Original Article

Effects of exogenous melatonin supplementation on health outcomes: an umbrella review of meta-analyses based on randomized controlled trials

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Abstract

Various melatonin supplementations have been developed to improve health outcomes in various clinical conditions. Thus, we sought to evaluate and summarize the effect of melatonin treatments in clinical settings for health outcomes. We searched PubMed/Medline, Embase, and Cochrane Library from inception to 4 February 2021. We included meta-analyses of randomized controlled trials investigating the melatonin intervention for any health outcome. Based on the different effect sizes of each meta-analysis, we calculated random models' standardized mean differences or risk ratios. We observed robust evidence supported by statistical significance with non-considerable heterogeneity between studies for sleep-related problems, cancer, surgical patients, and pregnant women. Patients with sleep disorder, sleep onset latency (SMD 0.33, 95% CI: 0.10 – 0.56, $P < 0.01$) were significantly improved whereas no clear evidence was shown with sleep efficiency (1.10, 95% CI: -0.26 – 2.45). The first analgesic requirement time (SMD 5.81, 95% CI: 2.57 - 9.05, $P < 0.001$) of surgical patients was distinctly improved. Female patients under artificial reproductive technologies had significant increase in the top-quality embryos (SMD 0.53, 95% CI: 0.27 – 0.79, $P < 0.001$), but no statistically clear evidence was found in the live birth rate (SMD 1.20, 95% CI: 0.83 – 1.72). Survival at one year (RR 1.90, 95% CI: 1.28 – 2.83, $P < 0.005$) significantly increased with cancer patients. Research on melatonin interventions to treat clinical symptoms and sleep problems among diverse health conditions was identified and provided considerable evidence. Future well-designed randomized clinical trials of high quality and subgroup quantitative analyses are essential.

Keywords

Melatonin; Umbrella review; Randomized controlled trial; Clinical outcome

63 **Chemical compounds studied in this article**

64 Melatonin (PubChem CID:896); Inositol (PubChem CID:892); Clozapine (PubChem
65 CID:135398737); Olanzapine (PubChem CID:135398745); Risperidone (PubChem
66 CID:5073); Quetiapine (PubChem CID:5002); Midazolam (PubChem CID:4192); Oxazepam
67 (PubChem CID:4616); Alprazolam (PubChem CID:2118)

68

1. Introduction

Melatonin is an antioxidant, functioning as a hormone in systemic circulation of mammals. It is synthesized in the suprachiasmatic nucleus of the anterior pituitary gland, released into the circulation stimulated by the onset of darkness. [1] The reduction in melatonin production induces insulin resistance, sleep disturbance, and metabolic circadian disorganizations.[2][3] Exogenous melatonin supplementation has been used for many medical and surgical diseases over the last decades,[4] while its clinical importance has been recognized, particularly relating to sleep.[5,6]

It has demonstrated encouraging results for multiple health outcomes from appropriate administration. Low dosage of melatonin also has value as a sleep-promoting agent for children, whereas high doses have shown the hypnotic effects.[7,8] Moreover, evidence also supports the use as an anesthetic agent.[9] It has demonstrated encouraging results in surgical patients' preoperative anxiety score and postoperative pain score.[10] Melatonin has also been observed to favorably affect blood pressure among those with metabolic disorders.[11] Additionally melatonin supplementation has been observed to decrease the 1-year mortality and depressive symptoms of cancer.[12,13]

Melatonin supplement also likely to be safe, only with mild adverse effects, such as dizziness, headache, nausea, and sleepiness.[14] On the other hand, while the stipulation of its prescription or over-the-counter (OTC) availability varies by country,[15] it is widely used as a remedial measure for sleep disorders [16] and is the fourth most popular natural product taken by adults, and the second by children in the United States. Indeed, a significant increase in its use from 0.1% in 2007 to 0.7% in 2012 was reported.[17]

Despite several studies conducted on the effect of exogenous melatonin, considering that a

sizable number of nonprofessional individuals can use melatonin autonomously as an OTC drug, we contemplated the need for comprehensive research about the tendency of effects by the specific conditions. We extracted available data on the association between a patient's specific health condition and the effects of exogenous melatonin. An umbrella review of the existing quantitative analyses is important to provide a comprehensive summary of the scientific literature,[18] and an overview of the methodology of melatonin supplementation in a single reference state.

Therefore, this study aimed to summarize the meta-analyses to identify the effects of suitable administration of exogenous melatonin supplements on patients with various health conditions.

2 Methods

2.1 Literature search and eligibility criteria

We conducted an umbrella review of meta-analyses based on randomized controlled trials (PROSPERO registration: CRD42021234788).

Inclusion criteria were as follows, established by using the PICOS strategy (Table. S2):

(a) Study type: reviews including meta-analyses of randomized clinical trials (RCTs) only.

(b) Participants: patients who underwent supplementation of melatonin, for any health condition.

(c) Intervention: treatment including melatonin, via any route.

(d) Control: passive controls such as placebo, sedatives, or active controls.

(e) Outcomes: multiple health outcomes according to the condition of the patient.

We systematically searched PubMed/Medline, Embase, and the Cochrane Database of Systematic Reviews from database inception to Feb 4, 2021. Full details of the search strategy, including search terms used, are included in Appendix 1. In addition, we manually searched 11 articles to identify additional primary studies for the systematic search. Two investigators (LSJ and PS) identified eligible themes, independently screening the titles, abstracts, and full texts (Fig. 1). Any disagreements were resolved by consensus with a third reviewer (SJI).

Fig. 1. Search strategy: Flow diagram of selection of meta-analyses for the umbrella review

We included systematic reviews including network meta-analyses that provided meta-analyses of interventional studies, only with randomized controlled trials, that pooled any

combination of continuous variables, relative risk, or odds ratio comparing the same exposure with the same health outcome. For example, participants could be healthy, have a preexisting illness, or be pregnant. We included studies published in English only. The present study explored all health outcomes accessible through search inclusions. We excluded reviews that did not include a meta-analysis or did not present sufficient specific data (number of case and control, effect size, and 95% confidence intervals (CI)) for reanalysis, non-human studies, and meta-analyses that had melatonin analogs in the intervention but provided no independent quantitative analysis of melatonin.

If two or more meta-analyses studied a similar topic with the same patients' condition, we selected only one meta-analysis to avoid duplicate estimates. However, when the scope covered by the subject or the control condition in the study was different, it was classified and included. Finally, we included the latest article dealing with the same scope as the subject regardless of the number of RCTs included.

2.2 Data extraction

For each eligible study, two investigators (LSJ and PS) independently extracted the name of the first author, publication year, condition of the patient, number of subjects assigned to the intervention and control groups, or number of event/total each, and the metrics used in the original meta-analyses (e.g., Cohen's d, Hedges' g, the weighted mean difference [WMD], relative risk [RR] or odds ratio [OR]) along with the corresponding 95% confidence interval (CI) and quality of studies included in the meta-analyses, the interpretation under heterogeneity, and the publication bias. The dose of melatonin and comparative treatments was generally provided in mg/day, and we did not modify the original units of the data.

We extracted data from any study comparing melatonin exposure, including subgroup

analysis of high versus low dose responses. If a study presented several meta-analyses for various conditions or outcomes, we considered each of these separately.

Any disagreements between the two researchers (LSJ and PS) in extracted data were resolved by discussion with a third researcher (SJI).

2.3 Assessment of methodological quality of included studies

To assess the methodological quality of the meta-analyses, two investigators (LSJ and PS) independently assessed each eligible study using the AMSTAR 2 (A Measurement Tool to Assess Systematic Reviews 2), and any disagreements were resolved by discussion.[19]

AMSTAR 2 is a valid instrument to measure the construct validity and reliability of systematic reviews.[19] The assessment of quality scoring consists of 16 items, including critical domains of 7 items. It allows the critical judgment of the methodological of a systematic review. We recorded the total (A2) and the critical domain score (A2-CD) of each article by AMSTAR2. Criteria other than the main perspective of the AMSTAR 2 questionnaire were not included in the scoring.

2.4 Statistical Analysis

We aimed to provide the metrics of estimates from meta-analyses with random-effect models or risk ratio based on random-effect models.

We reanalyzed the data using the extracted individual study estimates using Comprehensive Meta-Analysis Software. We continued to use the data's original value correspondingly when standardized mean differences based on random effect models were provided. We converted a mean difference to standardized metrics and estimates of odds ratio to risk ratio, except for one association that provided insufficient data to reanalyze.[20] We calculated the summary effect

estimates and P values of reanalyzed meta-analyses with random effect models.

For continuous variables, we decided to organize consistent directional effect estimates. Regardless of the original direction of the outcomes provided, we decided to set the positive direction of the effect estimate to a beneficial direction. The positive direction of the effect size has converted to the helpful direction. We conserved the numerical estimates from previous studies in the same order if they were in the same direction as our aim. The effect size was converted to a positive value for calculations in the opposite direction to maintain consistent orientation. We evaluated heterogeneity between studies using the I^2 statistics.[21] We also performed Egger's test in order to detect publication bias.[22] Where I^2 exceeded 50% or 75%, heterogeneity was considered substantial or considerable, respectively.[23]

We preserved the original summary data provided by the meta-analysis of the review when the measurement was available but when data in the meta-analysis could not be reanalyzed.

We estimated the confidence interval in 95% prediction. We determined the statistical significance by the boundary of $P < 0.05$ and further assessed P values below 10^{-2}, 10^{-3}, and 10^{-4}.

2.5 Role of funding source

There was no funding source for this study. All authors had full access to all studies, and the corresponding authors had final responsibility for submitting for publication.

3 Results

3.1 Study selection

We identified 654 articles and excluded 595 after screening titles and abstracts (including duplicates). Of the 59 remaining articles, we excluded 35 articles after full-text screening for different reasons (Fig. 1). The 24 remaining articles reported data from 111 different meta-analyses. In addition, we included manually searched 11 articles to investigate supplementary studies for the systematic search.

The exclusion of thirty-five articles from systematic search was from the reasons provided. We provided the list of the excluded articles and reasons for exclusion in Appendix 3 and 4.

3.2 Study characteristics

The characteristics of the included studies are presented in Table. S3. These studies were published between 2010 and 2021. All studies were published in English.

After full-text screening, we independently assessed the total and critical domain score of AMSTAR2 (N = 35). The mean total AMSTAR2 score was 5.5±1.0 and the mean critical domain section of AMSTAR2 score was 13.7±1.3.

Twenty-two studies compared the effect of melatonin against, passive control including placebo, and thirteen studies of these studies used placebo controls alone. All the analyses included 3 to 30 randomized controlled trials, and the range of sample size was from 121 to 2673. Two studies compared with active control of benzodiazepine.[24,25] Four studies included children in the population,[25-28] and three of these conducted the meta-analyses only on children.[25,26,28]

Psychiatric disorder and Alzheimer's disease patients were the studied population in seven studies, sleep disorders in seven studies, surgical patients in five studies, perimenopausal or females of pregnant women in three studies, and metabolic syndrome in two studies. Patients suffering from oxidative stress, cancer, or non-intensive treatment rooms were considered in one study each.

All studies administered melatonin doses in the range of 1 to 20 mg per day for adults and 0.05mg/kg to 9mg for children. Overall, the duration of melatonin administration ranged from 3 to 3.5 years, or preoperative temporarily.[24,25,29] Diagnostic criteria for reported mental illness also varied, using NINCDS-ADRDA, ICD-10, or DSM-IV. [20,30-32]

The most frequently performed subgroup analysis was high versus low dose of melatonin. Six studies conducted such comparisons,[7,25,33-36] and the high-low dose boundary was considered 5 mg for adults and 0.2 mg/kg for children.

3.3 Psychiatric disorder, dementia, Alzheimer's disease

Based on patients with a psychiatric disorder, the health outcomes according to the underlying disorder or the sleep condition were comprehensively summarized. Overall, the analyzed meta-analysis outcomes had non-significant heterogeneity ($I^2 < 50\%$).

Table 1 Summary estimates of the associations between psychiatric disorder, dementia, Alzheimer’s disease outcomes, and melatonin treatment. Melatonin treatment versus passive control.

AD: Alzheimer’s disease, ADAS-cog: Alzheimer's Disease Assessment Scale cognitive subscale, ADHD: attention deficit hyperactivity disorder, MMSE: Mini-Mental State

231 Examination, NA: not available, NR: not recorded, N trials: number of RCT trials included in
232 meta-analysis, N total: number of patients included in meta-analysis, SMD: standardized mean
233 difference

234 º Indicates that the direction of positive effect size has been reversed

235 † Indicates the effect size obtained by reanalysis

236 * $p < 0.05$, ** $p < 0.01$, *** $p < 0.005$

237

238 **Fig. 2** Summary estimates of the associations between psychiatric disorder, dementia,
239 Alzheimer's disease outcomes, and melatonin treatment

240 Melatonin treatment versus passive control. Positive direction of the effect size has converted
241 to the beneficial direction.
242 A2: AMSTAR 2 total score, A2-CD: AMSTAR 2 critical domain score, AD: Alzheimer's
243 disease, ADAS-cog: Alzheimer's Disease Assessment Scale cognitive subscale, ADHD:
244 attention deficit hyperactivity disorder, d: day/days, MMSE: Mini-Mental State Examination,
245 NA: not available, NR: not recorded, SMD: standardized mean difference, w: week/weeks
246 Diamond indicates significant difference from control, $P < 0.05$; Circle indicates non-
247 significant effects.
248 º Indicates that the direction of positive effect size has been reversed

249 † Indicates the effect size obtained by reanalysis

250 * $p < 0.05$, ** $p < 0.01$, *** $p < 0.005$

251

As shown in Table 1 and Fig. 2, six reviews were included and meta-analysis of the psychiatric patients. We subdivided psychiatric disorders into specific conditioned of Alzheimer's disease, dementia, and other psychiatric disorders, including neurodevelopmental disorders, such as schizophrenia, autistic spectrum disorder, and attention deficit hyperactivity disorder (ADHD).

