Alerting effects of light in healthy individuals: a systematic review and meta-analysis

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Introduction
Alertness is a psychological construct closely related to attention, and refers to a behavioral and physiological state of responsiveness to incoming stimuli (Rosner, 2008). For practical reasons, alertness has been regarded as the opposite of sleepiness (Kaida et al., 2006). Alertness is essential for independent functioning in our daily lives, and is an important factor that contributes to the quality of work performance. For instance, it is essential for a student to be alert when attending a lecture, reading a textbook, or writing a report. In contrast, fatigue or daytime sleepiness can negatively affect cognitive and physiological functions, and have a series of consequences on an individual’s safety and quality of life. For instance, one study showed that fatigued train drivers performed less consistently and committed more speeding violations than well-rested drivers (Dorrian et al., 2007). Sleepiness is known to be a safety hazard in many 24/7 industries (Sallinen and Hublin, 2011). Daytime sleepiness has become pervasive, and it is becoming a serious concern in modern society.

Accumulated evidence from animal and human studies has demonstrated an important role of light on alertness. However, the efficacy of light intervention on alertness can vary according to properties such as illumination level, light wavelength, and measures of alertness (Cajochen, 2007). With regard to the illumination level of light, the first demonstration of a physiological effect of light was Lewy’s discovery in 1980, which indicated that at least 1000...
light of white light was required to suppress melatonin in healthy humans (Lewy et al., 1980). Cajochen and colleagues investigated the relationship between light intensity and alertness, and found increased levels of alertness with increases in illuminance level according to a logistic function (Cajochen et al., 2000). Several studies investigated the relationship between wavelength and alertness, and it seems that short-wavelength light is superior to long-wavelength light in improving alertness (Cajochen, 2007). This short-wavelength sensitivity corresponds closely to the spectral sensitivity of melatonin-expressing intrinsically photosensitive retinal ganglion cells (ipRGCs Amax ~480 nm) that primarily mediate the alerting and performance deficit on the vigilance task (Thapan et al., 2003). Although mounting studies have examined the effect of light on alertness and have consistently found a beneficial effect of light on alertness, there is still no clear consensus on the optimal protocol of light intervention to improve alertness. A systematic review of evidence on light intervention is needed to explore the relationship between light and alertness, and the mechanism underlying alerting effects. Several systematic review studies have been conducted in this field. For instance, Souman et al. (2018), who reviewed 68 studies, showed that exposure to higher intensities of polychromatic white light was reported to increase subjective alertness in many studies. It also remains unclear how different properties of light contribute to the alerting effect (Souman et al., 2018). The current study improves upon previous studies in at least 2 ways. Firstly, the current study provides more reliable conclusions by employing statistical methods to quantitatively synthesize the results of multiple studies. Secondly, we focused on a healthy population with a normal sleep-wake cycle and selected studies involving subjects who were night shift workers or disturbed sleep. Previous studies did not apply such restrictions on subjects. Stable and high levels of alertness can only be maintained when the phase relationship between the endogenous circadian timing system and the sleep/wake cycle is such that the circadian drive for sleep is at its maximum, during sleep inertia and under high homeostatic sleep pressure (Cajochen, 2007). Therefore, it is reasonable to postulate that compared with healthy individuals, subjects with disturbed sleep cycles are more sensitive to the alerting effects of light, and the mechanism underlying alerting effects may also be different between healthy individuals and individuals with disturbed sleep rhythms. In addition to alertness, light exerts profound effects on a wide range of physiologies and behaviors, such as entraining circadian rhythms (Aschoff et al., 1969; Czeisler et al., 1986), improving mood (Eastman et al., 1998), and affecting sleep (Chellappa et al., 2013). These non-image-forming effects are not associated with classical retinal ganglion cells (ipRGCs λmax 480 nm) that primarily mediate alerting effects and performance deficit on the vigilance task (Thapan et al., 2003). These non-image-forming effects are not associated with classical cones and rods, but are mainly mediated by ipRGCs (Provencio et al., 2000; Thapan et al., 2003). Accumulating evidence has suggested that ipRGCs play an essential role in the alerting effects of light. For example, one human study using 460 nm narrowband light to stimulate ipRGCs specifically improved alertness (Vandewege et al., 2017). The alerting-improving effects of exposure to bright light was absent in mice lacking melanopsin (Milosavljevic et al., 2016), which is the photosensitive protein expressed in ipRGCs (Berson et al., 2002). The efferent projections of the ipRGCs include those to multiple hypothalamic, thalamic, striatal, brainstem, and limbic regions (Provencio et al., 2000). Among the hypothalamic regions, the most studied are the suprachiasmatic nucleus (SCN), ventral lateral preoptic area, locus coeruleus (LC), and dorsal raphe. These pathways may regulate the alerting effects of light (Lok et al., 2018).

