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Melatonin treatment and light therapy for chronic sleep onset insomnia in children

Effects on sleep, cognition, health, and psychosocial functioning

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CHAPTER 5

The effects of light therapy on sleep problems

*A systematic review
and meta-analysis*

THIS CHAPTER IS BASED ON:

Van Maanen, A., Meijer, A. M., van der Heijden, K. B., & Oort, F. J. (2016). The effects of light therapy on sleep problems: A systematic review and meta-analysis.

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ABSTRACT

Although bright light therapy seems a promising treatment for sleep problems, research shows inconclusive results. This meta-analysis is the first to systematically review the effect of light therapy on sleep problems in general and on specific types of sleep problems in particular (circadian rhythm sleep disorders, insomnia, sleep problems related to Alzheimer's disease and dementia). Fifty-three studies with a total of 1154 participants were included. Overall effects and effects on separate circadian and sleep outcomes were examined. We calculated Hedges' g effect sizes and we investigated the effects of twelve moderators (design-related, treatment-related, participant-related). Light therapy was found effective in the treatment of sleep problems in general ($g = 0.39$), and for circadian rhythm sleep disorders ($g = 0.41$), insomnia ($g = 0.47$), and sleep problems related to Alzheimer's disease / dementia ($g = 0.30$) specifically. For circadian rhythm sleep disorders, effects were smaller for randomised controlled trials. For insomnia, we found larger effects for studies using a higher light intensity, and for sleep problems related to Alzheimer's disease / dementia larger effects were found for studies with more female participants. There was indication of publication bias. To conclude, light therapy is effective for sleep problems in general, particularly for circadian outcomes and insomnia symptoms. However, most effect sizes are small to medium.

INTRODUCTION

Light has an important influence on sleep and wakefulness. First, light influences the suprachiasmatic nucleus (SCN), a region in the hypothalamus that controls circadian rhythms, through the eye and the retinohypothalamic tract. Second, light inhibits the secretion of melatonin. Third, light is found to have alerting effects through indirect projections on the ascending arousal system, which in turn facilitates thalamic and cortical connections.^{1,2}

Because light is such an important factor in the regulation of sleep and wakefulness, light has been applied therapeutically as a treatment for sleep disorders. Bright light therapy is a natural, simple form of treatment that has relatively low costs. Moreover, light therapy does not lead to residual effects and tolerance, which are often associated with medication use,^{3,4} although light therapy also can have side effects such as headache, eye strain, autonomic hyper activation, and can possibly induce hypomania.⁵

Research on light therapy effectiveness has shown inconclusive results, with some studies reporting positive effects whereas others found minor or no effects.⁶⁻⁹ The reasons for these inconsistencies are not yet clear. To some extent, they might be explained by the large variety in sleep problems targeted with light therapy, large variety in studied groups (regarding age, comorbidity), or differences in study design and treatment characteristics (e.g., treatment duration, light intensity etc.).

Considering the high potential of light therapy for sleep disorders, it is important to gain insight in the general and specific effects of light therapy on different sleep problems, and to identify factors that influence its effectiveness. Therefore, in this meta-analysis we will investigate the effect of light therapy on sleep problems in general and specific sleep problems in particular. Furthermore, we aim to identify possible influences (moderators) on the effects of light therapy.

Current state of knowledge

In the early 1980s, Czeisler et al.¹⁰ first showed that the phase of the circadian rhythm in humans could be influenced by modifying the light-dark cycle. Lewy and colleagues found that nocturnal melatonin secretion could be suppressed by bright light.¹¹ Rosenthal et al.¹² first applied this principle to patients with delayed sleep phase syndrome (DSPS), a circadian rhythm sleep disorder (CRSD) in which the endogenous circadian rhythm is delayed with regard to what is

desired. They found that the circadian rhythm of core body temperature and the sleep-wake rhythm of DSPS patients could be shifted by two hours of bright light exposure in the morning and restriction of light in the evening.

After the first studies conducted in the 1980s, the research on light therapy has been extended to other sleep disorders, with different light characteristics and varying treatment durations. In 1995, several consensus reports of the Task Force on Light Treatment for Sleep Disorders have been published, summarising the research on light treatment for sleep disorders until then.¹³⁻¹⁹ In addition, several reviews appeared which mainly reported about the application of light for sleep problems in older, healthy adults²⁰ or in elderly with Alzheimer's disease or other types of dementia.²¹⁻²³ A systematic review of different treatment options for various forms of sleep disturbance (e.g., increased sleep latency, low sleep efficiency, long daytime sleep duration) in people with Alzheimer's disease / dementia concluded that of the non-pharmacological treatments analysed in that study, bright light was the most effective.²⁴

Treatment guidelines for the use of light therapy in sleep disorders

To date, there are no clear guidelines available for light therapy in sleep disorders related to Alzheimer's disease / dementia,²¹ and the research on light treatment for other sleep disorders has led to varying treatment recommendations.²⁵⁻²⁸ Although there is no consensus about the ideal treatment characteristics, there is agreement about the timing of treatment according to the phase response curve of light. This implies that exposure to light in the morning - after the lowest point of body temperature at around 04:00 h - shifts the biological clock rhythm to an earlier point in time, whereas light in the evening (before the nightly nadir in temperature) shifts it to a later time. Immediately before or after the temperature nadir, light exposure has its greatest phase-advancing effect, with diminishing effects further away from the temperature nadir. This implies that light therapy in the morning should occur as early as possible, however, without forcing individuals waking up too early, preventing sleepiness during the day.^{25,29,30}

Important factors to consider in studies of light treatment effectiveness

Although light therapy is nowadays applied to different types of sleep disorders, it was originally applied to CRSD.¹² The core problem of CRSD lies in the misalignment between the endogenous rhythm and the environment, or in the lack of an endogenous rhythm. As light therapy directly affects the circadian rhythm by its influence on the SCN,¹¹ it might be expected that light therapy would have stronger effects on CRSD than on other types of sleep disorders. We therefore hypothe-

sised that the type of sleep problem targeted would be an important factor to consider when investigating light therapy effectiveness (Moderators 1-4).

Another factor that could be of influence is the quality of the study design. Studies without a control group might find larger effects than randomised controlled trials (RCT's), as the latter control for placebo effects (Moderator 5).

Also, effects could be different for subjective and objective outcome measures of sleep (Moderator 6). Both measures have their own disadvantages, as people often have difficulty assessing their sleep and actigraphs cannot always reliably distinguish between inactivity and sleep or between restlessness during sleep and night-time awakenings. The latter is even more problematic in people experiencing sleep problems.^{31,32}

As mentioned earlier, there are several treatment characteristics that could impact treatment effects. Number of treatment days (Moderator 7), daily treatment duration (Moderator 8), and intensity and spectral characteristics of light (Moderator 9) seem important factors to take into account.²⁵⁻²⁸ Another factor to consider is whether additional instructions regarding sleep hygiene or bedtimes are provided (Moderator 10). Good sleep hygiene and regular bedtimes are important factors that can influence treatment effectiveness.^{26,27}

Sleep does not remain stable over the life course. The proportion of time spent in different sleep stages changes with age,³³ and in general older people have less consolidated sleep and they wake up earlier.³⁴ Moreover, age differences in effects of sleep treatment are found, e.g., melatonin treatment has larger effects in children than in adults,³⁵ although prolonged-release melatonin has been found effective for older adults.³⁶ Light treatment might have smaller effects in older people due to age-related changes in lens density.³⁷ We therefore expect age to be a moderator of light therapy effectiveness (Moderator 11).