Three studies analyzed the associations between melatonin and the psychiatric patients' improvement of health outcomes. Diastolic blood pressure (SMD = 0.76, 95% [CI]: 0.30 to1.22, $P < 0.005$; 3 trials, N = 80, $I^2 = 0.0\%$) and systolic blood pressure (SMD = 0.42, 95% [CI]: 0.05 to 0.79, $P < 0.05$; 4 trials, N = 118, $I^2 = 0.0\%$) decreased favorably in low heterogeneity.[37] The association between melatonin and the variables related to sleep problems was estimated only in children. Specifically, associations were on total sleep time (SMD = 0.33, 95% [CI]: 0.05 to 0.61, $P < 0.05$; 3 trials, N = 199, $I^2 = 0.0\%$) and sleep onset latency (SMD = 0.66, 95% [CI]: 0.36 to 0.96, $P < 0.001$; 3 trials, N = 183, $I^2 = 0.0\%$) of children with neurological disorders,[26] reaching significant effects at $P < 10^{-3}$ with non-substantive heterogeneity except for total sleep time of autistic spectrum children (SMD = 1.00, 95% [CI]: 0.28 to 1.73, $P < 0.01$; 4 trials, N = 213, $I^2 = 79.3\%$). For patients with schizophrenia, there was no clear evidence of improvement in abnormal involuntary movement scales (SMD = 0.66, 95% [CI]: -1.49 to 2.81, $P > 0.05$; 4 trials, N = 130, $I^2 = 93.2\%$).[38]

Two studies including dementia patients, showed either $P < 0.05$ or $P > 0.05$ in outcomes related to sleep problems. Daytime/nighttime sleep ratio (SMD = 0.33, 95% [CI]: 0.02 to 0.64, $P < 0.05$; 3 trials, N =184, $I^2 = 0.0\%$), total sleep time duration during 10 days to 10 weeks (SMD = 0.25, 95% [CI]: 0.01 to 0.49, $P < 0.05$; 8 trials, N = 491, $I^2 = 40.2\%$), more than 4 weeks (SMD = 0.32, 95% [CI]: 0.05 to 0.60, $P < 0.05$; 6 trials, N = 426, $I^2 = 46.9\%$), sleep efficiency during 10 days to 8 weeks (SMD = 0.29, 95% [CI]: 0.04 to 0.53, $P < 0.05$; 4 trials,

N = 375, I^2 = 32.0%) showed significant improvements ($P < 0.05$) with low heterogeneity ($I^2 <$ 50%).[30,31]

No clear evidence was found for improvements in cognitive evaluations in measurements of MMSE (SMD = 0.26, 95% [CI]: -0.28 to 0.80, $P > 0.05$; 3 trials, N = 162, I^2 = 52.1%), ADAS-cog (SMD = 0.19, 95% [CI]: -0.14 to 0.52, $P > 0.05$; 3 trials, N = 162, I^2 = 0.0%), the incidence of adverse events (SMD = 0.25, 95% [CI]: -0.10 to 0.60, $P > 0.05$; 2 trials, N = 151, I^2 = 0.0%), and activities of daily living (SMD = 0.12, 95% [CI]: -0.21 to 0.45, $P > 0.05$; 3 trials, N = 162, I^2 = 0.0%).[30,31]

Two studies were specifically on Alzheimer's disease patients. Outcomes related to sleep problems showed conflicting results, either $P < 0.05$ or $P > 0.05$ and overall low heterogeneity ($I^2 < 50\%$). No clear evidence was shown in terms of improvement of the cognitive evaluations.[31,39]

3.4 Sleep disorder

As shown in Table 2 and Fig. 3, we included patients with sleep disorders or patients with other conditions having sleep problems. Seven reviews with sleep problems as the major outcome were identified in the meta-analysis based on randomized controlled trials.[26,28,29,32,34,40-43] We analyzed the comprehensive range of patient conditions, including insomnia, shift work sleep disorder, secondary sleep disorder, and delayed sleep phase disorder.

Table 2 Summary estimates of the associations between sleep disorder outcomes, and melatonin treatment. Melatonin treatment versus passive control.

DSPD: delayed sleep phase disorder, MLT: melatonin

† Indicates the effect size obtained by reanalysis

†† Indicates that the original study designed network meta-analysis

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.005$

Fig. 3. Summary estimates of the associations between sleep disorder outcomes, and melatonin treatment

Melatonin treatment versus passive control. Positive direction of the effect size has converted to the beneficial direction.

A2: AMSTAR 2 total score, A2-CD: AMSTAR 2 critical domain score, DSPD: delayed sleep phase disorder, MLT: melatonin, NA: not available, SMD: standardized mean difference

Diamond indicates significant difference from control, $p < 0.05$; Circle indicates non-significant effects.

† Indicates the effect size obtained by reanalysis

†† Indicates that the original study designed network meta-analysis

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.005$

Among children and adolescents with sleep-onset insomnia, sleep onset latency (SMD = 0.92, 95% [CI]: 0.48 to 1.36, $P < 0.001$; 6 trials, N = 326, $I^2 = 70.5\%$), total sleep time (SMD = 0.46, 95% [CI]: 0.21 to 0.71, $P < 0.001$; 5 trials, N = 262, $I^2 = 3.4\%$), and sleep onset time (SMD = 0.79, 95% [CI]: 0.54 to 1.04, $P < 0.001$; 6 trials, N = 323, $I^2 = 0.0\%$) were significantly improved, commonly reaching $P < 10^{-3}$. The effect of dim light melatonin onset, wake-up time, and light-off time showed no clear evidence ($P > 0.05$).[28]

In patients with sleep disorders including, shift work, overall data had non-significant heterogeneity ($I^2 < 50\%$). Total sleep time either next day or night and nocturnal sleep time was significantly improved, presenting $P < 0.05$. No statistically distinct difference was found between sleep onset latency, sleep quality, and nocturnal awakening frequency assessed subjectively and physiologically.[32,34]

Outcomes of patients with a secondary sleep disorder showed significantly improved sleep onset latency (SMD = 0.33, 95% [CI]: 0.10 to 0.56, $P < 0.01$; 7 trials, N = 304, $I^2 = 2.9\%$) and total sleep time (SMD = 0.54, 95% [CI]: 0.06 to 1.02, $P < 0.05$; 3 trials, N = 142, $I^2 = 32.6\%$) reaching $P < 0.05$ but there was no clear evidence on sleep efficiency (SMD = 1.10, 95% [CI]; -0.26 to 2.45, P > 0.05l-; 3 trials, N = 142, $I^2 = 88.3\%$.)[38]

Outcomes of patients with delayed sleep phase disorder showed substantial or considerable heterogeneity ($I^2 > 50\%$ or $I^2 > 75\%$). Analyses demonstrated distinct improvement on dim light melatonin onset (SMD = 1.66, 95% [CI]: 1.20 to 2.12, $P < 0.001$; 6 trials, N = 238, $I^2 = 51.3\%$), sleep onset latency (SMD = 1.34, 95% [CI]: 0.74 to 1.95, $P < 0.001$; 8 trials, N = 317, $I^2 = 80.7\%$), sleep onset time (SMD = 0.98, 95% [CI]: 0.60 to 1.36, $P < 0.001$; 9 trials, N = 304, $I^2 = 54.2\%$), all $P < 10^{-3}$, and wake-up time (SMD = 0.58, 95% [CI]: 0.07 to 1.09, $P < 0.05$; 5 trials, N = 195, $I^2 = 59.5\%$). No clear evidence was shown for total sleep time (SMD = 0.93, 95%CI]: -0.02 to 1.88, $P > 0.05$; 6 trials, N = 235, $I^2 = 88.6\%$).[42]

Children with neurodevelopmental disorders also experienced significantly improved total sleep time (SMD = 0.82, 95% [CI]: 0.37 to 1.24, $P < 0.001$; 9 trials, N = 541, $I^2 = 80.1\%$) and sleep onset latency (SMD = 0.82, 95% [CI]: 0.45 to 1.17, $P < 0.001$;11 trials, N = 581, $I^2 = 73.9\%$), reaching $P < 10^{-3}$ both with a high level of heterogeneity ($I^2 > 50\%$). No clear evidence was demonstrated for nocturnal awakening frequency (SMD = 0.75, 95% [CI]: -0.38 to 1.89,

P > 0.05; 5 trials, N = 277, I^2 = 91.2%).[26]

3.5 Perioperative status

As shown in Table 3 and Fig. 4, we included surgical patients in this subdivision, considering postoperative pain as an outcome of significant interest. Four quantitative reviews presented meta-analyses on randomized controlled trials with postoperative pain, pre-and postoperative anxiety level, and postoperative course as the outcomes.

Table 3 Summary estimates of the associations between postoperative pain, surgical anxiety, postoperative course outcomes, and melatonin treatment. Melatonin treatment versus passive control.

A2: AMSTAR 2 total score, A2-CD: AMSTAR 2 critical domain score, h: hour/hours, SMD: standardized mean difference, STAI: state-trait anxiety inventory, VAS: visual analogue scale

† Indicates the effect size obtained by reanalysis

* P < 0.05, ** P < 0.01, *** P < 0.005

Fig. 4. Summary estimates of the associations between postoperative pain, surgical anxiety, postoperative course outcomes, and melatonin treatment

Melatonin treatment versus passive control. Positive direction of the effect size has converted to the beneficial direction.

A2: AMSTAR 2 total score, A2-CD: AMSTAR 2 critical domain score, h: hour/hours, SMD: standardized mean difference, STAI: state-trait anxiety inventory, VAS: visual analogue scale

Diamond indicates significant difference from control, p < 0.05; Circle indicates non-

significant effects.

† Indicates the effect size obtained by reanalysis

* P < 0.05, ** P < 0.01, *** P < 0.005

For overall surgical patients, the first analgesic requirement time was distinctly reduced (SMD = 5.81, 95% [CI]: 2.57 to 9.05, P < 0.001; 2 trials, N = 100, I^2 = 92.2%). Furthermore, post-, intraoperative opioid consumption (SMD = 1.23, 95% [CI]: 0.43 to 2.04, P < 0.005; 7 trials, N = 517, I^2 = 93.9%) and postoperative chronic pain (SMD = 0.65, 95% [CI]: 0.34 to 0.96, P: NR(not recorded); 5 trials, N = NR, I^2 = 39.4%) also was significantly reduced.[20,44]

Two tools of measurement, STAI (state-trait anxiety inventory) and VAS (visual analog scale) were used to quantify anxiety. Preoperative (SMD = 0.87, 95% [CI]: 0.56 to 1.19, P < 0.001; 18 trials, N = 1264, I^2 = 85.2%) and postoperative anxiety (SMD = 0.59, 95% [CI]: 0.08 to 1.09, P < 0.05; 7 trials, N = 524, I^2 = 86.5%) measured by VAS were distinctly reduced with considerable heterogeneity, while anxiety measured by STAI was also reduced significantly (SMD = 0.70, 95% [CI]: 0.23 to 1.18, P < 0.005; 2 trials, N = 73, I^2 = 0.0%) with non-substantive heterogeneity.[24]

Postoperative pain had different outcomes depending on the postoperative time. For 1 hour and 3 hours after the surgery, no clear evidence of improvement was observed (P > 0.05)[29], but 24 hours showed a significant improvement in pain (SMD = 1.94, 95% [CI]: 1.09 to 2.78, P < 0.001; 9 trials, N = 728, I^2 = 96.0%) with considerable heterogeneity.[20]

We found no clear evidence on postoperative course, including sleepiness after three days, sleep quality, and well-being (P > 0.05) with non-substantive heterogeneity (I^2 < 25%).[29]

Data on pain classified according to the type of anesthesia used was also available.[44]

389 Postoperative pain (SMD = 0.82, 95% [CI]: 0.25 to 1.40, P: NR; 11 trials, N = NR, I^2 = 93.0%)
390 and post-, intraoperative opioid consumption (SMD = 2.76, 95% [CI]: 1.53 to 4.00, P: NR; 7
391 trials, N = NR, I^2 = 96.3%) with acute pain in general anesthesia were significantly reduced.
392 Opioid consumption for acute procedural pain was also significantly reduced (SMD = 1.44,
393 95%CI: 0.53 to 3.44, P: NR; 3 trials, N = NR, I^2 = 97.5%), but acute pain in local/epidural
394 anesthesia did not show clear evidence in terms of postoperative pain ($P > 0.05$) with substantial
395 heterogeneity.