The alerting effect of light has previously been examined in narrative reviews (Cajochen, 2007; Lok et al., 2018; Souman et al., 2018; Xu and Lang, 2018). To the best of our knowledge, the present study is the first quantitative meta-analysis to investigate the efficacy of light exposure on the alertness of healthy volunteers. We evaluated the relationship between light exposure on subjective alertness and performance on objective performance measures of alertness. Subjective measures of alertness include standardized scales to rate the level of sleepiness and objective performance measures of alertness. Subjective measures of alertness and performance compared the alerting effects of low-intensity light (< 1000 lx) and high-intensity light (≥ 1000 lx). With regard to the timing of light, the studies were categorized into one of three groups: daytime light exposure (8:00–18:00), night-time light exposure (18:00–24:00), or whole-day light exposure (8:00–24:00).

The main research questions of this study were as follows: (1) Does light exposure effectively improve the alertness of healthy volunteers? and (2) What is the relationship between the efficacy of light and intervention properties, such as wavelength, CCT, illuminance level, and timing of light exposure (daytime, night-time, or all day)?

Materials and Methods

A literature search was conducted according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses statement (PRISMA) guidelines for systematic reviews and meta-analyses (Moher et al., 2015). This systematic review protocol was registered at PROSPERO (Registration ID: CRD42020181485).

Literature search

The first author searched the Web of Science, PubMed, and PsyCINFO databases for all studies investigating light intervention with healthy volunteers. The search was restricted to studies published in English, and the search period was January 1943 to August 2021. The search keywords were as follows: light OR light therapy OR light treatment OR phototherapy OR phototherapy and alertness OR vigilance OR arousal OR sleepiness OR tiredness OR fatigue. All reviews and bibliographic citations of relevant publications were examined by hand for additional references.

Inclusion and exclusion criteria

Studies were included in the meta-analysis according to the following criteria: (1) randomized controlled trials (RCTs) and nonrandomized trials that employed a crossover or parallel-group design; (2) included healthy adults aged 18 years and above; (3) at least one intervention group implemented light intervention; and (4) quantified the assessment of alertness. The exclusion criteria were as follows: (1) review, editorial material, proceedings paper, etc.; (2) participants with irregular working schedules, such as night shifts; (3) participants with major health problems indicating neurological or psychiatric disorders; (4) participants with vision or sleep problems; and (5) mean and standard deviations were not available after attempts to contact authors, and could not be calculated from descriptive data or statistical tests in the article.

Selection of studies

We imported all studies to EndNote X9 and removed duplicate records. Eligible studies were selected in two stages. Firstly, three authors (XDH, ZFH, and YMM) independently screened the title and abstract of each article identified by the systematic search. At this stage, we excluded all references that clearly did not fulfill the inclusion criteria. Secondly, the remaining full-text articles were further assessed independently by the same three authors (XDH, ZFH, and YMM). During both steps of the process, discrepancies were resolved by discussion, and decisions were made by the corresponding author (TQ). A flow chart illustrating the detailed selection process is depicted in Figure 1.

Data extraction

Two authors (XDH and ZFH) independently extracted the general characteristics from the included studies, including study design, characteristics of participants, intervention characteristics, control group, and outcome measures. The extracted data were matched and discussed in a consensus meeting, and disagreements were resolved. One author (XDH or YMM) transferred data into Review Manager Software (version 5.3.0; Cochrane Collaboration, Copenhagen, Denmark) (Higgins, 2011).

Data on specific properties of light intervention were also extracted. The following light parameters were identified for the subgroup analyses: wavelength of light exposure (short wavelength ~480 nm vs. long wavelength ~600 nm), CCT of light exposure (warm light ~3000 K vs. cold light ~5000 K), and illuminance level of light.
Results

General characteristics of studies

Of the 1256 studies identified during the initial stage of the literature search, 39 full-text articles were retrieved and evaluated based on the selection criteria. Twenty-nine studies satisfied the prespecified inclusion criteria, and the characteristics of these studies are shown in Table 1. Of the 29 included studies, 27 used crossover designs, and 2 used parallel-group designs. In total, 1210 participants were included in these studies; 596 participants (mean age 25.53 years, 318 (53.36%) male) received experimental light intervention and 614 participants (mean age 25.60 years, 318 (51.79%) male) received a placebo control. Experimental groups were administered light intervention with a short-wavelength, cold, or high-illumination light, while control groups received long-wavelength, warm, or low-illumination light.