Although little is known about differential effects of light therapy for men and women, Cajochen³⁸ recently showed that there are some gender differences in response to light. Women were found to prefer warmer light whereas this was not found for men. In addition, women more often have sleep complaints.^{39,40} Therefore, it might be expected that treatment effects vary between men and women (Moderator 12).

Present meta-analysis

The present meta-analysis is the first to systematically review the effect of light therapy on sleep problems in general and on specific types of sleep problems in particular. In the analyses we will not only examine the overall effect of light therapy on sleep, but also on the different circadian and sleep outcomes sepa-

rately. In addition, we will take into account whether specific study characteristics, treatment characteristics, and sample characteristics act as moderators.

METHODS

Selection of studies

As a primary search method, we did an extensive literature search using the databases of PsycINFO, Medline, Cinahl, Embase, and the Cochrane Library. We used the following keywords in our search: phototherapy, phototherap*, heliotherapy, heliotherap*, light treatment, light exposure, bright light, sunlight, artificial light, combined with sleep disorders, sleep*, insomnia*, dyssomnia*, somnolence, circadian rhythm, jet lag syndrome, jet lag*, night shift*. We excluded animal studies. Furthermore, an RCT filter was applied to make a selection of papers reporting on randomised controlled trials, to ease the screening process. The search was carried out in two phases. The initial search was carried out in November 2012. An update was done in March 2015. For an example of the full electronic search strategy, see Appendix S1.

In addition, we searched online thesis databases, we checked reference lists of relevant reviews and papers that we already included in our meta-analysis, and we searched proceedings of the last two editions of the most important sleep conferences (conferences of the World Sleep Federation, European Sleep Research Society, Associated Professional Sleep Societies, World Association of Sleep Medicine, Society of Light Treatment and Biological Rhythms). Finally, we contacted experts in the field to enquire about unpublished papers.

Studies were included in the present meta-analysis according to the following criteria: 1) participants were included in the study (amongst others) on the basis of a sleep disorder or sleep complaint (e.g., low sleep quality, disturbed sleep); 2) the study reported on a light intervention intended to diminish the sleep complaints (at least one sleep outcome had to be reported); 3) the study reported on a minimum of five participants (case study reports were excluded); 4) the paper was written in English. Studies reporting on light therapy for (seasonal) depression or other complaints than sleep were excluded. Studies reporting on shift work were only included if participants had a shift work disorder or had expressed complaints about their sleep. Studies investigating effects of light therapy on elderly persons in a home for the elderly, regardless of whether the individual participants expressed sleep complaints, or on healthy subjects who did not experience sleep problems, were not included. No restrictions with

regard to publication date, publication status, type of sleep disorder, age of participants, or study design were imposed.

The first phase of the literature search in the electronic databases yielded 3159 unique results. The studies that were found with the RCT filter were screened by at least two authors (AvM and AMM or KBvdH) independently. The studies that were not included with the RCT filter were screened by one author (AvM). After screening titles and abstracts, 3048 titles were excluded. The remaining 111 titles were evaluated in more detail. Disagreements about inclusion of studies were discussed until consensus was reached. Eventually, 41 studies obtained from the electronic database search were included. Nine studies were included with one of the other search strategies (one through searching reference lists, three from conference proceedings, five via contacting authors). In nine cases, we contacted authors because we could not obtain a copy of a dissertation or article. As in two cases two papers reported on the same sample but different outcome measures, we combined these papers and treated them as one study (^{41,42} and ^{43,44}).

The update of the search resulted in 805 new titles. After screening titles and abstracts, 777 titles were excluded. The remaining 28 studies were evaluated in more detail. Eventually, six new studies were added to the meta-analysis. However, one study was later excluded from further analyses, as it yielded an effect size that was considered an extreme outlier.⁴⁵ As a consequence, 53 unique studies were included in the present meta-analysis. See Figure 1 for a flow diagram of the study selection process, and Appendix S2 for the references of all included studies.

Coding

All studies were coded by two coders (AvM and AMM or KBvdH) for type of sleep problem, treatment characteristics (e.g., daily duration of treatment in hours per day, number of treatment days), participant characteristics (e.g., mean age, percentage of men in the sample), and characteristics of methods and results (e.g., type of design, subjective or objective outcomes). In case of discrepancies in the coding, the results were discussed until both coders agreed. See Table 1 for an overview of the studies and their characteristics.

Table 1. Overview of the studies included in the present meta-analysis

page 90 - 95 >>

| AUTHOR(S) | TYPE OF SLEEP PROBLEM¹ | STUDY DESIGN | TYPE OF MEASURES² |
|---------------------------------------|--|-------------------------------|-------------------------------------|
| Akyar & Akdemir 2013 [1] ³ | insomnia | within-subjects | subjective |
| Ando et al. 1999 [2] | CRSD ⁴ | RCT ⁵ | objective, subjective |
| Avery et al. 1993 [3] | other | RCT | subjective |
| Avery et al. 1994 [4] | other | RCT | subjective |
| Avery et al. 2002 [5] | other | RCT | subjective |
| Barbero 2013 [6] | CRSD | within-subjects | subjective |
| Bjorvatn et al. 2007 [7] | CRSD | randomised cross-over | objective, subjective |
| Burkhalter et al. 2015 [8] | other | RCT | objective |
| Burns et al. 2009 [9] | Alzheimer / dementia | within-subjects ⁸ | objective, subjective |
| Campbell & Dawson 1991 [10] | other | within-subjects ⁹ | objective |
| Campbell et al. 1993 [11] | CRSD | controlled trial | objective |
| Cole et al. 2002 [12] | CRSD | RCT | objective, subjective |
| Colenda et al. 1997 [13] | Alzheimer / dementia | within-subjects | objective |
| Cooke et al. 1998 [14] | insomnia | within-subjects | objective |
| Danielsson et al. 2012 [15] | CRSD | within-subjects ¹¹ | subjective |
| Dowling et al. 2008 [16] | Alzheimer / dementia | RCT | objective |
| Fetveit et al. 2003 [17] | Alzheimer / dementia | within-subjects | objective, subjective |
| Figueiro et al. 2014 [18] | Alzheimer / dementia | within-subjects | objective, subjective |
| Fontana-Gasio et al. 2003 [19] | Alzheimer / dementia | RCT | objective |
| Friedman et al. 2009 [20] | insomnia | RCT | objective, subjective |
| Geerdink et al. 2012 [21] | CRSD | cross-over | objective, subjective |
| Geerdink et al. 2013 [22] | CRSD | RCT | objective |
| Giménez et al. 2010 [23] | CRSD | randomised cross-over | objective, subjective |
| Guilleminault et al. 1995 [24] | insomnia | RCT ¹⁵ | objective, subjective |

