our meta-analysis agreed with the consensus of previous studies that ingestion of melatonin at a dose ≥ 10 mg at midday increased reaction time (Dollins et al., 1993; Lieberman et al., 1982; Nickelsen et al., 1989), while a dose of 5 mg of melatonin ingested at the same time of day had no such negative effect on reaction time (Atkinson et al., 2005; Suhner et al., 1998).

Our review had several intrinsic limitations, the most pronounced of which is that we were only able to find and combine small amounts of data, e.g., we only combined data on the global cognitive scale, and were not able to include other cognitive outcomes, including attention, short-term memory, and long-term memory in AD patients. In addition, we were unable to perform a meta-analysis of results in insomnia patients due to the heterogeneity of study design and outcome measures. Most of the included crossover studies did not provide sufficient details regarding selection, performance, and detection domain, which is a major drawback of these crossover studies and led to unclear risk of bias.

Despite the promising fields of application, various aspects require further research. The AD trials included in the analysis were primarily focused on the impacts of melatonin on the global cognitive score (MMSE, ASAS-Cog). Nonetheless, it would be intriguing to examine its effects on other cognitive domains, such as episodic memory. Furthermore, we could not determine the differential impacts of melatonin ingestion according to sex in AD patients, so further sex-specific trials are required. We were unable to perform meta-analysis of the results in insomnia patients due to heterogeneity of studies, and therefore additional parallel studies with larger sample sizes in different cognitive domains are required. Additionally, we were unable to analyze how melatonin individually impacts short-term, spatial, visual, and working memory due to the unavailability of the abundance of studies, and therefore more RCT with larger sample sizes in different memory domains are urgently warranted. Both immediate and sustained-release formulations of melatonin were used in our included trials. A study reported that these preparations exert similar therapeutic benefits related to melatonin's action as an antioxidant (Rybka et al., 2016). However, the question of whether different melatonin formulations have similar efficacy in improving cognition deserves further research in well-design multicenter clinical trials. Finally, we recommend improving the reporting system for crossover studies to reduce the risk of bias.

5. Conclusion

The available evidence suggests that melatonin treatment for > 12 weeks may be effective for improvement of cognitive functioning in AD. In particular, patients with mild AD may show greater beneficial effects of melatonin intervention than those with moderate AD. This will be valuable for caregivers to decrease the burden of AD. Although daytime melatonin administration produced a significant reduction of accuracy, the other cognitive subdomains, such as reaction time and memory, remained unchanged by melatonin treatment. Therefore, we propose that melatonin may be preferable to traditional hypnotics, such as benzodiazepines, in the management of circadian disruption and insomnia. Finally, before melatonin intervention can be recommended for the improvement of cognition, as adjuvant AD therapy or as an alternative of traditional hypnotics, further high-quality studies with larger sample sizes and longer duration are needed.

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Author contributions

Conceptualization, Y.H.; methodology, D.M.S. and J.C.; software, D.M.S., J.C. and Y.J.; validation, Y.H.; formal analysis, D.M.S., J.C. and Y.J.; investigation, D.M.S., J.C. and Y.J.; resources, D.M.S., J.C. and Y.J.;

data curation, D.M.S., J.C. and Y.J.; writing-original draft preparation, Y.H. and D.M.S.; writing-review and editing, Y.H. and D.M.S.; visualization, D.M.S., J.C. and Y.J.; supervision, Y.H.; project administration, Y.H.; funding acquisition, Y.H. All authors have read and agreed to the published version of the manuscript.

Declaration of Competing Interest

The authors report no declarations of interest.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.neubiorev.2021.04.034.

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