Twenty-one studies (Kohsaka et al., 1999; Cajochen et al., 2005; Crasson and Legros, 2005; Hansen et al., 2005; Rüger et al., 2006; Takasu et al., 2006; Viola et al., 2008; Chellappa et al., 2012; Sahin and Figueiro, 2013; Leichtfried et al., 2015; Okamoto and Nakagawa, 2015; Borragan et al., 2017; Rahman et al., 2017; Hartstein et al., 2018; Kazemi et al., 2018; de Zeeuw et al., 2019; Šmotek et al., 2019; Studer et al., 2019; Yang et al., 2019; Zhou et al., 2021) were included in the subgroup analyses on light characteristics; 6 studies were classified into the wavelength group (Cajochen et al., 2005; Sahin and Figueiro, 2013; Okamoto and Nakagawa, 2015; de Zeeuw et al., 2019; Šmotek et al., 2019; Studer et al., 2019). 7 studies were classified into the CCT group (Viola et al., 2008; Chellappa et al., 2012; Rahman et al., 2017; Hartstein et al., 2018; Kazemi et al., 2018; Choi et al., 2019; Yang et al., 2019), and 8 studies were classified into the illuminance group (Kohsaka et al., 1999; Crasson and Legros, 2005; Hansen et al., 2005; Rüger et al., 2006; Takasu et al., 2006; Leichtfried et al., 2015; Okamoto et al., 2015; Studer et al., 2019). 70% of the 8 studies that were not included in the subgroup analyses on light characteristics, 2 did not use monochromatic light, and 6 used experimental and control light that were either higher or lower than the grouping definition of CCT or illuminance. Twenty-seven studies were included in subgroup analyses on timing characteristics (Kohsaka et al., 1999; O’Brien and O’Connor, 2000; Cajochen et al., 2005; Crasson and Legros, 2005; Hansen et al., 2005; Rüger et al., 2006; Takasu et al., 2006; Viola et al., 2008; Chellappa et al., 2012; Sahin et al., 2012; Sahin and Figueiro, 2013; Sahin et al., 2014; Leichtfried et al., 2015; Okamoto and Nakagawa, 2015; Muench et al., 2016; Borragan et al., 2017; Rodriguez-Morilla et al., 2017; Hartstein et al., 2018; Kazemi et al., 2018; Cajochen et al., 2019; Choi et al., 2019; de Zeeuw et al., 2019; Šmotek et al., 2019; Studer et al., 2019; Yang et al., 2019; Zhou et al., 2021) comprised the daytime group (Kohsaka et al., 1999; O’Brien and O’Connor, 2000; Crasson and Legros, 2005; Hansen et al., 2005; Rüger et al., 2006; Takasu et al., 2006; Sahin et al., 2012; Sahin and Figueiro, 2013; Sahin et al., 2014; Leichtfried et al., 2015; Okamoto and Nakagawa, 2015; Muench et al., 2016; Borragan et al., 2017; Hartstein et al., 2018; Kazemi et al., 2018; Choi et al., 2019; de Zeeuw et al., 2019; Šmotek et al., 2019; Studer et al., 2019; te Kulve et al., 2019; Yang et al., 2019; Zhou et al., 2021). 3 studies comprised the night-time group (Cajochen et al., 2005; Chellappa et al., 2012; Sahin et al., 2012; Sahin and Figueiro, 2013; Sahin et al., 2014; Leichtfried et al., 2015; Okamoto and Nakagawa, 2015; Muench et al., 2016; Borragan et al., 2017; Hartstein et al., 2018; Kazemi et al., 2018; Choi et al., 2019; de Zeeuw et al., 2019; Šmotek et al., 2019; Studer et al., 2019; te Kulve et al., 2019; Yang et al., 2019; Zhou et al., 2021), and 2 comprised the whole-day group (Takasu et al., 2006; Cajochen et al., 2019). Two studies were not included in the subgroup analyses on timing characteristics because the intervention lasted from the afternoon to the evening.