| NR. OF TREATMENT DAYS | DAILY TREATMENT DURATION (h / day) | NR. OF PARTICIPANTS (light condition)² | MEAN AGE (light condition) | % MEN TOTAL (light condition) |
|------------------------------|---|--|-----------------------------------|--------------------------------------|
| 30 | 0.5 | 24 (24) | 80.0 (80.0) | 33.3 (33.3) |
| 12 | 3 | 10 (5) | 33.5 (34.4) | 70.0 (80.0) |
| 7 | 2 | 20 (11) | 35.3 (35.0) | 29.6 (28.6) |
| 7 | 1.5 | 19 (10) | 37.6 (35.8) | 10.5 (10.0) |
| 7 | 1.8 | 50 (28) | 37.3 (36.3) | 14.0 (17.9) |
| 14 | 1.3 ⁶ | 23 (23) | 15.0 (15.0) | 72.0 (72.0) |
| 4 ⁷ | 0.5 | 17 (17) | 42.0 (42.0) | 94.1 (94.1) |
| 21 | 0.5 | 28 (14) | 59.6 (60.7) | 50.0 (53.3) |
| 14 | 2 | 22 (22) | 84.5 (84.5) | 27.3 (27.3) |
| 8.5 ¹⁰ | 2 | 6 (6) | 68.4 (68.4) | unknown |
| 12 | 2 | 16 (8) | 70.4 (unknown) | 43.8 (50.0) |
| 26 | 4 | 54 (28) | 25.0 (unknown) | 54.2 (unknown) |
| 10 | 2 | 5 (5) | 76.4 (76.4) | unknown |
| 14 | 0.5 | 10 (10) | 79.4 (79.4) | 0 (0) |
| 14 | unknown | 30 (30) | 22.0 (22.0) | 50.0 (50.0) |
| 50 | 1 | 35 (18) | 85.5 (89.0) | 14.0 (unknown) |
| 14 | 2 | 11 (11) | 86.1 (86.1) | 9.1 (9.1) |
| 28 | 11 | 14 (14) | 86.9 (86.9) | 35.7 (35.7) |
| 21 | 1 | 13 (9) | 85.6 (86.8) | 7.7 (0) |
| 84 | 0.8 | 26 (19) 25 (18) ¹² | 63.6 (unknown) | 29.4 (unknown) |
| 3 | 1 ¹³ | 13 (13) | 25.0 (25.0) ¹⁴ | 53.8 (53.8) |
| 9 | 0.5 | 42 (21) | 21.4 (unknown) | 45.2 (unknown) |
| 14 | 0.5 | 23 (23) | 30.0 (30.0) | 45.7 (45.7) |
| 28 | 0.8 | 20 (10) | 44.0 (unknown) | 43.8 (unknown) |

| AUTHOR(S) | TYPE OF SLEEP PROBLEM¹ | STUDY DESIGN | TYPE OF MEASURES² |
|--|--|-------------------------------|-------------------------------------|
| Hajek et al. 1989 [25] | other | within-subjects | objective, subjective |
| Hansen et al. 1987 [26] & Lingjaerde et al. 1985 [36] | other | within-subjects ¹⁶ | objective, subjective |
| Ho 2001 [27] | insomnia | within-subjects | objective, subjective |
| Kirisoglu & Guilleminault 2004 [28] | insomnia | within-subjects | objective, subjective |
| Kobayashi et al. 2001 [29] | Alzheimer / dementia | within-subjects | subjective |
| Lack & Wright 1993 [31] | insomnia | within-subjects ¹⁸ | objective |
| Lack et al. 1994 [34] | insomnia | within-subjects ¹⁹ | objective |
| Lack et al. 2005 [32] | insomnia | controlled trial | objective, subjective |
| Lack et al. 2007a [30] | CRSD | RCT | objective, subjective |
| Lack et al. 2007b [33] | insomnia | RCT | objective, subjective |
| Lederle et al. 2010 [35] | insomnia | randomised cross-over | objective, subjective |
| McCurry et al. 2011 [37] | Alzheimer / dementia | RCT | objective |
| Mishima et al. 1994 [38] | Alzheimer / dementia | within-subjects ¹⁶ | objective, subjective |
| Münch et al. 2011 [39] | insomnia | within-subjects ²⁰ | objective, subjective |
| Murphy & Campbell 1996 [40] | insomnia | within-subjects | objective |
| Pallesen et al. 2005 [41] | insomnia | RCT | objective, subjective |
| Palmer et al. 2003 [42] | CRSD | RCT | objective, subjective |
| Rosenthal et al. 1990 [43] | CRSD | randomised cross-over | objective, subjective |
| Satlin et al. 1992 [44] | Alzheimer / dementia | within-subjects | subjective |
| Saxvig et al. 2014 [45] & Wilhelmssen-Langeland et al. 2013 [54] | CRSD | RCT | objective, subjective |
| Sciolla et al. 1997 [46] | other | RCT | subjective |
| Sharkey et al. 2011 [47] | CRSD | RCT | objective, subjective |
| Sinclair et al. 2014 [48] | other | RCT | subjective |

| NR. OF TREATMENT DAYS | DAILY TREATMENT DURATION (h / day) | NR. OF PARTICIPANTS (light condition)² | MEAN AGE (light condition) | % MEN TOTAL (light condition) |
|------------------------------|---|--|-----------------------------------|--------------------------------------|
| 10 | 4 | 7 (7) | 55.0 (55.0) | 85.7 (85.7) |
| 5 | 0.5 | 9 (9) | 40.7 (40.7) | 77.8 (77.8) |
| 2 | 3 | 38 (38) | 79.8 (79.8) | 0 (0) |
| 60 | 0.8 ¹⁷ | 15 (15) | 65.3 (65.3) | 26.7 (26.7) |
| 21 | 1 | 10 (10) | 81.2 (81.2) | 40.0 (40.0) |
| 2 | 4 | 9 (9) | 53.4 (53.4) | 55.6 (55.6) |
| 2 | 4 | 22 (11) | unknown | unknown |
| 2 | 4 | 24 (13) | 51.2 (unknown) | 48.0 (unknown) |
| 7 | 2 | 18 (12) | 28.2 (unknown) | 5.6 (unknown) |
| 7 | 1 | 16 (8) | 29.0 (unknown) | 31.3 (25.0) |
| 21 | 4 | 33 (33) | 66.5 (66.5) | 30.3 (30.3) |
| 49 | 1 | 67 (34) | 80.9 (80.6) | 46.5 (44.0) |
| 28 | 2 | 14 (14) | 75.0 (75.0) | unknown |
| 4 | 2 | 10 (10) | 63.3 (63.3) | 40.0 (40.0) |
| 12 | 2 | 16 (16) | 73.1 (73.1) | 50.0 (50.0) |
| 21 | 0.5 | 31 (17) | 63.1 (unknown) | 41.9 (23.5) |
| 28 | 2.5 | 47 (24 ²¹) | 70.0 (unknown) | 44.7 (unknown) |
| 14 | 2 | 20 (20) | unknown | unknown |
| 7 | 2 | 10 (10) | 70.1 (70.1) | 90.0 (90.0) |
| 14 | 0.6 ²² | 20 (10) | 20.8 (20.7) | 25.0 (20.0) |
| 14 | 1 | 6 (4) | 36.8 (unknown) | 100 (100) |
| 6 | 1 | 25 (12) | 21.8 (22.7) | 48.0 (50.0) |
| 28 | 0.8 | 20 (10) ²³ | 44.9 (47.2) | 75.0 (80.0) |

| AUTHOR(S) | TYPE OF SLEEP PROBLEM¹ | STUDY DESIGN | TYPE OF MEASURES² |
|--------------------------------|--|-------------------------------|-------------------------------------|
| Skjerve et al. 2004 [49] | Alzheimer / dementia | within-subjects | objective, subjective |
| Suhner et al. 2002 [50] | insomnia | within-subjects | objective |
| Van de Werken et al. 2010 [51] | CRSD | randomised cross-over | objective, subjective |
| Videnovic et al. 2014 [52] | other | within-subjects ²⁵ | subjective |
| Weber et al. 2013 [53] | other | RCT | objective, subjective |
| Williams et al. 2002 [55] | other | within-subjects ²⁷ | objective, subjective |