396 In addition, except for drowsiness, quality of sleep, and measurement of well-being,
397 subgroup analysis of surgical patients showed high level of heterogeneity in terms of
398 postoperative course ($I^2 > 75\%$).[29]

399 **3.6 Pregnancy, metabolic disease**

400 Five reviews contained the meta-analyses of in patients under ART (assisted reproductive
401 technology), COS (controlled ovarian stimulation), and patients with metabolic disease (Table
402 5, Fig. 5).[33,35,45-49] The number of mature oocytes (SMD = 0.56, 95% [CI]: 0.27 to 0.85,
403 $P < 0.001$; 7 trials, N = 738, I^2 = 66.0%) and top-quality embryos (SMD = 0.53, 95% [CI]: 0.27
404 to 0.79, $P < 0.001$; 3 trials, N = 232, I^2 = 0.0%) was significantly increased ($P < 10^{-3}$) in the
405 population of females under ART.[47] The number of oocytes retrieved was estimated in two
406 types of populations (under COS or ART), both with substantial heterogeneity. Patients under
407 ART showed significant improvements (SMD = 0.34, 95% [CI]: 0.01 to 0.67, $P < 0.05$; 7 trials,
408 N = 738, I^2 = 75.0%),[47] and although patients under COS had similar estimates (SMD = 0.30,
409 95% [CI]: -0.02 to 0.63, $P > 0.05$; 5 trials, N = 680, I^2 = 73.0%), this did not reach statistical
410 significance.[48]

411 Two articles analyzed about the insulin level and HOMA-IR (homeostasis model assessment

of insulin resistance)[35,46] (0.56, 95%CI: 0.24 to 0.89, P = 0.001; I^2=22.0%) and level of insulin (1.84, 95%CI: 1.13 to 2.56, P < 0.001; I^2=0.0%) were also significantly improved in patients with a metabolic syndrome with a low heterogeneity. Quantitative analyses also showed significant improvements in fasting glucose (0.30, 95%CI: 0.04 to 0.55, P < 0.05; 2 trials, N = 504, I^2 = 36.7%) and QUICKI (quantitative insulin sensitivity check index) (0.46, 95%CI: 0.09 to 0.83, P < 0.05; 2 trials, N = 114, I^2 = 0.0%), whereas a slight non-significant improvement was observed for hemoglobin A1c estimates (0.27, 95%CI: -0.02 to 0.55, P > 0.05; I^2 = 0.0%).[46]

Table 4 Summary estimates of the associations between pregnancy, tinnitus, metabolic syndrome outcomes, and melatonin treatment. Melatonin treatment versus passive control.

A2: AMSTAR 2 total score, A2-CD: AMSTAR 2 critical domain score, ART: artificial reproductive technologies, COS: controlled ovarian stimulation, HOMA-IR: homeostasis model assessment of insulin resistance, QUICKI: quantitative insulin sensitivity check index, SMD: standardized mean difference

º Indicates that the direction of positive effect size has been reversed

† Indicates the effect size obtained by reanalysis

†† Indicates that the original study designed network meta-analysis

* P < 0.05, ** P < 0.01, *** P < 0.005

Fig. 5. Summary estimates of the associations between pregnancy, tinnitus, metabolic

syndrome outcomes, and melatonin treatment

Melatonin treatment versus passive control. Positive direction of the effect size has converted to the beneficial direction.

A2: AMSTAR 2 total score, A2-CD: AMSTAR 2 critical domain score, ART: artificial reproductive technologies, COS: controlled ovarian stimulation, HOMA-IR: homeostasis model assessment of insulin resistance, QUICKI: quantitative insulin sensitivity check index, SMD: standardized mean difference

Diamond indicates significant difference from control, $p < 0.05$; Circle indicates non-significant effects.

† Indicates the effect size obtained by reanalysis

†† Indicates that the original study designed network meta-analysis

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.005$

Diastolic (SMD = 0.87, 95% [CI]: 0.38 to 1.36, $P < 0.001$; 9 trials, N = 510, $I^2 = 84.3\%$) and systolic blood pressure (SMD = 0.85, 95% [CI]: 0.51 to 1.20, $P < 0.005$; 9 trials, N = 510, $I^2 = 68.7\%$) were also improved in patients with metabolic disease ($P < 0.005$) with substantial heterogeneity (Fig. 5).[33] Quantitative analyses also showed significant improvements in fasting glucose (SMD = 0.30, 95% [CI]: 0.04 to 0.55, $P < 0.05$; 2 trials, N = 504, $I^2 = 36.7\%$) and QUICKI (quantitative insulin sensitivity check index) (SMD = 0.46, 95% [CI]: 0.09 to 0.83, $P < 0.05$; 2 trials, N = 114, $I^2 = 0.0\%$), whereas a slight non-significant improvement was observed for hemoglobin A1c estimates (SMD = 0.27, 95% [CI]: -0.02 to 0.55, $P > 0.05$; 4 trials, N = 182, $I^2 = 0.0\%$).[46]

455 No clear evidence (P > 0.05) was found for HOMA-IR (homeostasis model assessment of
456 insulin resistance) and level of insulin.[42]

457 **3.7 Oxidative stress**

458 Two reviews[27,50] provided quantitative analyses regarding health conditions associated
459 with oxidative stress but data on the range of P values or the total number of participants were
460 not available (Table 5, Fig. 6). Melatonin treatment in patients under oxidative stress was
461 associated with significantly improved SOD (superoxide dismutase) activity (SMD = 1.38, 95%
462 [CI]: 0.13 to 2.62; 3 trials, I^2 = 86.9%), Gpx (glutathione peroxidase) (SMD = 1.36, 95% [CI]:
463 0.46 to 2.30; 5 trials, I^2 = 89.3%), GR (glutathione reductase) (SMD = 1.21, 95% [CI]: 0.65 to
464 1.77; 2 trails, I^2 =0.0%), MDA (malondialdehyde) (SMD = 0.79, 95% [CI]: 0.39 to 1.19; 8
465 trials, I^2 = 73.1%), and TAC (total antioxidant capacity) (SMD = 0.76, 95% [CI]: 0.30 to 1.21;
466 8 trials, I^2 = 80.1%), and GSH (glutathione) (SMD = 0.57, 95% [CI]: 0.32 to 0.83; 5 trials, I^2 =
467 15.1%).

468

469 **Table 5** Summary estimates of the associations between oxidative stress outcomes, and
470 melatonin treatment. Melatonin treatment versus placebo control.

471 A2: AMSTAR 2 total score, A2-CD: AMSTAR 2 critical domain score, NR: not recorded, SMD:
472 standardized mean difference

473 º Indicates that the direction of positive effect size has been reversed

474 † Indicates the effect size obtained by reanalysis

475

476 **Fig. 6.** Summary estimates of the associations between oxidative stress outcomes, and
477 melatonin treatment. Melatonin treatment versus placebo control. Positive direction of the
478 effect size has converted to the beneficial direction.

479 A2: AMSTAR 2 total score, A2-CD: AMSTAR 2 critical domain score, NR: not recorded, SMD:
480 standardized mean difference

481 Diamond indicates significant difference from control, $P < 0.05$; Circle indicates non-
482 significant effects.

483 † Indicates the effect size obtained by reanalysis

484

485 Overall estimates commonly had substantial or considerable heterogeneity, except for GR
486 and GSH ($I^2 < 50\%$).

487 No clear evidence was found for CAT (catalase) activity (SMD = 1.38, 95% [CI]: -1.42 to
488 4.18; 3 trials, $I^2 = 96.6\%$) and NO (nitric oxide) (SMD = 0.24, 95% [CI]: -0.14 to 0.61; 2 trials,
489 $I^2 = 0.0\%$).

490 **3.8 Health outcomes of discrete variables**

491 As shown in Table 6 and Fig. 7, fifteen reviews provided meta-analyses consisting of discrete
492 variables.[7,20,25,28,29,39,43,47,48,51-56] Health outcomes related to cancer were associated
493 with distinct benefits. Remission of cancer had significantly increased (RR = 1.95, 95% [CI]:
494 1.49 to 2.54, $P < 0.0001$; 8 trials, N = 761, $I^2 = 0.0\%$), and survival at one year also had
495 significantly improved (RR = 1.90, 95% [CI]: 1.28 to 2.83, $P < 0.005$; 5 trials, N = 490, $I^2 =$
496 61.9%). Side effects of radiochemotherapy of cancer also improved with consumption of
497 melatonin, reducing the relative risk of fatigue (RR = 0.37, 95% [CI]: 0.28 to 0.48, $P < 0.0001$;

498 5 trials, N = 568, I^2 = 0.0%), neurotoxicity (RR = 0.19, 95% [CI]: 0.09 to 0.40, P < 0.0001; 5
499 trials, N = 568, I^2 = 0.0%), and thrombocytopenia (RR = 0.13, 95% [CI]: 0.06 to 0.28, P <
500 0.0001; 5 trials, N = 568, I^2 = 0.0%) with low heterogeneity (I^2 < 50%).[52]

501

502 **Table 6** Summary estimates of the association between multiple health outcomes, and
503 melatonin treatments made up of discrete variables. Melatonin treatment versus passive control.

504 A2: AMSTAR 2 total score, A2-CD: AMSTAR 2 critical domain score, AD: Alzheimer's
505 disease, ART: artificial reproductive technologies, COS: controlled ovarian stimulation, ICU:
506 intensive care unit, OR: odds ratio, RR: risk ratio, SMD: standardized mean difference

507 † Indicates the effect size obtained by reanalysis

508 †† Indicates that the original study designed network meta-analysis

509 ‡ Indicates that the obtained effect size is the odds ratio of the fixed effect model and the
510 original value of the study

511 § Indicates that active control is used for the comparison

512 * P < 0.05, ** P < 0.01, *** P < 0.005

513

514 **Fig. 7.** Summary estimates of the association between multiple health outcomes, and melatonin
515 treatments made up of discrete variables

516 Melatonin treatment versus passive control. Positive direction of the effect size has converted
517 to the beneficial direction.

518 A2: AMSTAR 2 total score, A2-CD: AMSTAR 2 critical domain score, AD: Alzheimer's
519 disease, ART: artificial reproductive technologies, COS: controlled ovarian stimulation, ICU:
520 intensive care unit, OR: odds ratio, RR: risk ratio, SMD: standardized mean difference
521 Diamond indicates significant difference from control, $P < 0.05$; Circle indicates non-
522 significant effects.
523 † Indicates the effect size obtained by reanalysis
524 †† Indicates that the original study designed network meta-analysis
525 ‡ Indicates that the obtained effect size is the odds ratio of the fixed effect model and the
526 original value of the study
527 § Indicates that active control is used for the comparison
528 * $P < 0.05$, ** $P < 0.01$, *** $P < 0.005$
529
530 Patients undergoing ART showed statistically significant improvement in biochemical (RR
531 = 1.23, 95% [CI]: 1.02 to 1.48, $P < 0.05$; 6 trials, N = 671, $I^2 = 0.0\%$) or clinical pregnancy
532 rates (RR = 1.23, 95% [CI]: 1.05 to 1.45, $P < 0.05$; 10 trials, N = 1023, $I^2 = 0.0\%$) with low
533 heterogeneity ($I^2 < 50\%$),[47] but no evidence was shown in patients undergoing COS in
534 clinical pregnancy rates (RR = 1.37, 95% [CI]: 0.99 to 1.88, $P > 0.05$; 5 trials, N = 680, I^2 =
535 0.0%).[48] Also, there was no clear evidence in terms of live birth rates and miscarriage rates
536 of ART patients ($P > 0.05$). [7,36,54,56]
537 Preoperative patients showed significant reduction in the incidence of emergence agitation
538 (RR = 0.31, 95% [CI]: 0.16 to 0.60, $P < 0.005$; 3 trials, N = 36, $I^2 = 0.0\%$) when compared with

539 placebo, but no clear evidence was found when compared with midazolam (RR = 0.48, 95%
540 [CI]: 0.15 to 1.52, $P > 0.05$; 3 trials, N = 31, $I^2 = 36.8\%$).[25]

541 Perioperative patients' need for analgesics was significantly reduced (RR = 0.50, 95% [CI]:
542 0.30 to 0.82, $P < 0.0001$; 5 trials, N = 411, $I^2 = 53.5\%$) with non-substantive heterogeneity (I^2
543 $< 50\%$).[20]

544 Other health outcomes (e.g., in-hospital mortality, discontinuations of all-cause of AD,[39]
545 drop-out for adverse effects/all causes of children/adolescents with sleep-onset
546 insomnia,[28,43] side effects including headache, nausea, dizziness, or depression among
547 surgical patients[29], incidence of delirium[7,36,55]) indicated no clear evidence ($P > 0.05$) for
548 the effect of exogenous melatonin.