Improvement in alertness was quantified by employing objective tests in 15 studies (Crasson and Legros, 2005; Hansen et al., 2005; Sahin et al., 2014; Leichtfried et al., 2015; Muench et al., 2016; Borragan et al., 2017; Rahman et al., 2017; Rodriguez-Morilla et al., 2017; Kazemi et al., 2018; Cajochen et al., 2019; Choi et al., 2019; de Zeeuw et al., 2019; Šmotek et al., 2019; te Kulve et al., 2019; Yang et al., 2019; Zhou et al., 2021) were included in the subgroup analyses on light characteristics; 2 did not use monochromatic light, and 6 used experimental and control light that were either higher or lower than the grouping definition of CCT or illuminance. Twenty-seven studies were included in subgroup analyses on timing characteristics (Kohsaka et al., 1999; O’Brien and O’Connor, 2000; Cajochen et al., 2005; Crasson and Legros, 2005; Hansen et al., 2005; Rüger et al., 2006; Takasu et al., 2006; Viola et al., 2008; Chellappa et al., 2012; Sahin et al., 2012; Sahin and Figueiro, 2013; Sahin et al., 2014; Leichtfried et al., 2015; Okamoto and Nakagawa, 2015; Muench et al., 2016; Borragan et al., 2017; Rodriguez-Morilla et al., 2017; Hartstein et al., 2018; Kazemi et al., 2018; Cajochen et al., 2019; Choi et al., 2019; de Zeeuw et al., 2019; Šmotek et al., 2019; Studer et al., 2019; te Kulve et al., 2019; Yang et al., 2019; Zhou et al., 2021) comprised the daytime group (Kohsaka et al., 1999; O’Brien and O’Connor, 2000; Crasson and Legros, 2005; Hansen et al., 2005; Rüger et al., 2006; Takasu et al., 2006; Sahin et al., 2012; Sahin and Figueiro, 2013; Sahin et al., 2014; Leichtfried et al., 2015; Okamoto and Nakagawa, 2015; Muench et al., 2016; Borragan et al., 2017; Hartstein et al., 2018; Kazemi et al., 2018; Choi et al., 2019; de Zeeuw et al., 2019; Šmotek et al., 2019; Studer et al., 2019; te Kulve et al., 2019; Yang et al., 2019; Zhou et al., 2021). 3 studies comprised the night-time group (Cajochen et al., 2005; Chellappa et al., 2012; Sahin et al., 2012; Sahin and Figueiro, 2013; Sahin et al., 2014; Leichtfried et al., 2015; Okamoto and Nakagawa, 2015; Muench et al., 2016; Borragan et al., 2017; Hartstein et al., 2018; Kazemi et al., 2018; Choi et al., 2019; de Zeeuw et al., 2019; Šmotek et al., 2019; Studer et al., 2019; te Kulve et al., 2019; Yang et al., 2019; Zhou et al., 2021), and 2 comprised the whole-day group (Takasu et al., 2006; Cajochen et al., 2019). Two studies were not included in the subgroup analyses on timing characteristics because the intervention lasted from the afternoon to the evening.

Conclusion

In summary, light exposure may have a potential effect on alertness. Further studies with more rigorous design, and standardized measurement methods are required to confirm the impact of light on alertness.
tests and standardized scales in 10 studies (Crasson and Legros, 2005; Leichtfried et al., 2015; Muench et al., 2016; Borragan et al., 2017; Rahman et al., 2017; Rodriguez-Morilla et al., 2017; Kazemi et al., 2018; Smotek et al., 2019; Yang et al., 2019; Zhou et al., 2021). The objective tests included Psychomotor Vigilance Testing (PVT, 7 studies) (Muench et al., 2016; Borragan et al., 2017; Rahman et al., 2017; Smotek et al., 2019; Yang et al., 2019; Park et al., 2020; Zhou et al., 2021), Go/No-Go task (3 studies) (Sahin et al., 2014; Hartstein et al., 2017; Smotek et al., 2019), and some other attention tasks (driving simulator, Harvard Cognitive Battery, sustained attention test, attention network test, and duration-discrimination task, 5 studies in total) (Crasson and Legros, 2005; Hansen et al., 2005; Leichtfried et al., 2015; Rodriguez-Morilla et al., 2017; Studer et al., 2019), while the subjective scales included the Karolinska Sleepiness Scale (KSS, 17 studies) (Cajochen et al., 2005; Rüger et al., 2006; Viola et al., 2008; Chellappa et al., 2012; Santitham et al., 2013; Santhi et al., 2015; Okamoto and Nakagawa, 2015; Muench et al., 2016; Borragan et al., 2017; Rahman et al., 2017; Rodriguez-Morilla et al., 2017; Kazemi et al., 2018; Cajochen et al., 2019; Choi et al., 2019; de Zeeuw et al., 2019; Smotek et al., 2019; Studer et al., 2019; te Kulve et al., 2019; Yang et al., 2019; Park et al., 2020; Zhou et al., 2021).