1. According to our classification in four categories.
2. For the outcomes analysed in this meta-analysis.
3. The reference numbers correspond with the references in Appendix S2.
4. Circadian rhythm sleep disorder.
5. Randomised controlled trial.
6. 30-120 minutes, but we took the average for the moderator analysis.
7. Participants received light treatment during four days of day shift and four days of night shift. We averaged the effect sizes.
8. This study was a RCT, but we did not use the control group data in our analyses.
9. This study had a control group, but we did not use the control group data in our analyses.
10. 7-10 days, but we took the average for the moderator analysis.
11. This study consisted of two groups of which the second group received cognitive behaviour therapy after receiving light therapy. However, we only included the light treatment data in our analyses.
12. This study reports effect sizes for both morning light therapy and evening light therapy. They were both included in the analyses.
13. There was also a condition with 30 minutes of light exposure, but we did not use this in our analyses.
14. 23-27, but we took the average for the moderator analysis.
15. This study had three groups. We calculated the effect size for the comparison between the structured sleep hygiene with early morning light therapy group and the structured sleep hygiene group.
16. This study also included a healthy control group, but we did not use these data in our analyses.
17. There was also a condition with 20 minutes of light exposure, but we did not use this in our analyses.
18. Two participants of this study also participated in a control condition, but we did not use this in our analyses.

| NR. OF TREATMENT DAYS | DAILY TREATMENT DURATION (h / day) | NR. OF PARTICIPANTS (light condition)² | MEAN AGE (light condition) | % MEN TOTAL (light condition) |
|------------------------------|---|--|-----------------------------------|--------------------------------------|
| 28 | 0.8 | 10 (10) | 79.4 (79.4) | 70.0 (70.0) |
| 10 ²⁴ | 2 | 15 (15) | 71.5 (71.5) | 53.3 (53.3) |
| 1 | 0.5 | 16 (16) | 22.8 (22.8) | 50.0 (50.0) |
| 14 | 2 | 15 (15) | 63.1 (unknown) | 43.3 (unknown) |
| 42 | 0.5 | 25 (13) ²⁶ | 24.3 (unknown) | 50.0 (unknown) |
| 84 | 1 | 30 (30) | 44.5 (44.5) | 43.3 (43.3) |

19. *This study is a RCT, but we did not use the control group in most of our analyses.*
20. *This study is a RCT with two light conditions, but we combined these data in our analyses.*
21. *The sample size of the light group was not reported, but we estimated this at 24.*
22. *30-45 minutes, but we took the average for the moderator analysis.*
23. *There was also a third group included in this study, but we did not use these data for our analyses.*
24. *9-11 days, but we took the average for the moderator analysis.*
25. *This study is a RCT, but we did not use the control group in our analyses.*
26. *There were 18 participants described in the abstract we used, but for two outcome measures we obtained additional information from one of the authors based on 25 participants.*
27. *This study used a cross-over design but we did not use these data in our analyses.*

**INITIAL PHASE LITERATURE SEARCH
(November 2012)**

**UPDATE LITERATURE SEARCH
(March 2015)**

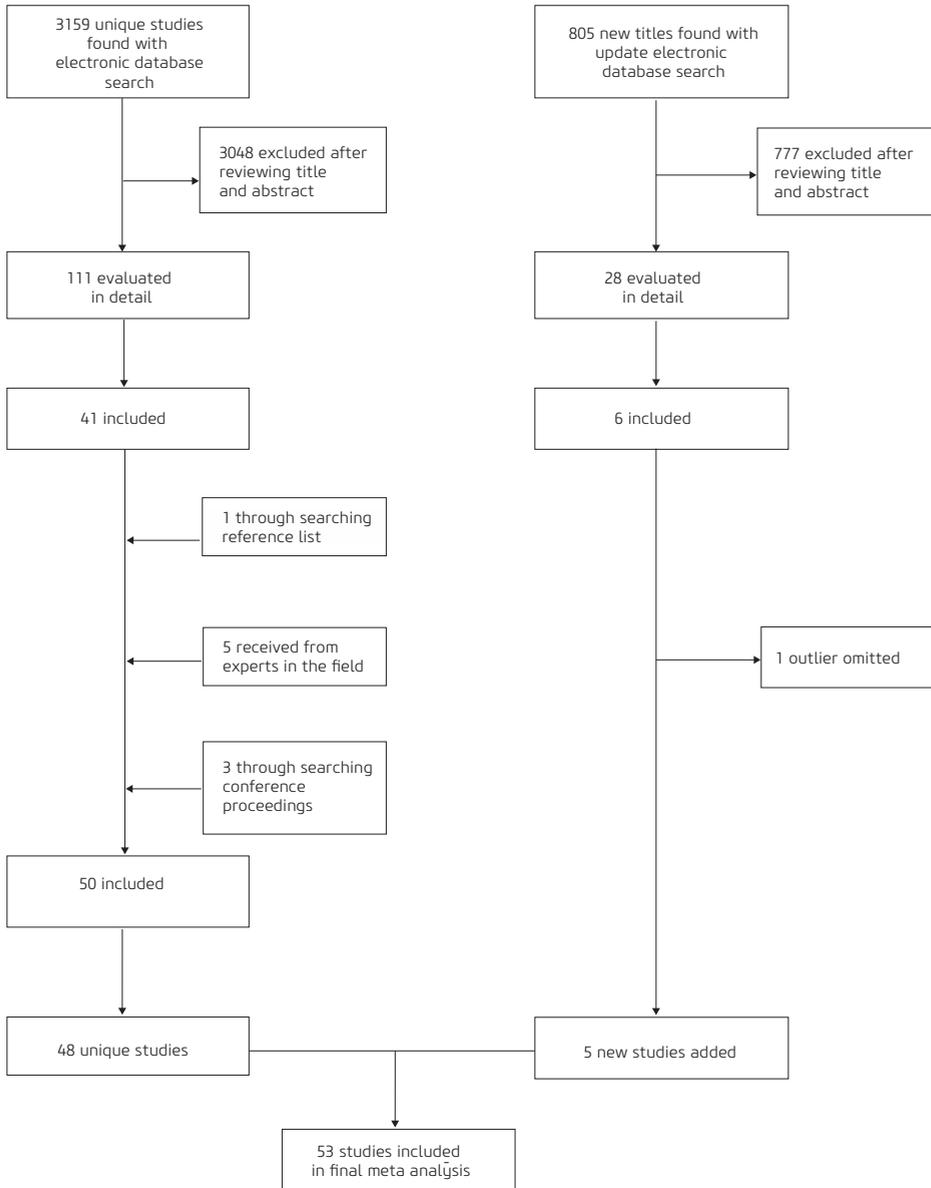


Figure 1. Flow chart of study selection process

In order to conduct analyses for specific sleep problems separately, we divided all studies in categories according to the primary sleep problem targeted in the study. In this way we found four categories: circadian rhythm sleep disorders, insomnia, sleep problems related to Alzheimer's disease / dementia, and other sleep problems. Papers reporting on participants with CRSD on basis of International Classification of Sleep Disorders (ICSD) criteria, sleep logs, or a clinical interview or screening questionnaire were assigned to the CRSD category. The insomnia category consists of papers reporting insomnia problems on ICSD criteria, self-reported insomnia complaints, a sleep diary, Pittsburgh Sleep Quality Index⁴⁶ > 5, or a clinical interview. Studies reporting on sleep problems in patients with Alzheimer or dementia were assigned to the category Alzheimer / dementia irrespective of the kind of sleep problem because of the institutionalised treatment of these patients. After categorising the first three types of sleep problems, a number of studies remained reporting on more diffuse sleep complaints, or sleep problems related to somatic complaints (e.g., traumatic brain injury, HIV, chronic fatigue syndrome) or mental disorders (e.g., winter depression). These studies were assigned to the category 'Other'.