549

550

551 **4 Discussion**

552 The present study is the first quantitative umbrella review based solely on randomized
553 controlled trials to estimate the association between the exogenous melatonin supplementation
554 and general health conditions as well as 84 different health outcomes. A significant proportion
555 of the included meta-analyses examined psychiatric patients, pregnancy patients, and surgical
556 patients.

557 Most summary estimates supported the notion that exogenous melatonin may provide a
558 solution to sleep problems, oxidative parameters, pregnancy rate, postoperative pain, and
559 anxiety.

560 We observed robust evidence, supported by a P-value less than 0.001 with non-considerable
561 heterogeneity, for studies on sleep-promoting effect, surgical outcomes (e.g., anxiety-
562 preoperative VAS, need for analgesic requirements), pregnancy (e.g., number of oocytes
563 retrieved, top-quality embryos), metabolic disease (diastolic blood pressure), and cancer (e.g.,
564 remission rate, 1-year survival rate, and side effects of fatigue and neurotoxicity).

565 We observed suggestive evidence supported by a P-value of less than 0.001 in surgical
566 patients with postoperative pain and metabolic disorders.

567 Exogenous melatonin overall did not affect the cognitive functions measured by MMSE and
568 ADAS-cog assessments of patients with psychiatric disorders or dementia, unlike the
569 effectiveness over sleep problems. Additionally, they had no improvement in the activities of
570 daily living in patients with dementia.

571 Differently, on add-on prolonged-release melatonin (PRM) in moderate Alzheimer's disease
572 was found to have improvement on cognitive performance measured by MMSE (P=0.044) and

573 Instrumental Activities of Daily Living (P=0.004) compared with placebo.[57] The range of
574 the duration of psychiatry patients included in our study is 1 week to 3.5 years, as shown in
575 Table. S3. The contrary result of the mentioned study suggests that the effectiveness of
576 exogenous melatonin may vary depending on the duration of melatonin release.

577 Our results on neurodegenerative diseases may be explained by the antioxidant and
578 neuroprotector role of melatonin. A direct regulatory effect of melatonin on the activities of
579 protein kinases and protein phosphates was reported.[58] Specifically the capacity of melatonin
580 to ameliorate β-amyloid pathology may play a role in the treatment of Alzheimer-like
581 neurodegeneration.[59]

582 The clinical pregnancy and biochemical pregnancy rates on women with ART have also
583 shown improvement with melatonin intervention. Melatonin supplementation can relate this
584 effect with its effect of reducing oxidative stress, as we summarized in Fig. 6. Oxidative stress
585 is known as a major contributing factor negatively affecting oocyte quality of development
586 after fertilization.[60,61] In the same context, our meta-analyses of oxidative stress reduction
587 may support the association with the effectiveness in human pregnancy. We can also explain
588 this association base on the ability of melatonin to correct the pathophysiology during
589 pregnancy due to abortion.[62]

590 Concerning cancer, melatonin as an anti-cancer agent is actively studied, which may involve
591 biochemical and molecular mechanisms,[63] including inhibition mechanisms of cancer
592 metastasis.[64] Specifically, melatonin may alter the adhesion and gap junctional intracellular
593 communication or induce apoptotic cell death.[63]

594

5 Conclusion

Present umbrella review provides a comprehensive summary of the published meta-analyses concerning the effect of exogenous melatonin supplementation on various health outcomes. To date, the randomized controlled trials have provided robust evidence for overall sleep problems, pregnancy rate and progression, postoperative course and pain, metabolic syndrome, and remission/side effects of cancer.

Relationships between exogenous melatonin and different health outcomes likely exist but are supported by still limited evidence. We could not specify the effect of melatonin on specific types of cancer. Well-designed randomized controlled studies with a large sample size are needed to supplement the considerable heterogeneity of surgical patients and the deficient number of studies. This information can further provide more in-depth knowledge on what types of cancer should be targeted with melatonin.

Future studies adopting detailed population reporting, attempting the subgroup analysis based on the duration of exogenous melatonin are needed. Through the investigation, the quantified association between health outcomes and the precise method of melatonin supplementation would have resulted.

Author contribution

All authors made substantial contributions to all the following: (1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, (3) final approval of the version to be submitted. This manuscript has been reviewed and approved by all authors.

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781

Tables

Table 1 Summary estimates of the associations between psychiatric disorder, dementia, Alzheimer's disease outcomes, and melatonin treatment

Melatonin treatment versus passive control. Positive direction of the effect size has converted to the beneficial direction.

Outcomes	Health Outcomes	Condition	Effect metrics	Effect size (95% CI)	N. trial	N. total	P value	I^2(%)	Egger's P	A2-CD / A2
Psychiatric Disorder	Diastolic blood pressure	Psychiatric disorders [37] ***	SMD*	0.76† (0.30 to 1.22)	3	80	0.001	0.0	0.502	6 / 15
	Abnormal involuntary movement scales	Schizophrenia [38]	SMD*	0.66† (-1.49 to 2.81)	4	130	0.547	93.2	0.000	6 / 14
	Systolic blood pressure	Psychiatric disorders [37] *	SMD*	0.42† (0.05 to 0.79)	4	118	0.020	0.0	0.837	6 / 15
	Total sleep time	Children with autistic spectrum disorder [26] **	SMD	1.00† (0.28 to 1.73)	4	213	0.007	79.3	0.002	6 / 15
		Children with neurodisability [26] *	SMD	0.33† (0.05 to 0.61)	3	199	0.023	0.0	0.895	6 / 15
	Sleep onset latency	Children with autistic spectrum disorder [26] ***	SMD*	0.95† (0.57 to 1.34)	4	213	0.000	35.6	0.198	6 / 15
		Children with neurodisability [27] ***	SMD*	0.66† (0.36 to 0.96)	3	183	0.000	0.0	0.865	6 / 15
		Children with ADHD [27] ***	SMD*	0.61† (0.27 to 0.94)	2	143	0.000	0.0	NA	6 / 15
Dementia	Daytime sleep / nighttime sleep ratio	Dementia [30] *	SMD*	0.33† (0.02 to 0.64)	3	184	0.036	0.0	0.922	7 / 16
	Total sleep time	Dementia, duration≥4weeks [31] *	SMD	0.32† (0.05 to 0.60)	6	426	0.022	46.9	0.093	6 / 13
		Dementia, duration 10d-10w [31] *	SMD	0.25† (0.01 to 0.49)	8	497	0.041	40.2	0.111	6 / 13
	Sleep efficiency	Dementia, duration 10d-8w [31] *	SMD	0.29† (0.04 to 0.53)	4	375	0.024	32.0	0.221	6 / 13
		Dementia [31]	SMD	0.18† (-0.06 to 0.43)	6	446	0.140	38.0	0.153	6 / 13
	MMSE	Dementia [30]	SMD	0.26† (-0.28 to 0.80)	3	162	0.343	52.1	0.124	7 / 16
	Number of adverse events per person	Dementia [30]	SMD*	0.25† (-0.10 to 0.60)	2	151	0.158	0.0	NA	7 / 16
	Nocturnal sleep time	Dementia [30]	SMD	0.24† (-0.07 to 0.55)	4	184	0.132	0.0	0.809	7 / 16
	ADAS-cog	Dementia [30]	SMD*	0.19† (-0.14 to 0.52)	3	162	0.265	0.0	0.596	7 / 16
	Nocturnal time awake	Dementia [30]	SMD*	0.18† (-0.17 to 0.52)	2	151	0.318	0.0	NA	7 / 16
	Activities of daily living	Dementia [30]	SMD*	0.12† (-0.21 to 0.45)	3	162	0.474	0.0	0.639	7 / 16
	Carer-rated sleep quality	Dementia [30]	SMD	0.07† (-0.35 to 0.50)	3	164	0.733	31.6	0.232	7 / 16
Alzheimer	Nocturnal sleep time	AD [38] *	SMD	0.26 (0.01 to 0.51)	6	305	0.040	9.0	0.360	6 / 14
	Sleep time during daytime	AD [39]	SMD	0.15 (-0.14 to 0.44)	4	210	0.310	0.0	0.940	6 / 14
	Sleep efficiency	AD, duration ≥ 4w [31] *	SMD	0.34† (0.06 to 0.63)	2	198	0.017	0.0	NA	6 / 13
		AD, duration 10d-8w [31] *	SMD	0.26† (0.01 to 0.52)	3	239	0.044	0.0	0.390	6 / 13
		AD [39]	SMD	0.14 (-0.17 to 0.44)	5	287	0.380	33.0	0.200	6 / 14
	ADAS-cog	AD [39]	SMD*	0.25 (-0.21 to 0.70)	2	75	0.290	0.0	NA	6 / 14
	MMSE	AD [39]	SMD*	-0.33 (-0.73 to 0.06)	4	182	0.090	38.0	0.190	6 / 14

A2: AMSTAR 2 total score, A2-CD: AMSTAR 2 critical domain score, AD: Alzheimer's disease, ADAS-cog: Alzheimer's Disease Assessment Scale cognitive subscale, ADHD: attention deficit hyperactivity disorder, d: day/days, MMSE: Mini-Mental State Examination, NA: not available, NR: not recorded, SMD: standardized mean difference, w: week/weeks

º Indicates that the direction of positive effect size has been reversed

† Indicates the effect size obtained by reanalysis

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.005$

Table 2 Summary estimates of the associations between sleep disorder outcomes, and melatonin treatment

Melatonin treatment versus passive control. Positive direction of the effect size has converted to the beneficial direction.

Outcomes	Health Outcomes	Condition	Effect metrics	Effect size (95% CI)	N. trial	N. total	P value	I^2(%)	Egger's P	A2-CD / A2
Sleep disorder	Dim light melatonin onset	DSPD [42] ***	SMD[+]	1.66[r] (1.20 to 2.12)	6	238	0.000	51.3	0.163	4 / 10
		Children and adolescent with sleep onset insomnia [28] ***	SMD[+]	0.00[r] (-0.08 to 0.08)	5	271	0.000	52.6	0.077	5 / 13
	Sleep onset latency	DSPD [42] ***	SMD[+]	1.34[r] (0.74 to 1.95)	8	317	0.000	80.7	0.000	4 / 10
		Children and adolescent with sleep onset insomnia [28] ***	SMD[+]	0.92[r] (0.48 to 1.36)	6	326	0.000	70.5	0.005	5 / 13
		Children with neurodevelopmental disorders [26] ***	SMD[+]	0.82[r] (0.45 to 1.17)	11	581	0.000	73.9	0.000	6 / 15
		Insomnia, by physiological indices [32] ††	SMD[+]	0.71 (0.35 to 1.08)	19	NR	NR	78.8	NR	4 / 13
		Secondary sleep disorder [41] **	SMD[+]	0.33[r] (0.10 to 0.56)	7	304	0.005	2.9	0.403	5 / 14
		Shift work sleep disorder, next day [34]	SMD	0.31[r] (-0.01 to 0.64)	5	148	0.060	0.0	0.820	7 / 15
		Insomnia [32] ††	SMD[+]	0.24 (0.15 to 0.33)	14	NR	NR	0.0	NR	4 / 13
		Shift work sleep disorder [34]	SMD[+]	0.10[r] (-0.35 to 0.55)	3	162	0.672	37.9	0.200	7 / 15
	Sleep efficiency	Secondary sleep disorder [41]	SMD	1.10[r] (-0.26 to 2.45)	3	142	0.110	88.3	0.000	5 / 14
		Insomnia, by physiological indices [32] ††	SMD	0.55 (-0.05 to 1.15)	18	NR	NR	87.9	NR	4 / 13
		Insomnia [32] ††	SMD	0.25 (-0.28 to 0.78)	16	NR	NR	95.7	NR	4 / 13
	Total sleep time	DSPD [42]	SMD	0.93[r] (-0.02 to 1.88)	6	235	0.054	88.6	0.000	4 / 10
		Children with neurodevelopmental disorders [18] ***	SMD	0.82[r] (0.37 to 1.24)	9	541	0.000	80.1	0.000	6 / 15
		Secondary sleep disorder [31] *	SMD	0.54[r] (0.06 to 1.02)	3	142	0.026	32.6	0.227	5 / 14
		Children and adolescent with sleep onset insomnia [20] ***	SMD	0.46[r] (0.21 to 0.71)	5	262	0.000	3.4	0.387	5 / 13
	Total sleep time, next day	Shift work sleep disorder [34] *	SMD	0.35[r] (0.07 to 0.63)	7	263	0.015	20.4	0.274	7 / 15
	Total sleep time, next night	Shift work sleep disorder [34] *	SMD	0.32[r] (0.02 to 0.58)	3	234	0.015	0.0	0.634	7 / 15
	Sleep onset time	DSPD [42] ***	SMD[+]	0.98[r] (0.60 to 1.36)	9	304	0.000	54.2	0.026	4 / 10
		Children and adolescent with sleep onset insomnia [28] ***	SMD[+]	0.79[r] (0.54 to 1.04)	6	323	0.000	0.0	0.966	5 / 13
	Wake-up time	DSPD [42] *	SMD[+]	0.58[r] (0.07 to 1.09)	5	195	0.027	59.5	0.042	4 / 10
		Children and adolescent with sleep onset insomnia [20]	SMD[+]	0.23[r] (-0.04 to 0.50)	4	209	0.099	0.0	0.764	5 / 13
	Nocturnal awakening frequency	Children with neurodevelopmental disorders [18]	SMD[+]	0.75[r] (-0.38 to 1.89)	5	277	0.190	91.2	0.000	6 / 15
		Insomnia, by physiological indices [20] ††	SMD[+]	0.07 (-0.29 to 0.44)	14	NR	NR	71.0	NR	4 / 13
		Insomnia [32] ††	SMD[+]	-0.18 (-4.16 to 3.81)	8	NR	NR	99.4	NR	4 / 13
	Sleep quality	Shift work sleep disorder [26]	SMD	0.25[r] (-0.19 to 0.69)	4	291	0.264	59.7	0.059	7 / 15
		After laparoscopic cholecystectomy [21]	SMD	-0.10[r] (-0.41 to 0.21)	2	165	0.530	0.0	NA	4 / 11
	Subjective severity of sleep problem	Insomnia [32] ††	SMD[+]	0.45 (-0.37 to 1.28)	18	NR	NR	94.4	NR	4 / 13