table 1
| Study | Participants (E/C) | Experimental | Control | Time of day | Duration | Outcomes |
|-------|---------------------|---------------|---------|-------------|----------|----------|
| Kohsaka et al., 1999 | Crossover 8/8 | Moderately bright light (1000 lx) | No light | Morning | 1 h/d, 6 d | VAS |
| O’Brien and O’Connor, 2000 | Crossover 12/12 | 6434 lx | 1411 lx | 8:00–18:00 | 20 min | VAS |
| Caochek et al., 2005 | Crossover 9/9 | Monochromatic light (460 nm) | No light (0 lx) | 21:30–23:30 | 2 h | KSS |
| Crasson and Legros, 2005 | Crossover 18/18 | Bright light (5000 lx) | Sham exposure | 13:00–14:00 | 30 min | VAS, duration-discrimination task, KSS |
| Hansen et al., 2005 | Parallel-group 19/37 | White light (1800 lx) | Red light (100 lx) | Morning | 93 min/d, 5 d/wk, 2 wk | KSS |
| Rüger et al., 2006 | Crossover 12/12 | Bright light (5000 lx) | Dim light (< 10 lx) | 12:00–16:00 | 4 h | KSS |
| Takasu et al., 2006 | Crossover 8/8 | Bright light (5000 lx) | Dim light (10 lx) | 8:00–24:00 | 16 h/d, 6 d | VAS |
| Viola et al., 2008 | Crossover 94/94 | Blue-enriched white light (17000 K, 316 lx) | White light (4000 K, 412 lx) | 8:30–16:45 | –8 h/d, 5 d/wk, 4 wk | KSS |
| Chellappa et al., 2012 | Crossover 18/18 | Blue-enriched light (6500 K, 40 lx) | Control light (2500 K, 40 lx) | Evening | 2 h | KSS |
| Santitham et al., 2012 | Crossover 22/22 | Bright blue-enhanced light (700 lx) | Near-darkness (1 lx) | 19:30–23:30 | 4 h | KSS |
| Sahin and Figueiro, 2013 | Crossover 13/13 | Short-wavelength blue light (470 nm, 40 lx) | Dark (< 0.01 lx) | 14:30–15:30 | 1 h | KSS |
| Sahin et al., 2014 | Crossover 13/13 | White light (3000 K, 360 lx) | Red light (630 nm, 210 lx) | Daytime | 2 h | Go/No-go task |
| Leichtfried et al., 2015 | Crossover 33/33 | Bright light (5000 lx) | Dim light (400 lx) | 7:40–8:10 | 30 min | VAS, Sustained Attention Test |
| Okamoto and Nakagawa, 2015 | Crossover 8/8 | Short-wavelength light (2600 K, 40 lx) | Darkness | 12:00–16:00 | 28 min | KSS |
| Muench et al., 2016 | Crossover 18/18 | Mixed blue-enriched light (3537 K, 750 lx) | Warm-white control light (2600 K, 40 lx) | 8:00–11:00 | 3 h/d, 3 d | VAS, PVT |
| Borragan et al., 2017 | Crossover 17/17 | Bright blue-enriched white light (4600 nm, 2000 lx) | Dim orange light (600 nm, < 200 lx) | 15:00–17:00 | 20 min | KSS, VAS, PVT |
| Rahman et al., 2017 | Crossover 16/16 | Standard fluorescent light (4100 K, 50 lx) | Blue-depleted circadian-sensitive light (50 lx) | 16:00–24:00 | 8 h | KSS, PVT |
| Rodriguez-Morilla et al., 2017 | Crossover 12/12 | Blue-enriched white light (440 nm, 469 lx) | Dim light (< 1 lx) | 21:45–23:00 | 75 min | KSS, driving simulator |
| Hartstein et al., 2018 | Crossover 40/40 | Cool experimental lighting (5000 K) | Warm experimental lighting (3500 K) | 9:00–11:00 | 20 min | Go/No-go task |
| Kazemi et al., 2018 | Crossover 20/20 | LED (6500 K) | Compact fluorescent (3500 K) | Daytime | 2 h | KSS, Go/No-go task |
| Cajochen et al., 2019 | Crossover 15/15 | Daylight LED (450 nm, 4000 K, 100 lx) | Conventional LED (4000 K, 100 lx) | 8:00–24:00 | 16 h | KSS |
| Choi et al., 2019 | Crossover 15/15 | Blue-enriched white light (460 nm, 6500 K, 500 lx) | Warm white light (625 nm, 3500 K, 500 lx) | 10:00–11:00 | 1 h | KSS |
| de Zeeuw et al., 2019 | Crossover 48/48 | High-mel light (480 nm, 3500K, 100 lx) | Dim light (< 5 lx) | 11:30–14:30 | 3 h | VAS |
| Smotek et al., 2019 | Crossover 12/12 | Short-wavelength light (455 nm) | Long-wavelength light (629 nm) | 12:00–15:00 | 20 min | KSS, PVT |
| Studer et al., 2019 | Crossover 28/28 | Blue-enriched light (458 nm, 876 lx) | Red-enriched light (611 nm, 1063 lx) | Morning | 1 h | Attention network test |
| te Kulve et al., 2019 | Crossover 12/12 | Bright light (750 lx) | Dim light (5 lx) | Night | 1 h | KSS |
| Yang et al., 2019 | Crossover 15/15 | Bright light (6000 K, 1000 lx) | Dim light (3600 K, < 5 lx) | Night | 3 h | KSS, PVT |
| Park et al., 2020 | Crossover 24/24 | LED (4000 K, 150 lx) | Dim light (< 10 lx) | 17:30–24:00 | 6.5 h | PVT |
| Zhou et al., 2021 | Crossover 17/17 | Blue-enriched bright light (6500 K, 1000 lx) | Normal indoor light (4000 K, 100 lx) | 14:00–14:30 | 30 min | KSS, PVT, Go/No-go task |