Calculation of effect sizes

We calculated Hedges' *g* effect sizes and associated standard errors using the formula's given by Lipsey and Wilson.⁴⁷ Hedges' *g* effect sizes are similar to Cohen's *d*, but are corrected for the bias inherent to Cohen's *d* that tends to overestimate effect sizes in small samples.⁴⁸

We distinguished the following outcome measures: circadian outcome (e.g., Dim Light Melatonin Onset, core body temperature rhythm), bedtime (or sleep onset time), get up time (or wake-up time), sleep onset latency, total sleep time, time in bed, wake after sleep onset (or number of awakenings), early morning awakening, sleep efficiency, sleepiness (or alertness), sleep quality, insomnia symptoms, and fatigue. Sleep quality is self-reported sleep quality (or satisfaction) or the score on a sleep quality questionnaire (e.g., Pittsburgh Sleep Quality Index).⁴⁶ The outcome variable insomnia symptoms was formed by scores on insomnia symptoms questionnaires (e.g., Insomnia Severity Index,⁴⁹ Bergen Insomnia Scale).⁵⁰

Effect sizes and standard errors were calculated on the basis of reported means, standard deviations, and *p*-values or correlations between pre- and post-measurements. For studies that did not report the exact *p*-value or the exact pre-post correlation, we estimated the effect sizes under the assumption of a 0.5 correlation. When means and standard deviations were not reported, as was the case in some of the within-subject designs, effect sizes were calculated

by using the p-value, sample size and correlation. If no exact p-value was given, we assumed a p-value of 0.5 for non-significant results and 0.05 for significant results, yielding a conservative estimate of the effect size and associated standard error. For some cases with missing statistics we were able to obtain additional information from the authors of the original publications.

Some studies also reported follow-up effects, but those studies differed in whether the light treatment continued until the follow-up. Therefore, we decided to calculate effect sizes for the change from pre- to post-treatment only. For studies with a control group, we only calculated effect sizes for comparisons with non-effective treatments such as placebo (dim light); we did not make comparisons with alternative treatments such as melatonin treatment. For studies with more than two active light conditions, we included the a-priori determined strongest light therapy condition (i.e. the condition with the highest light intensity,^{51,52} or the condition with the longest treatment duration).^{53,54}

For each study, at least one effect size was calculated by two independent coders (AvM and AMM or KBvdH). In case of a discrepancy, this was discussed until agreement was reached. For studies in which the same outcome variables were measured in multiple ways (e.g., by sleep diary and actigraphy), separate effect sizes for subjective and objective measures were calculated and included in the analyses.

To enable the possibility to conduct an overall analysis, effect sizes had to be coded in the same direction. Otherwise, for instance, phase advances in DSPS and phase delays in advanced sleep phase syndrome (ASPS) would level each other out. Therefore, effect sizes were given a positive sign if the effect was in the hypothesised direction (e.g., sleep latency decreased with light therapy), and a negative sign if the effect was not in the hypothesised direction. This was discussed for each individual study by at least two coders (AvM and AMM or KBvdH). Time in bed was always given a positive sign when it was extended and a negative sign when it was shortened, as it was often not clear whether the goal of the study was to increase or decrease time in bed. Time in bed was not included in the overall analysis. As sleepiness and alertness are opposite outcomes, we coded the effect sizes so that a positive effect indicates an improvement (i.e. a decrease in sleepiness or an increase in alertness).

Data analyses

The analyses were conducted with Metafor, a package in the computer program R that includes many different functions for conducting meta-analyses.⁵⁵ We carried out a multivariate meta-analysis of all outcome variables combined (except time in bed) and multiple univariate meta-analyses of each outcome variable separately. We checked whether there was variance in effect sizes between studies by conducting Q-tests for heterogeneity. We also tested moderator effects. All analyses were conducted once for all sleep problems and once for each sleep problem category. We took a multilevel approach to take the dependency between multiple outcomes within studies into account.

We applied random effects models. The random effects model assumes that the studies included in the meta-analysis yield a random sample of effect sizes, and allows for the true effect size to vary between studies.⁴⁸ As we consider the studies in this meta-analysis as heterogeneous, the random effects model was deemed applicable.

To investigate whether the studies included in our meta-analysis are a representative sample of all published and unpublished studies that are conducted in the field, we checked for publication bias, by adding the standard errors of the effect sizes as a moderator in the analyses (Egger's test).⁵⁶ Significant effects indicate publication bias.

RESULTS

Overall analyses

Average effect sizes are reported in Table 2. For the multivariate analyses of all outcome measures, we found significant effects of light therapy for all sleep problems combined, as well as for CRSD, insomnia, sleep problems related to Alzheimer's disease / dementia, and other types of sleep problems. The effects were in the expected directions, indicating that light therapy was effective in diminishing sleep problems.

In the analyses of separate outcome measures for all sleep problems combined, we also found significant effect sizes in the expected directions. Only for early morning awakening no significant effect was found. Effect sizes for the sleep time variables were generally smaller than for sleep complaints, such as sleepiness, fatigue or insomnia symptoms. The largest effect sizes were found for circadian outcomes and insomnia symptoms. See the forest plot in Figure 2 for an illustration of the effect sizes for circadian outcomes for the separate studies.

Table 2. Light therapy effect size estimates for all sleep problems combined and by category of sleep problems

| Outcome | ALL SLEEP PROBLEMS | | | | CRSD | | | |
|-------------------------------|--------------------|------|---------|----------|------|-----|--------|----------|
| | k | n | g | Q | k | n | g | Q |
| Multivariate an. | | | | | | | | |
| All outcomes | 53 | 1154 | 0.39** | 648.84** | 15 | 374 | 0.41** | 193.59** |
| Univariate an. | | | | | | | | |
| Circadian | 22 | 436 | 0.63** | 62.40** | 10 | 237 | 0.62** | 33.70** |
| Bedtime / sleep onset time | 20 | 489 | 0.27* | 61.15** | 10 | 263 | 0.32† | 28.38** |
| Get-up time / wake-up time | 18 | 440 | 0.26** | 33.67* | 10 | 285 | 0.33* | 18.31* |
| Sleep onset latency | 20 | 387 | 0.42** | 72.09** | 5 | 123 | 0.22 | 9.42 |
| Total sleep time | 32 | 689 | 0.25** | 111.66** | 7 | 166 | -0.01 | 20.16* |
| Time in bed | 10 | 251 | -0.25** | 11.32 | 3 | 46 | -0.37 | 1.01 |
| Wake after sleep onset | 17 | 421 | 0.35** | 51.46** | 3 | 83 | 0.30 | 11.44* |
| Early morning awakening | 4 | 72 | 0.21 | 13.80* | 1 | 20 | -0.19 | 5.18* |
| Sleep efficiency | 20 | 451 | 0.35** | 56.85** | 4 | 100 | 0.26 | 13.97* |
| Sleepiness / alertness | 20 | 437 | 0.41** | 37.00* | 8 | 179 | 0.37** | 14.61 |
| Sleep quality | 18 | 396 | 0.49** | 42.85** | 4 | 102 | 0.29 | 2.01 |
| Insomnia symptoms | 5 | 140 | 0.73** | 13.56* | 3 | 73 | 0.66† | 7.81* |
| Fatigue | 7 | 123 | 0.47* | 21.57** | 1 | 20 | - | - |