	Sleep disturbance	Menopausal women [43] ††	SMD°	0.42 (-0.54 to 1.38)	NR	NR	NR	NR	NR	7 / 16
	Sleep time during daytime	Shift work sleep disorder [34] ***	SMD	0.36° (0.12 to 0.61)	7	263	0.004	0.0	0.440	7 / 15
	Nocturnal sleep time	Shift work sleep disorder [34] *	SMD	0.32° (0.06 to 0.58)	3	234	0.015	0.0	0.634	7 / 15
	Daytime sleepiness	Insomnia [32] ††	SMD°	0.27 (0.06 to 0.48)	4	NR	NR	0.0	NR	4 / 13
	Light-off time	Children and adolescent with sleep onset insomnia [28]	SMD°	0.08° (-0.22 to 0.37)	3	179	0.604	0.0	0.627	5 / 13

A2: AMSTAR 2 total score, A2-CD: AMSTAR 2 critical domain score, DSPD: delayed sleep phase disorder, MLT: melatonin, NA: not available, SMD: standardized mean difference

° Indicates that the direction of positive effect size has been reversed

† Indicates the effect size obtained by reanalysis

†† Indicates that the original study designed network meta-analysis

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.005$

Table 3 Summary estimates of the associations between postoperative pain, surgical anxiety, postoperative course outcomes, and melatonin treatment

Melatonin treatment versus passive control. Positive direction of the effect size has converted to the beneficial direction.

Outcomes	Health Outcomes	Condition	Effect metrics	Effect size (95% CI)	N. trial	N. total	P value	I^2(%)	Egger's P	A2-CD / A2
Pain	Time for the first analgesic requirement	Surgical patients [20] ***	SMD	5.81† (2.57 to 9.05)	2	100	0.000	92.2	NA	5 / 14
	Postoperative pain	24h postoperative [20] ***	SMD°	1.94† (1.09 to 2.78)	9	728	0.000	96.0	0.000	5 / 14
		Surgical patients, acute pain, general anesthesia [44]	SMD°	0.82 (0.25 to 1.40)	11	NR	NR	93.0	NR	6 / 14
		Surgical patients, acute pain, local, epidural anesthesia [44]	SMD°	0.28 (-0.28 to 0.83)	3	NR	NR	62.2	NR	6 / 14
	Post-, intraoperative opioid consumption	Surgical patients, acute pain, general anesthesia [44]	SMD°	2.76 (1.53 to 4.00)	7	NR	NR	96.3	NR	6 / 14
		Surgical patients, acute, procedural pain [44]	SMD°	1.44 (0.53 to 3.44)	3	NR	NR	97.5	NR	6 / 14
		Surgical patients [20] ***	SMD°	1.23† (0.43 to 2.04)	7	517	0.003	93.9	0.000	5 / 14
	Postoperative pain	3h after laparoscopic cholecystectomy [29]	SMD°	0.86† (-0.97 to 2.69)	2	165	0.360	95.0	NA	4 / 11
		1h after laparoscopic cholecystectomy [29]	SMD°	0.26† (-0.56 to 1.08)	2	165	0.530	81.0	NA	4 / 11
	Chronic pain	Surgical patients [44]	SMD°	0.65 (0.34 to 0.96)	5	NR	NR	39.4	NR	6 / 14
	Procedural pain	Surgical patients, acute pain [44]	SMD°	0.50 (-0.54 to 1.54)	2	NR	NR	85.3	NA	6 / 14
Anxiety	Anxiety-preoperative VAS	Preoperative and postoperative [24] ***	SMD°	0.87† (0.56 to 1.19)	18	1264	0.000	85.2	0.000	7 / 16
	Postoperative anxiety STAI	Preoperative and postoperative [24] ***	SMD°	0.70† (0.23 to 1.18)	2	73	0.004	0.0	NA	7 / 16
	Anxiety-postoperative VAS	Preoperative and postoperative [24] *	SMD°	0.59† (0.08 to 1.09)	7	524	0.022	86.5	0.000	7 / 16
Postoperative course	Sleepiness after 3 days	After laparoscopic cholecystectomy [29]	SMD°	0.10† (-0.23 to 0.44)	2	162	0.540	9.0	NA	4 / 11
	Sleep quality	After laparoscopic cholecystectomy [29]	SMD°	0.10† (-0.21 to 0.41)	2	162	0.530	0.0	NA	4 / 11
	Well-being	After laparoscopic cholecystectomy [29]	SMD°	-0.05† (-0.36 to 0.26)	2	162	0.760	0.0	NA	4 / 11

A2: AMSTAR 2 total score, A2-CD: AMSTAR 2 critical domain score, h: hour/hours, SMD: standardized mean difference, STAI: state-trait anxiety inventory, VAS: visual analogue scale

° Indicates that the direction of positive effect size has been reversed

† Indicates the effect size obtained by reanalysis

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.005$

Table 4 Summary estimates of the associations between pregnancy, tinnitus, metabolic syndrome outcomes, and melatonin treatment

Melatonin treatment versus passive control. Positive direction of the effect size has converted to the beneficial direction.

Outcomes	Health Outcomes	Condition	Effect metrics	Effect size (95% CI)	N. trial	N. total	P value	I^2(%)	Egger's P	A2-CD / A2
Metabolic syndrome	Insulin	Metabolic syndrome [35] ***	SMD*	1.84 (1.13 to 2.56)	8	376	0.000	0.00	0.540	5 / 14
		Metabolic syndrome [46]	SMD*	0.15† (-0.35 to 0.66)	4	182	0.553	63.4	0.042	4 / 12
	Systolic blood pressure	Metabolic syndrome [33] ***	SMD*	0.87 (0.38 to 1.36)	9	510	0.000	84.3	NR	6 / 15
	Diastolic blood pressure	Metabolic syndrome [33] ***	SMD*	0.85 (0.51 to 1.20)	9	510	0.001	68.7	NR	6 / 15
	HOMA-IR	Metabolic syndrome [35] **	SMD*	0.56 (0.24 to 0.89)	7	344	0.001	22.0	0.260	5 / 14
		Metabolic syndrome [46]	SMD*	0.17† (-0.28 to 0.63)	3	150	0.459	48.3	0.145	4 / 12
	Body weight	Obesity [49] *	SMD	0.48 (0.02 to 0.94)	17	1065	0.038	92.0	< 0.01	6 / 13
	QUICKI	Metabolic syndrome [46] *	SMD*	0.46† (0.09 to 0.83)	2	114	0.016	0.0	NA	4 / 12
		Metabolic syndrome [35] ***	SMD*	0.01 (0.01 to 0.01)	5	276	0.000	0.0	0.590	5 / 14
	BMI	Obesity [49] *	SMD	0.31 (0.00 to 0.63)	18	877	0.049	80	< 0.01	6 / 13
	Fasting glucose	Metabolic syndrome [46] *	SMD*	0.30† (0.04 to 0.55)	2	504	0.022	36.7	NA	4 / 12
	Hemoglobin A1c	Metabolic syndrome [46]	SMD*	0.27† (-0.02 to 0.55)	3	194	0.065	0.0	0.560	4 / 12
	Waist circumference	Obesity [49]	SMD	0.18 (-0.23 to 0.60)	12	607	0.383	83.0	0.378	6 / 13
	Severity of tinnitus	Tinnitus [53]	SMD*	-0.13 (-0.74 to 0.48)	NR	NR	NR	NR	NR	7 / 16
Migraine	Migraine frequency	Episodic migraine [55] ††	SMD*	1.71 (0.14 to 3.27)	NR	NR	NR	NR	NR	7 / 16
Pregnancy	Number of matured oocytes	ART [47] ***	SMD	0.56 (0.27 to 0.85)	7	738	0.000	66.0	0.007	6 / 14
	Number of top-quality embryos	ART [47] ***	SMD	0.53 (0.27 to 0.79)	3	232	0.000	0.0	0.816	6 / 14
	Number of oocytes retrieved	ART [47] *	SMD	0.34 (0.01 to 0.67)	7	738	0.040	75.0	0.001	6 / 14
		COS [48]	SMD	0.30† (-0.02 to 0.63)	5	680	0.071	73.0	0.005	6 / 15
Menopausal women	Psychological symptoms	Menopausal women [56]	SMD*	0.00 (-0.32 to 0.37)	6	NR	0.884	70.3	0.005	4 / 13
	Sleep quality	Menopausal women [56]	SMD*	-0.66 (-1.54 to 0.22)	4	NR	0.141	89.40	0.000	4 / 13

A2: AMSTAR 2 total score, A2-CD: AMSTAR 2 critical domain score, ART: artificial reproductive technologies, BMI: body mass index, COS: controlled ovarian stimulation, HOMA-IR: homeostasis model assessment of insulin resistance, QUICKI: quantitative insulin sensitivity check index, SMD: standardized mean difference

º Indicates that the direction of positive effect size has been reversed

† Indicates the effect size obtained by reanalysis

†† Indicates that the original study designed network meta-analysis

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.005$

Table 5 Summary estimates of the associations between oxidative stress outcomes, and melatonin treatment

Melatonin treatment versus placebo control. Positive direction of the effect size has converted to the beneficial direction.

Outcomes	Health Outcomes	Condition	Effect metrics	Effect size (95% CI)	N. trial	N. total	P value	I2(%)	Egger's P	A2-CD / A2
Oxidative stress	PCO (protein carbonyl)	Under oxidative stress [50] ***	SMD º	1.78 (0.58 to 2.97)	3	NR	0.004	95.6	0.040	5 / 13
	CAT (catalase) activity	Under oxidative stress [13]	SMD	1.38 (-1.42 to 4.18)	3	NR	NR	96.6	0.000	7 / 14
	SOD (superoxide dismutase) activity	Under oxidative stress [13]	SMD	1.38 (0.13 to 2.62)	3	NR	NR	86.9	0.000	7 / 14
		Under oxidative stress [50] ***	SMD	0.24 (-0.36 to 0.83)	2	NR	0.439	0.0	NR	5 / 13
	Gpx (glutathione peroxidase)	Under oxidative stress [13]	SMD	1.36 (0.46 to 2.30)	5	NR	NR	89.3	0.000	7 / 14
		Under oxidative stress [50] ***	SMD	-0.61 (-1.91 to 0.67)	3	NR	0.350	83.6	NR	5 / 13
	GR (glutathione reductase)	Under oxidative stress [13]	SMD	1.21 (0.65 to 1.77)	2	NR	NR	0.0	0.679	7 / 14
	TAC (total antioxidant capacity)	Under oxidative stress [50] *	SMD	1.03 (0.24 to 1.81)	8	NR	0.011	91.6	NR	5 / 13
		Under oxidative stress [13]	SMD	0.76 (0.30 to 1.21)	8	NR	NR	80.1	0.000	7 / 14
	MDA (malondialdehyde)	Under oxidative stress [50] ***	SMD º	0.84 (0.40 to 1.48)	9	NR	0.001	83.8	0.007	5 / 13
		Under oxidative stress [13]	SMD º	0.79 (0.39 to 1.19)	8	NR	NR	73.1	0.001	7 / 14
	GSH (glutathione)	Under oxidative stress [13]	SMD	0.57 (0.32 to 0.83)	5	NR	NR	15.1	0.319	7 / 14
		Under oxidative stress [50] ***	SMD	0.41 (-0.16 to 0.98)	5	NR	0.163	79.1	NR	5 / 13
	NO (nitric oxide)	Under oxidative stress [13]	SMD º	0.24 (-0.14 to 0.61)	2	NR	NR	0.0	0.941	7 / 14
		Under oxidative stress [50] ***	SMD º	0.03 (-1.18 to 1.24)	8	NR	0.962	95.6	NR	5 / 13

A2: AMSTAR 2 total score, A2-CD: AMSTAR 2 critical domain score, NR: not recorded, SMD: standardized mean difference

º Indicates that the direction of positive effect size has been reversed

† Indicates the effect size obtained by reanalysis

Table 6 Summary estimates of the association between multiple health outcomes, and melatonin treatments made up of discrete variables

Melatonin treatment versus passive control. Positive direction of the effect size has converted to the beneficial direction.