E/C: number of participants received experimental intervention/number of participants received control intervention; KSS: Karolinska Sleepiness Scale; LED: Light-emitting diode; PVT: Psychomotor Vigilance Testing; VAS: Visual Analogue Scales.
Rahman et al., 2017; Hartstein et al., 2018; Studer et al., 2019), 21 scored a “moderate” global final rating (Kohsaka et al., 1999; Cajochen et al., 2005; Rüger et al., 2006; Chellappa et al., 2012; Santhi et al., 2012; Sahin and Figueiro, 2013; Sahin et al., 2014; Leichfried et al., 2015; Okamoto and Nakagawa, 2015; Muench et al., 2016; Borragan et al., 2017; Rodriguez-Morilla et al., 2017; Kazemi et al., 2018; Cajochen et al., 2019; Choi et al., 2019; de Zeeuw et al., 2019; Smoek et al., 2019; Yang et al., 2019; Park et al., 2020; Zhou et al., 2021), and 2 scored a “weak” global final rating (Hansen et al., 2005; Takasu et al., 2006). The 21 “moderate” studies had “weak” scorings in the blinding criteria, as they did not mention whether a blinding method was used. One study had “weak” scoring in the selection bias criteria as the method of grouping was not illustrated, and “weak” scoring in the withdrawal and dropout criteria as the sample size decreased without any reason provided (Hansen et al., 2005). Another study had “weak” scoring in the selection bias criteria, as the method of grouping was not illustrated, and “weak” scoring in the blinding criteria, as they did not mention whether the blinding method was used (Takasu et al., 2006). The results are summarized in Additional Table 1.

**Overall intervention effects on subjective alertness**

The meta-analysis of the pooled data from the 24 studies with subjective measures showed that light intervention can significantly improve subjective alertness (SMD = –0.28, 95% CI: –0.49 to –0.06, P = 0.01, I² = 60%, REM; Figure 2). The effect size was robust, as assessed by the sensitivity analyses in which the “weak” studies with low quality were excluded (SMD = –0.28, 95% CI: –0.50 to –0.06, P = 0.01, I² = 60%, REM). Using the funnel plot analysis of the outcome, the results showed that the funnel plot distribution was basically symmetrical, which indicated that the result was stable and reliable (Figure 3).

**Figure 2** | Meta-analysis of subjective alertness.

The forest plot was drawn from the effect sizes and 95% confidence intervals (CIs) of 24 independent studies using subjective scales. Each dash represents the 95% CI, and the green rectangle represents the standardized mean difference (SMD). The prismatic symbol at the bottom represents the comprehensive result of the included studies, which does not intersect with SMD = 0 and is on the left, indicating that the experimental intervention was significantly effective.

**Figure 3** | Funnel plot assessing publication bias of studies with subjective measures.

The vertical line represents the meta-analysis summary estimate, and the scatter plot represents single studies. In the absence of publication bias, studies will be distributed symmetrically right and left of the vertical line. SE(SMD), standard error of the SMD; SMD: Standardized mean difference.

**Table 2** | Subgroup analysis of the efficacy of light intervention on subjective alertness

| Subgroups | N | Sample size | I² (%) | SMD (95% CI) | P-value |
|-----------|---|-------------|--------|--------------|---------|
| Parameters of light | 17 | 738 | 70 | –0.30 (–0.59, –0.01) | 0.04 |
| Wavelength | 4 | 156 | 0 | –0.13 (–0.44, 0.19) | NS |
| Correlated Color Temperature | 6 | 356 | 26 | –0.37 (–0.65, –0.10) | 0.007 |
| Illuminance | 7 | 226 | 86 | –0.40 (–1.17, 0.38) | NS |
| Timing of light intervention | 23 | 921 | 60 | –0.23 (–0.37, –0.10) | 0.005 |
| Daytime | 15 | 690 | 74 | –0.22 (–0.37, –0.07) | 0.005 |
| Night-time | 6 | 176 | 0 | –0.32 (–0.61, –0.02) | 0.04 |
| Whole-day | 2 | 46 | 0 | –0.14 (–0.71, 0.44) | NS |

CI: Confidence interval; N: number of studies; NS: not significant; SMD: standardized mean difference.

**Overall intervention effects on objective alertness**

Although 15 studies used objective tests to assess alertness, data from 14 studies could be quantitatively combined. The aggregated data from these 14 studies showed that light intervention effectively improved objective alertness (SMD = –0.34, 95% CI: –0.68 to –0.01, P = 0.04, I² = 74%, REM; Figure 4). The effect size was robust, as assessed by the sensitivity analyses in which the “weak” studies with low quality were excluded (SMD = –0.36, 95% CI: –0.73 to 0.00, P = 0.05, I² = 75%, REM). The funnel plot results showed that the two sides of the graph were not completely symmetrical, which indicated a possible publication bias (Figure 5).