Note: k = number of studies included in the analysis; n = number of participants in the analysis (the total numbers of outcomes and observations included in the analyses are larger as most studies report on multiple outcomes. For example, for the multivariate analysis of all sleep problems the total number of outcomes is 251 (from 53 studies) and the total number of observations is 5546 (from 1154 participants)); g = average effect size (Hedges' g); Q = Q-statistic for the heterogeneity test.

| INSOMNIA | | | | ALZHEIMER / DEMENTIA | | | | OTHER SLEEP PROBLEMS | | | |
|----------|-----|-------------------|--------------------|----------------------|-----|---------|--------------------|----------------------|-----|--------|-------------------|
| k | n | g | Q | k | n | g | Q | k | n | g | Q |
| 15 | 334 | 0.47** | 321.46** | 11 | 211 | 0.30** | 48.99 [†] | 12 | 235 | 0.39** | 79.96** |
| 7 | 112 | 0.95** | 6.68 | 1 | 14 | - | - | 4 | 73 | 0.21 | 4.23 |
| 7 | 166 | 0.09 | 19.78* | 1 | 13 | - | - | 2 | 47 | 0.49 | 1.94 |
| 5 | 95 | 0.29 [†] | 11.27 [†] | 1 | 13 | - | - | 2 | 47 | 0.07 | 0.29 |
| 9 | 179 | 0.45 [†] | 52.99** | 4 | 48 | 0.58* | 5.78 | 2 | 37 | 0.41* | 0.62 |
| 13 | 285 | 0.44* | 62.68** | 8 | 181 | 0.26** | 6.72 | 4 | 57 | 0.13 | 13.12** |
| 4 | 114 | -0.28 | 5.29 | 3 | 91 | -0.37** | 2.09 | - | - | - | - |
| 8 | 204 | 0.47 [†] | 16.62 | 5 | 128 | 0.20 | 10.37 [†] | 1 | 6 | - | - |
| 1 | 31 | 0.24 | 3.43 [†] | 2 | 21 | 0.54 | 2.04 | - | - | - | - |
| 8 | 195 | 0.38 [†] | 22.72* | 5 | 115 | 0.38** | 6.09 | 3 | 41 | 0.90 | 8.60* |
| 4 | 108 | 0.44** | 3.72 | 1 | 10 | - | - | 7 | 140 | 0.48* | 18.12* |
| 4 | 144 | 0.77 [†] | 28.31** | 4 | 45 | 0.66* | 7.10 [†] | 6 | 105 | 0.41** | 3.13 |
| 2 | 67 | 0.80** | 5.74 [†] | - | - | - | - | - | - | - | - |
| 2 | 31 | 1.13** | 0.78 | - | - | - | - | 4 | 72 | 0.16 | 7.41 [†] |

A significant Q-statistic indicates that there is substantial variability in effect sizes between studies.

CRSD = circadian rhythm sleep disorder. [†] = $p < .10$, * = $p < .05$, ** = $p < .01$.

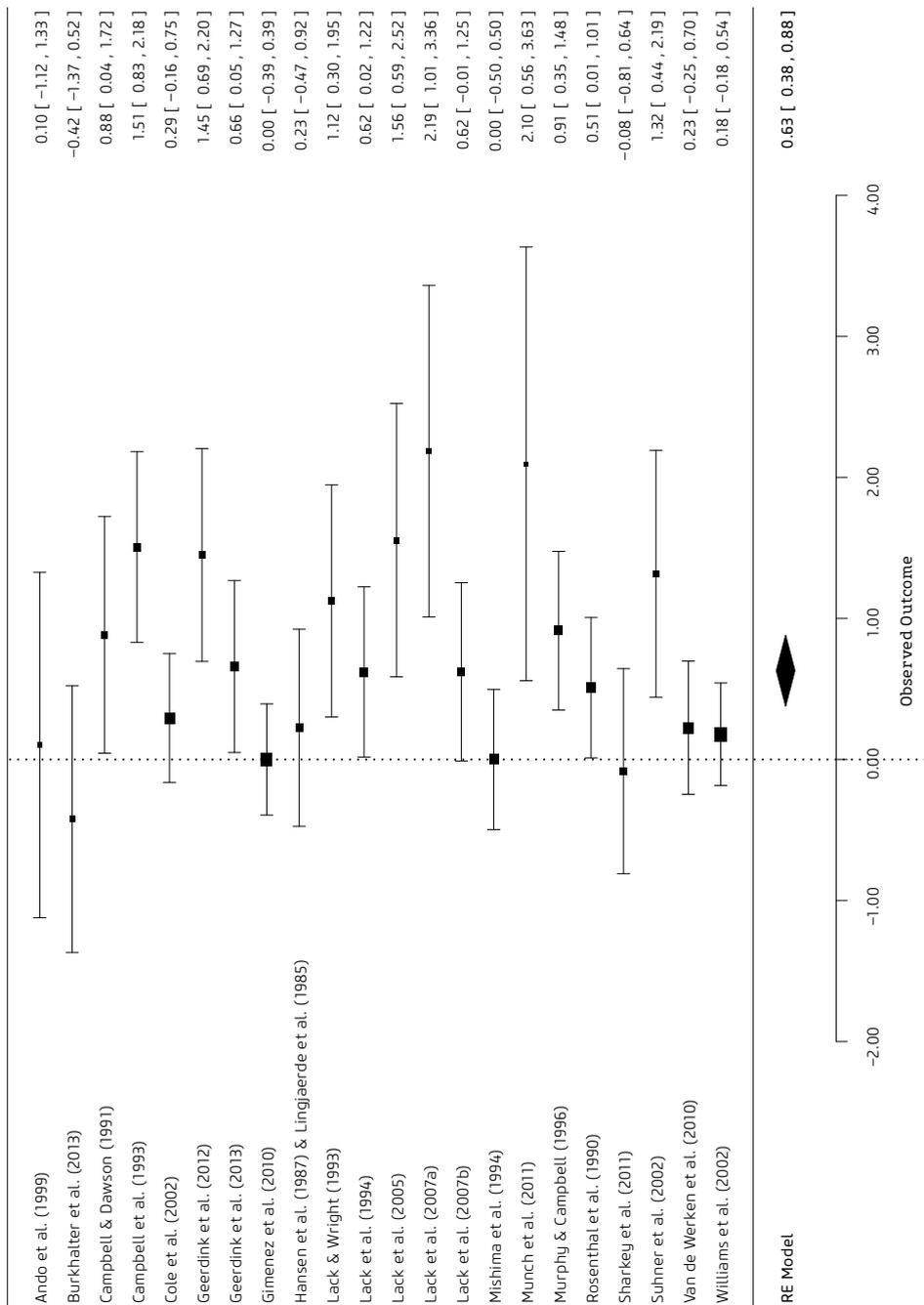


Figure 2. Forest plot of studies included in the overall analysis with circadian outcome \cup

When we evaluated the average effect sizes per outcome variable for the four categories of sleep problems separately, we found that for CRSD 3 out of 12 outcomes were significant, and for insomnia 5 out of 13 outcomes were significant. Five out of 7 outcomes were significant for sleep problems related to Alzheimer's disease / dementia, and for other sleep problems 3 out of 9 outcomes were significant. Effect sizes for the sleep outcomes in the different sleep problem categories showed an inconsistent pattern. Apart from non-significant outcomes for bedtime (or sleep onset time), wake after sleep onset, and early morning awakening, for each outcome a significant effect size was found in at least one sleep problem category. Although the overall effect sizes were positive, negative results (i.e. negative or opposite effects) for at least one outcome were found in 25% (other category) to 53% (CRSD category) of the studies.