Condition / Outcome	Health Outcomes	Condition / Control	Effect metrics	Effect size (95% CI)	N. trial	N. total	P value	I^2(%)	Egger's P	A2-CD / A2
Tinnitus	Response rate	Tinnitus [53] ††	RR	41.00 (2.42 to 693.88)	NR	NR	NR	NR	NR	7 / 16
Cancer	Remission	Cancer [52] ***	RR	1.95 (1.49 to 2.54)	8	761	<0.0001	0.0	0.980	3 / 11
	Survival at 1 year	Cancer [52] **	RR	1.90 (1.28 to 2.83)	5	490	0.001	61.9	0.030	3 / 11
Pregnancy	Rate of clinical pregnancy	COS [48]	RR	1.37† (0.99 to 1.88)	5	680	0.056	0.0	0.796	6 / 15
		ART [47] *	RR	1.23† (1.05 to 1.45)	10	1203	0.012	0.0	0.944	6 / 14
	Biochemical pregnancy rate	ART [47] *	RR	1.23† (1.02 to 1.48)	6	671	0.032	0.0	0.481	6 / 14
	Miscarriage rate	ART [47]	RR	1.25† (0.66 to 2.37)	5	674	0.496	0.0	0.933	6 / 14
	Live birth rate	ART [47]	RR	1.20† (0.83 to 1.72)	3	291	0.335	0.0	0.812	6 / 14
Migraine	Response rate	Episodic migraine [54] ††	OR	1.19‡ (0.37 to 3.78)	NR	NR	NR	NR	NR	7 / 16
Mortality	In-hospital mortality	Non-ICU patients [51]	RR	0.84 (0.37 to 1.88)	3	543	0.670	0.0	0.710	6 / 15
Alzheimer	Discontinuation of all cause	AD [39]	RR	0.77 (0.51 to 1.16)	6	453	0.210	0.0	0.430	6 / 14
Delirium	Incidence of delirium	Delirium patients [55] ††	OR	0.76‡ (0.30 to 1.87)	NR	NR	NR	NR	NR	7 / 16
		Non-ICU patients [38]	RR	0.41 (0.09 to 1.89)	3	529	0.250	78.0	0.010	6 / 15
		Delirium patients [7] ††	OR	0.16‡ (0.03 to 0.75)	NR	NR	NR	NR	NR	6 / 15
		Pediatric patients after sevoflurane anesthesia [36] ††	OR	0.05‡ (0.01 to 0.46)	NR	NR	NR	NR	NR	7 / 16
Pain	Need for analgesic requirements	Surgical patients [52] **	RR	0.50† (0.30 to 0.82)	5	411	0.006	53.5	0.072	5 / 14
Preoperative	Incidence of emergence agitation	Preoperative children / Midazolam [17]	RR§	0.48 (0.15 to 1.52)	3	31	0.209	36.8	0.205	6 / 14
		Preoperative children [17] **	RR	0.31 (0.16 to 0.60)	3	36	0.001	0.0	0.375	6 / 14
Side-effects	Drop-out for adverse effects	Children and adolescent with sleep onset insomnia [28]	RR	3.22† (0.14 to 75.8)	7	431	0.468	0.0	1.000	5 / 13
	Headache	After laparoscopic cholecystectomy [29]	RR	1.25 (0.42 to 3.71)	2	162	0.680	7.0	NA	4 / 11
	Drop-out for all causes	Children and adolescent with sleep onset insomnia [28]	RR	1.23† (0.52 to 2.91)	7	431	0.639	0.0	0.573	5 / 13
		Menopausal women [43] ††	RR	1.21 (0.30 to 4.78)	NR	NR	NR	NR	NR	7 / 16
	Nausea	Surgical patients [20]	OR	1.15‡ (0.68 to 1.94)	5	417	0.590	0.0	NR	5 / 14
	Dizziness	After laparoscopic cholecystectomy [29]	RR	1.09 (0.14 to 8.40)	2	162	0.940	51.0	NA	4 / 11
	Depression	After laparoscopic cholecystectomy [29]	RR	1.03 (0.15 to 7.21)	2	162	0.970	0.0	NA	4 / 11
	Fatigue	After radiochemotherapy of cancer [52] ***	RR	0.37 (0.28 to 0.48)	5	568	<0.0001	0.0	0.530	3 / 11
	Neurotoxicity	After radiochemotherapy of cancer [52] ***	RR	0.19 (0.09 to 0.40)	5	568	<0.0001	0.0	0.950	3 / 11
	Thrombocytopenia	After radiochemotherapy of cancer [52] ***	RR	0.13 (0.06 to 0.28)	5	568	<0.0001	0.0	0.990	3 / 11

A2: AMSTAR 2 total score, A2-CD: AMSTAR 2 critical domain score, AD: Alzheimer's disease, ART: artificial reproductive technologies, COS: controlled ovarian stimulation, ICU: intensive care unit, OR: odds ratio, RR: risk ratio, SMD: standardized mean difference

† Indicates the effect size obtained by reanalysis

†† Indicates that the original study designed network meta-analysis

‡ Indicates that the obtained effect size is the odds ratio of the fixed effect model and the original value of the study

§ Indicates that active control is used for the comparison

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.005$

Figures

Figure 1

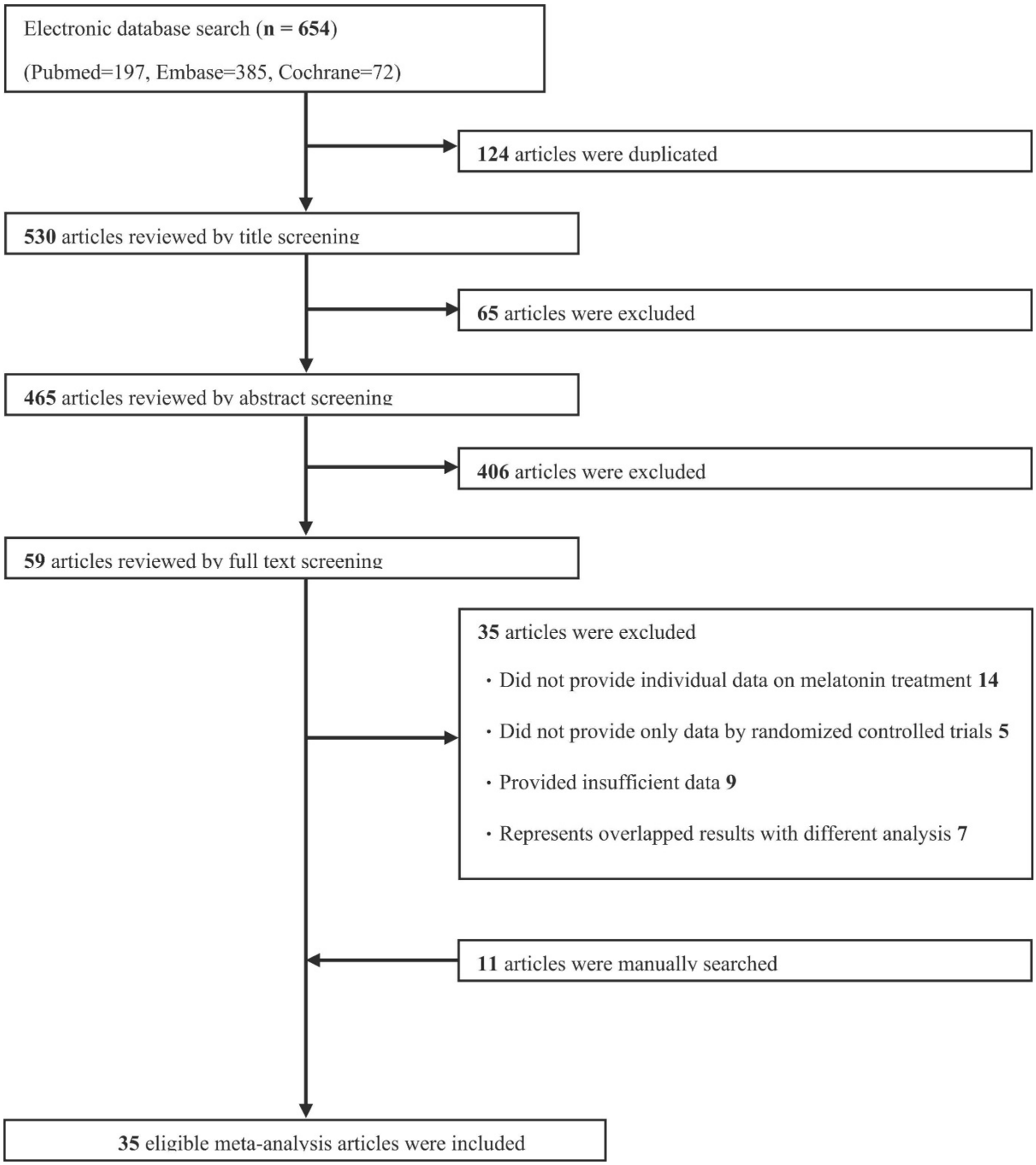


Figure 2

Outcome	Condition	N.trial	N.total	Effect size (95% CI)	P value	I^2(%)	Egger's P value	A2	A2-CD
Psychiatric Disorder									
Diastolic blood pressure	Psychiatric disorder [37] ***	3	80	0.76† (0.30 to 1.22)	0.001	0.00	0.502	15	6
Abnormal involuntary movement scales	Schizophrenia [38]	4	130	0.66† (-1.49 to 2.81)	0.547	93.21	0.000	14	6
Systolic blood pressure	Psychiatric disorder [37] *	4	118	0.42† (0.05 to 0.79)	0.020	0.00	0.837	15	6
Total sleep time	Children with autistic spectrum disorder [26] **	4	213	1.00† (0.28 to 1.73)	0.007	79.33	0.002	15	6
	Children with neurodisability [26] *	3	199	0.33† (0.05 to 0.61)	0.023	0.00	0.895	15	6
Sleep onset latency	Children with autistic spectrum disorder [26] ***	4	213	0.95† (0.57 to 1.34)	0.000	35.63	0.198	15	6
	Children with neurodisability [26] ***	3	183	0.66† (0.36 to 0.96)	0.000	0.00	0.865	15	6
	Children with ADHD [26] ***	2	143	0.61† (0.27 to 0.94)	0.000	0.00	NA	15	6
Dementia									
Daytime sleep / nighttime sleep ratio	Dementia [30] *	3	184	0.33† (0.02 to 0.64)	0.036	0.00	0.922	16	7
Total sleep time	Dementia, duration≥4weeks [31] *	6	426	0.32† (0.05 to 0.60)	0.022	46.93	0.093	13	6
	Dementia, duration 10d-10w [31] *	8	497	0.25† (0.01 to 0.49)	0.041	40.18	0.111	13	6
Sleep efficiency	Dementia, duration 10d-8w [31] *	4	375	0.29† (0.04 to 0.53)	0.024	31.95	0.221	13	6
	Dementia [31]	6	446	0.18† (-0.06 to 0.43)	0.140	38.96	0.153	13	6
MMSE	Dementia [30]	3	162	0.26† (-0.28 to 0.80)	0.343	52.10	0.124	16	7
Number of adverse events per person	Dementia [30]	2	151	0.25† (-0.10 to 0.60)	0.158	0.00	NA	16	7
Nocturnal sleep time	Dementia [30]	4	184	0.24† (-0.07 to 0.55)	0.132	0.00	0.809	16	7
ADAS-cog	Dementia [30]	3	162	0.19† (-0.14 to 0.52)	0.265	0.00	0.596	16	7
Nocturnal time awake	Dementia [30]	2	151	0.18† (-0.17 to 0.52)	0.318	0.00	NA	16	7
Activities of daily living	Dementia [30]	3	162	0.12† (-0.21 to 0.45)	0.474	0.00	0.639	16	7
Carer-rated sleep quality	Dementia [30]	3	164	0.07† (-0.35 to 0.50)	0.733	31.61	0.232	16	7
Alzheimer									
Nocturnal sleep time	AD [39] *	6	305	0.26 (0.01 to 0.51)	0.040	9.00	0.360	14	6
Sleep time during daytime	AD [39]	4	210	0.15 (-0.14 to 0.44)	0.310	0.00	0.940	14	6
Sleep efficiency	AD, duration ≥ 4w [31] *	2	198	0.34† (0.06 to 0.63)	0.017	0.00	NA	13	6
	AD, duration 10d-8w [31] *	3	239	0.26† (0.01 to 0.52)	0.044	0.00	0.390	13	6
	AD [39]	5	287	0.14 (-0.17 to 0.44)	0.380	33.00	0.200	14	6
ADAS-cog	AD [39]	2	75	0.25 (-0.21 to 0.70)	0.290	0.00	NA	14	6
MMSE	AD [39]	4	182	-0.33† (-0.73 to 0.06)	0.090	38.00	0.190	14	6