**Figure 4** | Meta-analysis of objective alertness.

The forest plot was drawn from the effect sizes and 95% confidence intervals (CIs) of 14 independent studies using objective tests. The overall effect size revealed that light intervention effectively improved objective alertness.
Discussion

In this meta-analysis, we included 29 studies with a total of 1210 healthy participants enrolled in light intervention and control arms. Since these studies used the same or similar methods to quantify changes in alertness, the results were combined based on subjective alertness (the KSS or VAS) and objective alertness (the PVT, Go/No-Go, or another measure). The main results were as follows: (1) light intervention significantly improved subjective and objective alertness; (2) light exposure with a higher CCT was more effective in improving alertness than exposure to low-intensity light; (3) timing of light exposure; the results revealed no significant effect of daytime light exposure; (4) no significant effect of night-time light exposure; and (5) the effect of light on alertness is different across studies.

We found that light intervention improved both subjective and objective alertness. In light studies, subjective alertness may introduce bias by simply asking individuals to rate their levels of sleepiness or fatigue, particularly when the participants may expect to be more alert in a lit environment than in darkness. These placebo effects should be taken into consideration when interpreting the results of subjective measures of alertness. In addition, self-report measures tend to be unreliable. In contrast to subjective alertness, performance measures of alertness are objective in light intervention studies. The most widely used performance measure of alertness is the PVT, which is based on reaction time to a visual or auditory stimulus. The PVT is valid, reliable, and sensitive, but it measures sustained attention rather than alertness, per se. Nevertheless, a recent review called for a multimodal approach to evaluate the effect of light intervention on alertness (Lok et al., 2018). Although subjective and objective alertness measurements may be different, even within the same intervention (Van Dongen et al., 2003; Van Dongen et al., 2004; Zhou et al., 2012), the current results confirmed that light intervention improved both subjective and objective alertness.

It is well known that ipRGCs play an important role in the light-regulated effects on non-visual responses. IpRGCs signals project to the SCN (the biological clock) and then to a variety of brain areas involved in alertness, mood, and cognition. For instance, irradiance information can be transferred to the forebrain through a multisynaptic pathway involving the LC, which receives indirect SCN inputs from the dorsomedial hypothalamus (DMH) (Aston-Jones et al., 2001). Furthermore, a light-induced change in activity detected in the thalamus has been found to be related to the improvement in subjective alertness induced by light exposure (Vandewalle et al., 2006). The effect of light on the thalamus likely results in widespread cortical effects. The rodent intergeniculate leaflet of the thalamus, which corresponds to the human dorsal lateral geniculate nucleus, receives strong retinal innervations (Muscatin and Morin, 2006). It has strong connections with the SCN and projects to and receives afferents from numerous brainstem and hypothalamic nuclei involved in arousal regulation. The modulation of cortical activity by light reflects the recruitment of multiple cortical (and thalamic) components. These modifications of cortical function can in turn lead to behavioral changes such as alertness (Vandewalle et al., 2009).

Limitations

This meta-analysis has several limitations. Firstly, the overall quality of the included studies was not particularly high, and no studies met the RCT standard. Future well-designed RCTs are needed to advance our knowledge of light intervention. Secondly, we assumed that different types of performance tasks were comparable across studies. However, distinct tasks may reflect different aspects of alertness. For instance, three

Table 1 - Subgroup analysis of the efficacy of light intervention on objective alertness

| Subgroups | N | Sample size | % | SMD (95% CI) | P-value |
|-----------|---|-------------|---|-------------|---------|
| Parameters of light | 10 | 450 | 75 | –0.44 (–0.83, –0.07) | 0.03 |
| Wavelength | 2 | 80 | 7 | –0.39 (–0.86, 0.07) | NS |
| Correlated color temperature | 4 | 178 | 0 | –0.36 (–0.66, –0.07) | 0.02 |
| Illuminance | 4 | 192 | 91 | –0.69 (–1.77, 0.39) | 0.39 |
| Timing of light intervention | 12 | 504 | 75 | –0.29 (–0.66, 0.09) | 0.59 |
| Daytime | 10 | 450 | 79 | –0.35 (–0.78, 0.08) | 0.08 |
| Night-time | 2 | 54 | 0 | 0.03 (–0.51, 0.56) | 0.92 |

CI: Confidence interval; N: number of studies; NS: not significant; SMD: standardized mean difference.
studies used the Go/No-Go task, which is generally considered to measure inhibitory control, which can only partially reflect alertness. Finally, the outcome measure of our review only included subjective scales and objective performance tests. Many studies have used physiological measures, such as electroencephalogram, pupil fluctuations, and CBT, to assess the alerting effects of light. These studies were excluded during the literature search and selection process, because their dynamic real-time indicators were difficult to quantitatively combine.

Conclusions

Our findings suggest that light exposure is associated with significant improvement in subjective alertness, as measured by both standardized scales and objective alertness assessed using performance tasks. The results of the subgroup analyses suggest that light exposure with a higher CCT more effectively improves alertness than does light exposure with a lower CCT. With regard to the timing of light intervention, both daytime and night-time light exposure improved subjective alertness. The quality of evidence was moderate or high for most outcomes.