In several cases, the Q-test for heterogeneity showed a significant result. This indicated that there was substantial variability in effect sizes between studies. In subsequent analyses, we investigated whether this variability could be explained by moderator variables.

Moderator analyses

We first examined moderators for all sleep problems combined, but none of the moderators was found significant (see Table 3 for an overview). When we examined moderators within the separate categories of sleep problems we found a moderating effect of study design for CRSD, which indicates that smaller effects were found for RCT's than for other types of study design. A subsequent analysis showed that the overall effect of light therapy in CRSD ($g = 0.41$, $p < 0.01$) became smaller if we only considered the 12 RCT's ($g = 0.27$, $p = 0.02$). A significant positive effect of light intensity was found for insomnia, indicating that effect sizes were larger in studies using a stronger light intensity. For studies in the insomnia category, the mean reported light intensity was 4800 lux, and the effect size for light therapy was $g = 0.47$. The moderator effect of light intensity ($b = 0.08$) indicates that the expected effect size in an insomnia study using, for example, 6800 lux would be estimated at 0.63. We also found an effect of the number of men in the sample for studies investigating light therapy in sleep problems related to Alzheimer's disease / dementia. Studies with a higher percentage of men reported a smaller effect size.

In most analyses there was still significant residual heterogeneity left. However, this was not true for some analyses in the category sleep problems related to Alzheimer's disease / dementia, where heterogeneity was sufficiently explained.

Table 3. Moderator analyses for all sleep problems combined and by category of sleep problems

| Moderator | ALL SLEEP PROBLEMS | | CRSD | | INSOMNIA | | ALZHEIMER / DEMENTIA | | OTHER SLEEP PROBLEMS | |
|---------------------------------------|--------------------|-------|------|---------|----------|--------------------|----------------------|--------------------|----------------------|--------------------|
| | k | est. | k | est. | k | est. | k | | k | est. |
| 1. CRSD | 53 | 0.01 | | | | | | | | |
| 2. Insomnia | 53 | 0.09 | | | | | | | | |
| 3. Alzheimer / dementia | 53 | -0.11 | | | | | | | | |
| 4. Other sleep problems | 53 | -0.03 | | | | | | | | |
| 5. Study design ⁱ | 53 | -0.14 | 15 | -0.68** | 15 | -0.08 | 11 | 0.13 | 12 | -0.07 |
| 6. Type of measures ⁱⁱ | 53 | -0.03 | 15 | 0.00 | 15 | -0.04 | 11 | -0.10 [†] | 12 | 0.07 |
| 7. Nr. of treatment days | 53 | 0.00 | 15 | -0.01 | 15 | 0.01 | 11 | 0.00 | 12 | -0.00 |
| 8. Daily treatment duration (h / day) | 52 | -0.02 | 14 | 0.02 | 15 | -0.13 [†] | 11 | 0.01 | 12 | -0.01 |
| 9. Lux (in thousands) | 48 | 0.02 | 12 | -0.01 | 14 | 0.08* | 11 | -0.01 | 11 | -0.02 |
| 10. Instructions | 53 | -0.02 | 15 | -0.09 | 15 | 0.22 | 11 | 0.03 | 12 | -0.43 [†] |
| 11. Mean age (years) | 51 | -0.00 | 14 | -0.00 | 14 | -0.00 | 11 | 0.02 | 12 | 0.00 |
| 12. % men | 48 | 0.00 | 14 | 0.00 | 14 | 0.00 | 9 | -0.01* | 11 | 0.01 |

Note: only one moderator was included in each analysis. CRSD = circadian rhythm sleep disorder; k = number of studies (the total number of outcomes included in the analyses is larger as most studies report on multiple outcomes); RCT = randomised controlled trial. [†] = $p < 0.10$, * = $p < 0.05$, ** = $p < 0.01$.

i. Coded as: 0) other than RCT and 1) RCT. Two studies^{7,66} that assigned participants alternately to the two conditions and randomised cross-over designs were also coded as RCTs.

ii. Coded as subjective vs. objective.

Publication bias

To check for publication bias, we conducted Egger's tests. We found significant effects for the following outcomes: circadian ($t(20) = 3.34, p < 0.01$), bedtime (or sleep onset time) ($t(22) = 3.04, p < 0.01$), wake after sleep onset ($t(23) = 2.18, p = 0.04$), sleepiness ($t(22) = 2.36, p = 0.03$), and sleep quality ($t(17) = 2.79, p = 0.01$). These findings imply that for 5 out of 13 outcomes there was an indication of publication bias.

DISCUSSION

The results of this meta-analysis showed that in general, light therapy is effective in treating sleep problems. For the overall analysis in which different sleep problems were combined, significant effects were found on all outcome variables, except early morning awakening, and all effects were in the expected directions. Most effect sizes indicated small to medium effects. The largest effects were found on circadian outcomes and insomnia symptoms.

In the analyses for the separate categories of sleep problems, we found significant effect sizes for CRSD, insomnia, sleep problems related to Alzheimer's disease / dementia, and other types of sleep problems. Effect sizes for sleep complaints, such as sleepiness, fatigue or insomnia symptoms were generally larger than for sleep time variables. Within the insomnia category large effects were found on circadian outcomes, insomnia symptoms, and fatigue.

Although light therapy leads to a shift in the circadian rhythm in CRSD and has an effect on get-up time, only a small effect on bedtime was found. This is contrary to results of a meta-analysis investigating effects of melatonin treatment on DSPS, in which an effect on sleep onset time but not on wake-up time was found.³⁵ A possible explanation for the effect on get-up time could be that light therapy often requires participants to get up early.

The finding that light therapy had larger effects on circadian outcomes than on sleep times is in accordance with results often found for melatonin treatment in DSPS.³⁵ This may not be surprising, as light is considered to exert a direct effect on the circadian rhythm, and may apart from its direct effect on alertness, more indirectly influence other aspects of sleep.² The absence of an effect on total sleep time corresponds with the fact that short sleep duration is not a primary characteristic of CRSD.⁵⁷ However, an effect on sleep onset latency would be expected, but was not significant.

Surprisingly, for studies investigating light therapy effects on participants

with insomnia, the effect on circadian outcomes was also larger than on the other sleep outcomes, and this effect was even larger than in CRSD. However, it must be noted that the majority of studies investigating circadian outcomes in insomnia used within-subjects designs, whereas none of the 10 studies for CRSD was a within-subjects design. So the effect for insomnia was not placebo-controlled. Similar to the results for CRSD, no significant effect was found on bedtime, but a borderline significant effect was found on get-up time.

A moderating design effect was found within the CRSD category, which indicated that effect sizes were smaller for RCT's. This result was according to our expectations, as we expected that studies with a control group (i.e. a higher quality of study design) would show smaller effects because of controlling for a placebo effect. It is surprising that only for CRSD an effect of RCT was found, as we had expected to find moderating effects of RCT for all sleep problem categories.