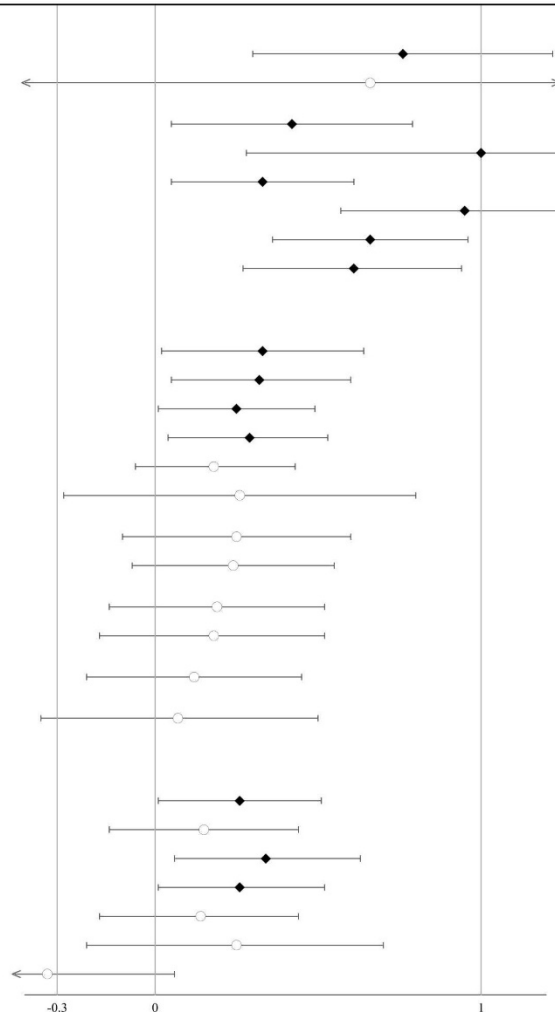


Figure 3

Outcome	Condition	N.trial	N.total	Effect size (95% CI)	P value	I^2(%)	Egger's P value	A2	A2-CD
Sleep disorder									
Dim light melatonin onset	DSPD [42] ***	6	238	1.66 (1.20 to 2.12)	0.000	51.3	0.163	10	4
	Children and adolescent with sleep onset insomnia [28] ***	5	271	0.00 (-0.08 to 0.08)	0.000	52.6	0.077	13	5
Sleep onset latency	DSPD [42] ***	8	317	1.34 (0.74 to 1.95)	0.000	80.7	0.000	10	4
	Children and adolescent with sleep onset insomnia [28] ***	6	326	0.92 (0.48 to 1.36)	0.000	70.5	0.005	13	5
	Children with neurodevelopmental disorders [26] ***	11	581	0.82 (0.45 to 1.17)	0.000	73.9	0.000	15	6
	Insomnia, by physiological indices [32] ††	19	NR	0.71 (0.35 to 1.08)	NR	78.8	NR	13	4
	Secondary sleep disorder [41] **	7	304	0.33 (0.10 to 0.56)	0.005	2.90	0.403	14	5
	Shift work sleep disorder, next day [34]	5	148	0.31 (-0.01 to 0.64)	0.060	0.00	0.820	15	7
	Insomnia [32] ††	14		0.24 (0.15 to 0.33)	NR	0.00	NR	13	4
	Shift work sleep disorder [34]	3	162	0.10 (-0.35 to 0.55)	0.672	37.9	0.200	15	7
Sleep efficiency	Secondary sleep disorder [41]	3	142	1.10 (-0.26 to 2.45)	0.110	88.3	0.000	14	5
	Insomnia, by physiological indices [32] ††	18	NR	0.55 (-0.05 to 1.15)	NR	87.9	NR	13	4
	Insomnia [32] ††	16	NR	0.25 (-0.28 to 0.78)	NR	95.7	NR	13	4
Total sleep time	DSPD [42]	6	235	0.93 (-0.02 to 1.88)	0.054	88.6	0.000	10	4
	Children with neurodevelopmental disorders [18] ***	9	541	0.82 (0.37 to 1.24)	0.000	80.1	0.000	15	6
	Secondary sleep disorder [31] *	3	142	0.54 (0.06 to 1.02)	0.026	32.6	0.227	14	5
	Children and adolescent with sleep onset insomnia [20] ***	5	262	0.46 (0.21 to 0.71)	0.000	3.40	0.387	13	5
Total sleep time, next day	Shift work sleep disorder [34] *	7	263	0.35 (0.07 to 0.63)	0.015	20.4	0.274	15	7
Total sleep time, next night	Shift work sleep disorder [34] *	3	234	0.32 (0.02 to 0.58)	0.015	0.00	0.634	15	7
Sleep onset time	DSPD 42 ***	9	304	0.98 (0.60 to 1.36)	0.000	54.2	0.026	10	4
	Children and adolescent with sleep onset insomnia [28] ***	6	323	0.07 (-0.35 to 0.50)	0.000	0.00	0.966	13	5
Wake-up time	DSPD [42] ***	5	195	0.58 (0.07 to 1.09)	0.027	59.5	0.042	10	4
	Children and adolescent with sleep onset insomnia [28] ***	4	209	0.23 (-0.04 to 0.50)	0.099	0.00	0.764	13	5
Nocturnal awakening frequency	Children with neurodevelopmental disorders [18]	5	277	0.75 (-0.38 to 1.89)	0.190	91.2	0.000	15	6
	Insomnia, by physiological indices [20] ††	14	NR	0.07 (-0.29 to 0.44)	NR	71.0	NR	13	4
	Insomnia [32] ††	8	NR	-0.18 (-4.16 to 3.81)	NR	99.4	NR	13	4
Sleep quality	Shift work sleep disorder [26]	4	291	0.25 (-0.19 to 0.69)	0.264	59.7	0.059	15	7
	After laparoscopic cholecystectomy [21]	2	165	-0.10 (-0.41 to 0.21)	0.530	0.00	NA	11	4
Subjective severity of sleep problem	Insomnia [32] ††	18	NR	0.45 (-0.37 to 1.28)	NR	94.4	NR	13	4
Sleep disturbance	Menopausal women [43] ††	NR	NR	0.42 (-0.54 to 1.38)	NR	NR	NR	16	7
Sleep time during daytime	Shift work sleep disorder [34] ***	7	263	0.36 (0.12 to 0.61)	0.004	0.00	0.440	15	7
Nocturnal sleep time	Shift work sleep disorder [34] *	3	234	0.32 (0.06 to 0.58)	0.015	0.00	0.634	15	7
Daytime sleepiness	Insomnia [32] ††	4	NR	0.27 (0.06 to 0.48)	NR	0.00	NR	13	4
Light-off time	Children and adolescent with sleep onset insomnia [28]	3	179	0.08 (-0.22 to 0.37)	0.604	0.00	0.627	13	5

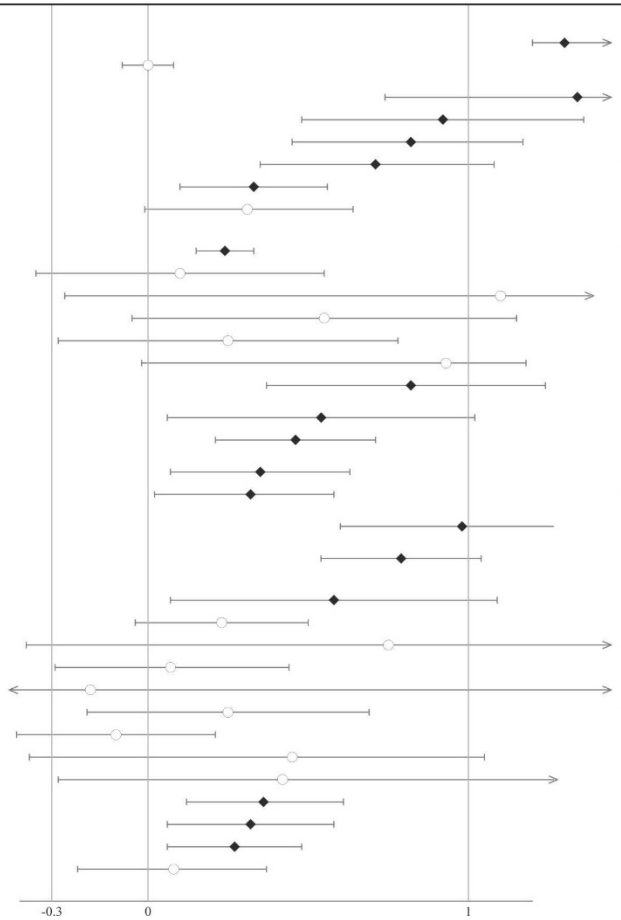


Figure 4

Outcome	Condition	N.trial	N.total	Effect size (95% CI)	P value	I^2(%)	Egger's P value	A2	A2-CD
Pain									
Time for the first analgesic requirement	Surgical patients [20 ***]	2	100	5.81† (2.57 to 9.05)	0.000	92.2	NA	14	5
Postoperative pain	24h postoperative [20 *** °]	9	728	1.94† (1.09 to 2.78)	0.000	96.0	0.000	14	5
	Surgical patients, acute pain, general anesthesia [44 °]	11	NR	0.82 (0.25 to 1.40)	NR	93.0	NR	14	6
	Surgical patients, acute pain, local, epidural anesthesia [44 °]	3	NR	0.28 (-0.28 to 0.83)	NR	62.2	NR	14	6
Post-, intraoperative opioid consumption	Surgical patients, acute pain, general anesthesia [44 °]	7	NR	2.76 (1.53 to 4.00)	NR	96.3	NR	14	6
	Surgical patients, acute, procedural pain [44 °]	3	NR	1.44 (0.53 to 3.44)	NR	97.5	NR	14	6
	Surgical patients [20 *** °]	7	517	1.23† (0.43 to 2.04)	0.003	93.9	0.000	14	5
Postoperative pain	3h after laparoscopic cholecystectomy [29 °]	2	165	0.86† (-0.97 to 2.69)	0.360	95.0	NA	11	4
	1h after laparoscopic cholecystectomy [29 °]	2	165	0.26† (-0.56 to 1.08)	0.530	81.0	NA	11	4
Chronic pain	Surgical patients [44 °]	5	NR	0.65 (0.34 to 0.96)	NR	39.4	NR	14	6
Procedural pain	Surgical patients, acute pain [44 °]	2	NR	0.50 (-0.54 to 1.54)	NR	85.3	NA	14	6
Anxiety									
Anxiety-preoperative VAS	Preoperative and postoperative [24 °]	18	1264	0.87† (0.56 to 1.19)	0.000	85.2	0.000	16	7
Postoperative anxiety STAI	Preoperative and postoperative [24 °]	2	73	0.70† (0.23 to 1.18)	0.004	0.0	NA	16	7
Anxiety-postoperative VAS	Preoperative and postoperative [24 °]	7	524	0.59† (0.08 to 1.09)	0.022	86.5	0.000	16	7
Postoperative course									
Sleepiness after 3 days	After laparoscopic cholecystectomy [29 °]	2	162	0.10† (-0.23 to 0.44)	0.540	9.0	NA	11	4
Sleep quality	After laparoscopic cholecystectomy [29 °]	2	162	0.10† (-0.21 to 0.41)	0.530	0.0	NA	11	4
Well-being	After laparoscopic cholecystectomy [29 °]	2	162	-0.05† (-0.36 to 0.26)	0.760	0.0	NA	11	4