Author contributions: YMM conducted the search, conducted the full text screening, transferred data, conducted the analysis, and drafted the manuscript. XDH and ZFH screened the abstracts, conducted the full text screening, and extracted data. SZ is a statistician responsible for statistical analysis. KFS and CRR supervised the meta-analysis and contributed to the interpretation of the results. QT designed the study, supervised the meta-analysis, revised the manuscript, and contributed to the interpretation and discussion of results. All authors approved the final version of this paper.

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Availability of data and materials: All data generated or analyzed during this study are included in this published article and its supplementary information files.

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Additional file: Additional Table 1: The quality assessment of the included trials.

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### Additional Table 1 The quality assessment of the included trials

| Study                          | Selection bias | Study design | Confounders | Blinding | Data collection | Withdrawals and dropouts | Intervention integrity | Analysis appropriate to question | Global rating |
|-------------------------------|----------------|--------------|-------------|----------|----------------|--------------------------|------------------------|---------------------------------|---------------|
| Kohsaka et al., 1999          | 1              | 1            | 1           | 3        | 1              | 1                        | 1                      | 1                               | 2             |
| O'Brien and O'Connor, 2000    | 1              | 1            | 1           | 2        | 1              | 1                        | 1                      | 1                               | 1             |
| Cajoche et al., 2005          | 1              | 1            | 1           | 3        | 2              | 1                        | 1                      | 1                               | 2             |
| Crasson and Legros, 2005      | 1              | 1            | 1           | 1        | 1              | 1                        | 1                      | 1                               | 1             |
| Hansen et al., 2005           | 3              | 1            | 1           | 2        | 3              | 1                        | 1                      | 1                               | 3             |
| Ruger et al., 2006            | 1              | 1            | 1           | 3        | 1              | 1                        | 1                      | 1                               | 2             |
| Takasu et al., 2006           | 3              | 1            | 1           | 3        | 1              | 1                        | 1                      | 1                               | 3             |
| Viola et al., 2008            | 1              | 1            | 1           | 2        | 2              | 1                        | 1                      | 1                               | 1             |
| Chellappa et al., 2012        | 1              | 1            | 1           | 3        | 1              | 1                        | 1                      | 1                               | 2             |
| Santhi et al., 2012           | 1              | 1            | 1           | 3        | 1              | 1                        | 1                      | 1                               | 2             |
| Sahin and Figueiro, 2013      | 1              | 1            | 1           | 3        | 1              | 1                        | 1                      | 1                               | 2             |
| Sahin et al., 2014            | 1              | 1            | 1           | 3        | 1              | 1                        | 1                      | 1                               | 2             |
| Leichtfried et al., 2015      | 1              | 1            | 1           | 3        | 1              | 2                        | 1                      | 1                               | 2             |
| Okamoto and Nakagawa, 2015    | 1              | 1            | 1           | 3        | 1              | 1                        | 1                      | 1                               | 2             |
| Muench et al., 2016           | 1              | 1            | 1           | 3        | 1              | 1                        | 1                      | 1                               | 2             |
| Borragan et al., 2017         | 1              | 1            | 1           | 3        | 1              | 2                        | 1                      | 1                               | 2             |
| Rahman et al., 2017           | 1              | 1            | 1           | 2        | 1              | 1                        | 1                      | 1                               | 1             |
| Rodriguez-Morilla et al., 2017| 1              | 1            | 1           | 3        | 1              | 1                        | 1                      | 1                               | 2             |
| Hartstein et al., 2018        | 1              | 1            | 1           | 2        | 1              | 2                        | 1                      | 1                               | 1             |
| Kazemi et al., 2018           | 1              | 1            | 1           | 3        | 1              | 1                        | 1                      | 1                               | 2             |
| Cajoche et al., 2019          | 1              | 1            | 1           | 3        | 1              | 1                        | 1                      | 1                               | 2             |
| Cho et al., 2019              | 1              | 1            | 1           | 3        | 1              | 1                        | 1                      | 1                               | 2             |
| de Zeeuw et al., 2019         | 1              | 1            | 1           | 3        | 1              | 1                        | 1                      | 1                               | 2             |
| Šmotek et al., 2019           | 1              | 1            | 1           | 3        | 1              | 1                        | 1                      | 1                               | 2             |
| Studer et al., 2019           | 1              | 1            | 1           | 2        | 1              | 2                        | 1                      | 1                               | 1             |
| Šte Kulve et al., 2019        | 1              | 1            | 1           | 3        | 1              | 1                        | 1                      | 1                               | 2             |
| Yang et al., 2019             | 1              | 1            | 1           | 3        | 1              | 1                        | 1                      | 1                               | 2             |
| Park et al., 2020             | 1              | 1            | 1           | 3        | 1              | 1                        | 1                      | 1                               | 2             |
| Zhou et al., 2021             | 1              | 1            | 1           | 3        | 1              | 1                        | 1                      | 1                               | 2             |

1: Strong; 2: moderate; 3: weak.