For insomnia we found a significant moderating effect of light intensity, indicating that studies using a higher light intensity found larger effects. This effect was according to our expectation, and we had hypothesised to find this effect for all sleep problem categories. The fact that we did not find significant effects of light intensity in the other categories of sleep problems might be explained by the fact that light intensity in itself is not always informative, as also wavelength and colour temperature should be taken into account.^{58,59} Possibly, studies with higher light intensity had less optimal other light characteristics. However, it must also be noted that most studies used 2000 to 10000 lux, which may not differ that much in effectiveness. Unfortunately we could not include other light characteristics in our analyses, as this information was not reported for the majority of studies. To gain better insight into the effects of light treatment, we recommend reporting full information on light characteristics in future studies.

For studies investigating light therapy for sleep problems related to Alzheimer's disease / dementia, we found that larger effect sizes were reported in studies with more female participants. A possible explanation may be that women generally report more sleep complaints than men,^{39,40} leaving more room for improvement after therapy.

The present meta-analysis has several limitations. First, as not all studies diagnosed participants according to the ICSD⁵⁷ or Diagnostic and Statistical Manual of Mental Disorders (DSM)⁶⁰ criteria, there might be a discrepancy in diagnoses among studies. However, because the applied criteria are generally used in clinical practice, we believe that most studies are well categorised. For future studies, diagnoses according to official criteria would contribute to the validity of the results.

Second, as we could not find any studies on light therapy in children that met our inclusion criteria and only one study that investigated light therapy in adolescents, we could not thoroughly examine whether light therapy has similar effects across the entire lifespan. As most studies focussed on (older) adults, more research should be conducted on light therapy effectiveness in children and adolescents.

Third, there remained significant residual heterogeneity for the majority of outcomes, which could not be explained by the moderators included in our study. This can partly be explained by the fact that we investigated each moderator separately as the number of studies in the analyses was not large enough to include multiple moderators in one analysis. In addition, for each moderator there are many other aspects of the treatment that are co-varying (e.g., number of treatment days, daily treatment duration, light intensity etc.). In our meta-analysis, many studies with a relatively short daily treatment duration used a stronger light intensity, so that we could not differentiate between different moderator effects. This may explain that no significant moderating effects were found of treatment characteristics such as number of treatment days and daily treatment duration. In order to isolate the effect of a treatment characteristic, a controlled study would be needed, such as the study of Dewan et al.²⁹ that found that increasing light duration from 1 to 3 hours increased the effect of light therapy, whereas increasing light intensity did not. Another limitation is that we were not able to investigate additional moderators such as wavelength and colour temperature of light, socio-economic status, and psychiatric comorbidity because the number of studies reporting these aspects was too small. Also, the majority of studies did not take into account, or did not report that they did, the recommendations provided by Van der Ploeg and O'Connor,⁶¹ e.g., measuring baseline light levels and ensuring treatment adherence. For optimal treatment, Eastman suggests to use a large light box, to try to cover the largest possible part of the visual field and to give light treatment during the optimal timing of the phase response curve.⁶² In future research, to optimally inform clinicians and researchers, it is desirable to include information about all these treatment aspects in research papers.

Finally, we found evidence of publication bias for 5 out of 13 sleep outcomes. This indicates that despite our effort to include non-published studies by checking conference proceedings, thesis databases and contacting authors, the studies that were included in our meta-analysis seem to systematically differ from studies that have been conducted but have not been reported. Typically, studies with larger significant effects are more easily published and therefore overrepresented.⁴⁸

The results of this meta-analysis show that overall light therapy has a small to medium effect. When examining the effect of light therapy on the different outcome measures and within the different sleep problem categories, light therapy showed significant effects on varying outcomes over the sleep problem categories, but most were small to medium. Considering the relatively small effects, light therapy does not seem a good alternative for, for example, cognitive behavioural treatment (CBT) for insomnia, for which large effects have been found.^{63,64} However, light therapy might be combined with CBT, to see whether there is an additive treatment effect. Gradisar et al. found positive effects when combining light therapy and adjusted CBT in DSPS.⁶⁵

The present meta-analysis is the first comprehensive review of the effectiveness of light therapy on different types of sleep problems. The results show generally small to medium treatment effects on sleep problems in general and on specific sleep problems in particular. However, we did find positive effect sizes for a large number of outcome measures. Interestingly and as expected, we found significant treatment effects for circadian outcomes. Furthermore, self-report measures such as insomnia symptoms showed medium to large effect sizes, indicating treatment improvement according to participants. We recommend therefore investigating in more detail the optimal use and technical aspects of light therapy.^{61,62}

PRACTICE POINTS

1. Generally, light therapy is effective for the treatment of sleep problems such as circadian rhythm sleep disorders, insomnia, and sleep problems related to Alzheimer's disease and dementia. However, most effect sizes indicate only small to medium effects.
2. Light therapy has largest effects on circadian outcomes and insomnia symptoms.
3. In the treatment of circadian rhythm sleep disorders, smaller effects of light therapy are found for randomised controlled trials.
4. In the treatment of insomnia, higher effect sizes were found for studies using a stronger light intensity.
5. In the treatment of sleep problems related to Alzheimer's disease / dementia, stronger effects were found for studies with more female participants.

RESEARCH AGENDA

1. Papers reporting on light therapy effectiveness should include full information on light (intensity, colour temperature, wavelength), treatment (duration, timing), and sample characteristics.
 2. Studies should take baseline light levels into account.
 3. Studies should report information on treatment adherence.
 4. Studies should apply RCT designs.
 5. More research should be conducted on the effectiveness of light therapy in children and adolescents.
 6. As mostly small effects were found, it may be recommended to further investigate the use of light therapy in combination with other treatments that have been proven effective, such as cognitive behavioural treatment.
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Conflicts of interest

The authors do not have any conflicts of interest to disclose.

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**The most important references are denoted by an asterisk.*

APPENDIX S1

Search strategy

MEDLINE

(Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R))

1. phototherapy/
2. phototherap*.ti,ab.3. heliotherapy/
4. heliotherap*.ti,ab.
5. (light adj3 (treatment* or exposure)).ti,ab.
6. bright light.ti,ab.
7. sunlight/
8. sunlight.ti,ab.
9. artificial light.ti,ab.
10. or/1-9
11. exp sleep disorders/
12. sleep*.ti,ab.
13. insomnia*.ti,ab.
14. dyssomnia*.ti,ab.
15. somnolence.ti,ab.
16. circadian rhythm/
17. jet lag syndrome/
18. jet lag*.ti,ab.
19. jetlag*.ti,ab.
20. night shift*.ti,ab.
21. nightshift*.ti,ab.
22. or/11-21
23. animals/ not humans/
24. 10 and 22
25. 24 not 23
26. randomized controlled trials as topic/
27. randomized controlled trial/
28. random allocation/
29. double blind method/
30. single blind method/
31. clinical trial/
32. clinical trial, phase i.pt.
33. clinical trial, phase ii.pt.
34. clinical trial, phase iii.pt.
35. clinical trial, phase iv.pt.
36. controlled clinical trial.pt.
37. randomized controlled trial.pt.
38. multicenter study.pt.
39. clinical trial.pt.
40. exp clinical trials as topic/
41. (clinical adj trial*).tw.
42. ((singl* or doubl* or treb* or tripl*) adj (blind*3 or mask*3)).tw.
43. placebos/
44. placebo*.tw.
45. randomly allocated.tw.
46. (allocated adj2 random*).tw.
47. or/26-46
48. case report.tw.
49. letter/
50. historical article/
51. or/48-50
52. 47 not 51
53. 25 and 52

APPENDIX S2

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