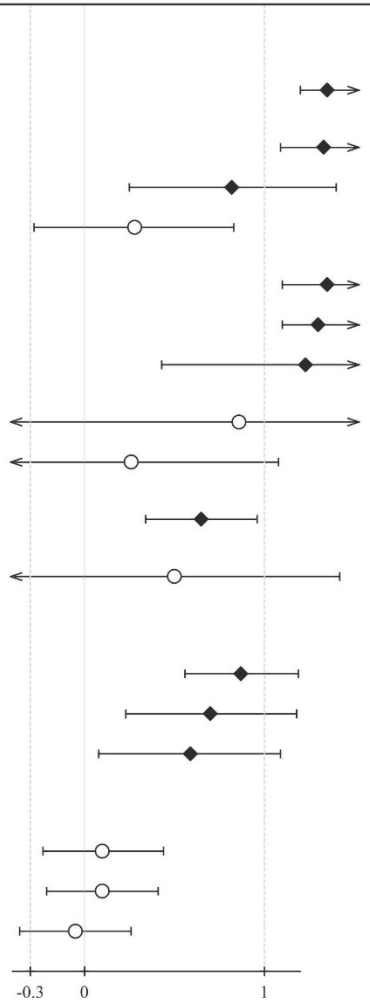


Figure 5

Outcome	Condition	N.trial	N.total	Effect size (95% CI)	P value	I^2(%)	Egger's P value	A2	A2-CD
Metabolic syndrome									
Insulin	Metabolic syndrome [35] ***	8	376	1.84 (1.13 to 2.56)	0.000	0.00	0.540	14	5
	Metabolic syndrome [46]	4	182	0.15† (-0.35 to 0.66)	0.553	63.4	0.042	12	4
Systolic blood pressure	Metabolic syndrome [33] ***	9	510	0.87 (0.38 to 1.36)	0.000	84.3	NR	15	6
Diastolic blood pressure	Metabolic syndrome [33] ***	9	510	0.85 (0.51 to 1.20)	0.001	68.7	NR	15	6
HOMA-IR	Metabolic syndrome [35] **	7	344	0.56 (0.24 to 0.89)	0.001	22.0	0.260	14	5
	Metabolic syndrome [46]	3	150	0.17† (-0.28 to 0.63)	0.459	48.3	0.145	12	4
Body weight	Obesity [49] *	17	1065	0.48 (0.02 to 0.94)	0.038	92.0	< 0.01	13	6
QUICKI	Metabolic syndrome [46] *	2	114	0.46† (0.09 to 0.83)	0.016	0.00	NA	12	4
	Metabolic syndrome [35] ***	5		0.01 (0.01 to 0.01)	0.000	0.00	0.590	14	5
BMI	Obesity [49] *	18	877	0.31 (0.00 to 0.63)	0.049	80.0	< 0.01	13	6
Fasting glucose	Metabolic syndrome [46] *	2	504	0.30† (0.04 to 0.55)	0.022	36.7	NA	12	4
Hemoglobin A1c	Metabolic syndrome [46]	3	194	0.27† (-0.02 to 0.55)	0.065	0.00	0.560	12	4
Waist circumference	Obesity [49]	12	607	0.18 (-0.23 to 0.60)	0.383	83.0	0.378	13	6
Severity of tinnitus	Tinnitus [53]	NR	NR	-0.13 (-0.74 to 0.48)	NR	NR	NR	16	7
Migraine									
Migraine frequency	Episodic migraine [55] ††	NR	NR	1.71 (0.14 to 3.27)	NR	NR	NR	16	7
Pregnancy									
Number of matured oocytes	ART [47] ***	7	738	0.56 (0.27 to 0.85)	0.000	66.0	0.007	14	6
Number of top-quality embryos	ART [47] ***	3	232	0.53 (0.27 to 0.79)	0.000	0.00	0.816	14	6
Number of oocytes retrieved	ART [47] *	7	738	0.34 (0.01 to 0.67)	0.040	75.0	0.001	14	6
	COS [48]	5	680	0.30† (-0.02 to 0.63)	0.071	73.0	0.005	15	6
Menopausal women									
Psychological symptoms	Menopausal women [56]	6	NR	0.00 (-0.32 to 0.37)	0.884	70.3	0.005	13	4
Sleep quality	Menopausal women [56]	4	NR	-0.66 (-1.54 to 0.22)	0.141	89.4	0.000	13	4

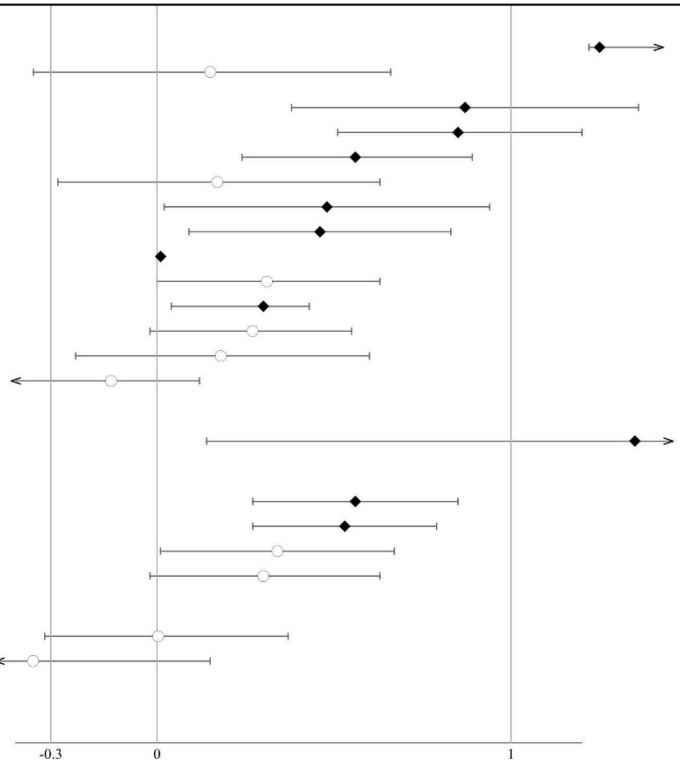


Figure 6

Outcome	Condition	N.trial	N.total	Effect size (95% CI)	P value	I^2(%)	Egger's P value	A2	A2-CD
Oxidative stress									
PCO (protein carbonyl)	Under oxidative stress [50 ***]	3	NR	1.78 (0.58 to 2.97)	0.004	95.6	0.040	13	5
CAT (catalase) activity	Under oxidative stress [13]	3	NR	1.38 (-1.42 to 4.18)	NR	96.6	0.000	14	7
SOD (superoxide dismutase) activity	Under oxidative stress [13]	3	NR	1.38 (0.13 to 2.62)	NR	86.9	0.000	14	7
	Under oxidative stress [50 ***]	2	NR	0.24 (-0.36 to 0.83)	0.439	0.00	NR	13	5
Gpx (glutathione peroxidase)	Under oxidative stress [13]	5	NR	1.36 (0.46 to 2.30)	NR	89.3	0.000	14	7
	Under oxidative stress [50 ***]	3	NR	-0.61 (-1.91 to 0.67)	0.350	83.6	NR	13	5
GR (glutathione reductase)	Under oxidative stress [13]	2	NR	1.21 (0.65 to 1.77)	NR	0.00	0.679	14	7
TAC (total antioxidant capacity)	Under oxidative stress *	8	NR	1.03 (0.24 to 1.81)	0.011	91.6	NR	13	5
	Under oxidative stress [13]	8	NR	0.76 (0.30 to 1.21)	NR	80.1	0.000	14	7
MDA (malondialdehyde)	Under oxidative stress [50 ***]	9	NR	0.84 (0.40 to 1.48)	0.001	83.8	0.007	13	5
	Under oxidative stress [13]	8	NR	0.79 (0.39 to 1.19)	NR	73.1	0.001	14	7
GSH (glutathione)	Under oxidative stress [13]	5	NR	0.57 (0.32 to 0.83)	NR	15.1	0.319	14	7
	Under oxidative stress [50 ***]	5	NR	0.41 (-0.16 to 0.98)	0.163	79.1	NR	13	5
NO (nitric oxide)	Under oxidative stress [13]	2	NR	0.24 (-0.14 to 0.61)	NR	0.00	0.941	14	7
	Under oxidative stress [50 ***]	8	NR	0.03 (-1.18 to 1.24)	0.962	95.6	NR	13	5

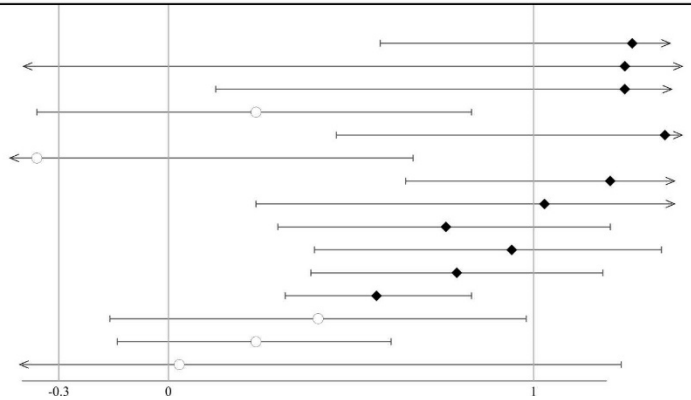
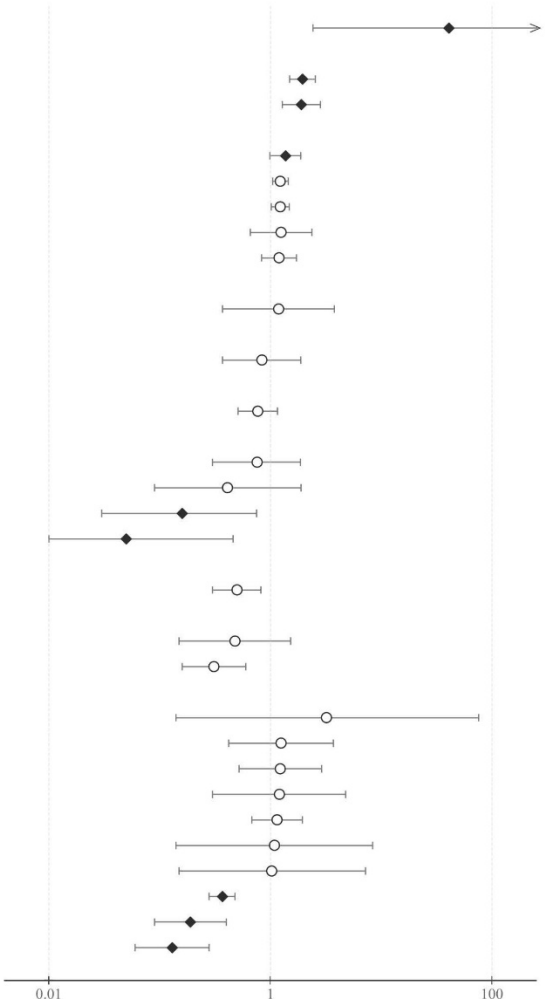


Figure 7

Health Outcomes / Control	Condition / Control	Effet size (95% CI)	P value	I^2(%)	Egger's P value	A2	A2-CD
Tinnitus							
Response rate	Tinnitus [53] ††	41.00 (2.42 to 693.88)	NR	NR	NR	16	7
Cancer							
Remission	Cancer [52] ***	1.95 (1.49 to 2.54)	<0.0001	0.00	0.980	11	3
Survival at 1 year	Cancer [52]	1.90 (1.28 to 2.83)	0.001	61.9	0.030	11	3
Pregnancy							
Rate of clinical pregnancy	COS [48]	1.37† (0.99 to 1.88)	0.056	0.00	0.796	15	6
	ART [47] *	1.23† (1.05 to 1.45)	0.012	0.00	0.944	14	6
Biochemical pregnancy rate	ART [47] *	1.23† (1.02 to 1.48)	0.032	0.00	0.481	14	6
Miscarriage rate	ART [47]	1.25† (0.66 to 2.37)	0.496	0.00	0.933	14	6
Live birth rate	ART [47]	1.20† (0.83 to 1.72)	0.335	0.00	0.812	14	6
Migraine							
Response rate	Episodic migraine [54] ††	1.19‡ (0.37 to 3.78)	NR	NR	NR	16	7
Mortality							
In-hospital mortality	Non-ICU patients [51]	0.84 (0.37 to 1.88)	0.67	0.00	0.710	15	6
Alzheimer							
Discontinuation of all cause	AD [39]	0.77 (0.51 to 1.16)	0.21	0.00	0.430	14	6
Delirium							
Incidence of delirium	Delirium patients [55] ††	0.76‡ (0.30 to 1.87)	NR	NR	NR	16	7
	Non-ICU patients [38]	0.41 (0.09 to 1.89)	0.25	78.0	0.010	15	6
	Delirium patients [7] ††	0.16‡ (0.03 to 0.75)	NR	NR	NR	15	6
	Pediatric patients after sevoflurane anesthesia [36] ††	0.05‡ (0.01 to 0.46)	NR	NR	NR	16	7
Pain							
Need for analgesic requirement	Surgical patients [52] **	0.50† (0.30 to 0.82)	0.006	53.5	0.072	14	5
Preoperative							
Incidence of emergence agitation	Preoperative children / Midazolam [17]	0.48 (0.15 to 1.52)	0.209	36.8	0.205	14	6
	Preoperative children [17] **	0.31 (0.16 to 0.60)	0.001	0.00	0.375	14	6
Side effects							
Drop-out for adverse effects	Children and adolescent with sleep onset insomnia [28]	3.22† (0.14 to 75.8)	0.468	0.00	1.000	13	5
Headache	After laparoscopic cholecystectomy [29]	1.25 (0.42 to 3.71)	0.68	7.0	NA	11	4
Drop-out for all causes	Children and adolescent with sleep onset insomnia [28]	1.23† (0.52 to 2.91)	0.639	0.00	0.573	13	5
	Menopausal women [43] ††	1.21 (0.30 to 4.78)	NR	NR	NR	16	7
Nausea	Surgical patients [20]	1.15‡ (0.68 to 1.94)	0.590	0.00	NR	14	5
Dizziness	After laparoscopic cholecystectomy [29]	1.09 (0.14 to 8.40)	0.940	51.0	NA	11	4
Depression	After laparoscopic cholecystectomy [29]	1.03 (0.15 to 7.21)	0.970	0.00	NA	11	4
Fatigue	After radiochemotherapy of cancer [52] ***	0.37 (0.28 to 0.48)	<0.0001	0.00	0.53	11	3
Neurotoxicity	After radiochemotherapy of cancer [52] ***	0.19 (0.09 to 0.40)	<0.0001	0.00	0.95	11	3
Thrombocytopenia	After radiochemotherapy of cancer [52] ***	0.13 (0.06 to 0.28)	<0.0001	0.00	0.99	11	3