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CLINICAL REVIEW

What works for jetlag? A systematic review of non-pharmacological interventions

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S U M M A R Y

Jetlag is a combination of travel fatigue and circadian misalignment resulting from air travel across time zones. Routinely recommended interventions based on circadian science include timely exposure to light and darkness (scheduled sleep), but the real-world effectiveness of these and other non-circadian strategies is unknown. We systematically reviewed the evidence for non-pharmacological interventions for jetlag. PubMed, EMBASE, Scopus, and Web of Science were searched. Studies reviewed 1) involved human participants undergoing air travel with a corresponding shift in the external light–dark cycle; 2) administered a non-pharmacological intervention; 3) had a control or comparison group; and 4) examined outcomes such as jetlag symptoms, sleep, cognitive/physical performance, mood, fatigue, or circadian markers. Thirteen studies used light exposure, physical activity, diet, chiropractic treatment, or a multifaceted intervention to counteract jetlag. Nine studies found no significant change in the outcomes, three reported mixed findings, and one was positive. The null findings are likely due to poorly designed circadian interventions and neglect of contributors to travel fatigue. Higher quality studies that schedule darkness as well as light, in the periods before, during, and after flight are needed to reduce the circadian component of jetlag. Interventions should also address the stressors that contribute to travel fatigue.

Introduction

Jetlag occurs with air travel across time zones [1]. Symptoms of jetlag include sleep disruption, fatigue, reduced cognitive performance, alterations in mood, and gastrointestinal disturbances, but the pattern of symptoms varies widely across individuals [2]. With increasing international travel and growth in long- and ultra-long-haul flights of more than 12 h, the symptoms of jetlag are becoming more than a transient inconvenience. Jetlag can impair the judgment of business travellers and politicians, and compromise the performance of athletes [3], defence personnel [4] and airline crew [5] with implications for international relations, multinational corporations, and the safety of ordinary people.

Circadian science suggests that jetlag is a direct result of circadian misalignment and points to light and other zeitgebers as strategies for re-entraining the circadian system to a new time zone, thereby minimising jetlag symptoms and mitigating their negative consequences. Pharmacotherapies such as synthetic melatonin have been shown to effectively reduce the symptoms of fatigue associated with jetlag [6,7]. However, non-pharmacological strategies may be preferred when applied to diverse groups of travellers that include children, the elderly, those with pre-existing health conditions, as well as those who simply prefer non-drug solutions. We therefore systematically reviewed the literature to evaluate the evidence for non-pharmacological strategies in reducing jetlag symptoms.

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Methods

Eligibility criteria

We searched the literature for randomised controlled trials, experimental studies, or observational studies that included the following:

- Population: Human participants undergoing transmeridian air travel (actual or simulated) with a shift in the external light–dark cycle.
- Intervention: Any non-pharmacological intervention, including but not limited to light exposure, sleep scheduling, meal timing, physical activity, and advice or information.
- Comparator: Existence of an appropriate control or comparison group.
- Outcomes: At least one of jetlag symptoms, sleep, cognitive performance, physical performance, mood, fatigue, or biological marker of circadian phase.

Excluded were studies that:

- Shifted the light–dark or sleep-wake cycle, without a period of travel or simulated travel.
- Examined strategies for reducing fatigue or jetlag in aircrew which promoted circadian entrainment to home time zone, rather than promoting re-entrainment to a new time zone (i.e., promoted adaptation to shiftwork).
- Investigated the impact of pharmacotherapies such as melatonin and sedative hypnotic drugs.

We focused on studies of human participants undergoing actual or simulated air travel so that we can comment on the effectiveness or usefulness of interventions to real-world situations, rather than the efficacy of light and other strategies to phase shift circadian rhythms under well-controlled laboratory conditions.

We note that our definition of pharmacotherapy includes synthetic melatonin and excludes caffeine and alcohol taken as beverages. This was a pragmatic decision based on a traveller's perspective: melatonin is only available by prescription in many countries outside North America and most travellers would consider taking a pill a form of drug therapy, while caffeinated and alcoholic drinks would be considered part of diet.

Search strategy

Search of PubMed, Embase, Scopus, and Web of Science were conducted on the 8th March 2017 and updated on the 25th June 2018. The general strategy involved “jet lag” or “circadian rhythm” keywords combined with intervention keywords and restricted to studies conducted in humans (where possible) and published in English. No date restriction was placed on the results and all databases were searched from the earliest available to the 25th June 2018. The detailed search strategy for each database can be found in Supplementary Tables S1 and S2.

Study selection and data extraction

Fig. 1 documents the flow of study selection. Titles and abstracts were reviewed for eligibility by one reviewer (YSB). The full text of manuscripts was reviewed when eligibility was unclear. Reference lists of the included studies, similar articles, and articles that cited the included studies were also examined for relevant studies. Study data was extracted by two reviewers (YSB and SP) according to the predetermined data fields in Table 1. Reporting of this review was guided by the PRISMA statement for the reporting of systematic reviews and meta-analyses [8].

Study appraisal and synthesis

Since both observational and experimental studies were included for review, study appraisal could not rely on standard risk of bias assessment tools. Instead we referred to the Cochrane Collaboration's risk of bias tool for clinical trials [9] and the STROBE guidelines for observational studies [10] to guide the process of quality assessment.

We considered studies to have an overall positive result in favour of the intervention if there were statistically significant differences on all outcomes compared to the control group; if no statistically significant differences on any of the outcomes were detected then overall results were negative; if there was a mix of positive and negative results depending on the outcome then findings were considered mixed.

The quality of included studies was appraised by categorising studies into low, moderate, or high risk for 1) selection bias, 2) information bias in the exposure (intervention/control), 3) information bias in the outcome, and 4) generalizability to travellers beyond those in the study. Selection bias refers to biases in the assignment of participants to the intervention and comparison groups. Information bias in the exposure refers to whether participants and researchers know which group participants are in at the time of the intervention and during the analysis of the results. Information bias in the outcome refers to measurement or reporting errors that may have systematically influenced the results.

Due to the small number of expected studies, we did not plan meta-analyses to synthesize the results or to quantify the risk of bias across studies.

Results

Study characteristics

The search revealed 13 studies and these are summarised in Table 1. Of these, seven studies used light as a standalone intervention [11–17]; one used physical activity combined with outdoor light exposure [18]; one used a multifactorial intervention that combined light with sleep hygiene and noise reduction [19]; one observed the impact of pre-flight physical activity [20]; one investigated the impact of diet [21]; one trialled chiropractic treatments [22], and one examined the impact of transcranial light delivered through the ear canal [23]. Only one study demonstrated a positive impact of the intervention on jetlag and this was an observational study of diet on jetlag symptoms [21]. In three studies, the results were mixed with the interventions affecting some outcomes but not others [12,18,23]; while the remaining nine studies found no significant effect of the intervention overall.

The study designs were varied: five were randomised controlled trials, three were controlled trials with no mention of randomisation, four were observational studies with the intervention selected by participants, and one was a randomised cross-over study. Twelve studies were conducted in the field with participants travelling for up to 15 h across 3 to 15 time zones whilst one study involved a simulated flight of 24-hours across 10 time zones.

A total of 392 participants were included across studies although sample sizes ranged from four to 186 with a median of 15 participants per study. More than 80% of all participants studied were male and participants were predominately young adults of around 30 y of age. Most participants (47% of all participants) were found in the study that examined the impact of diet in American

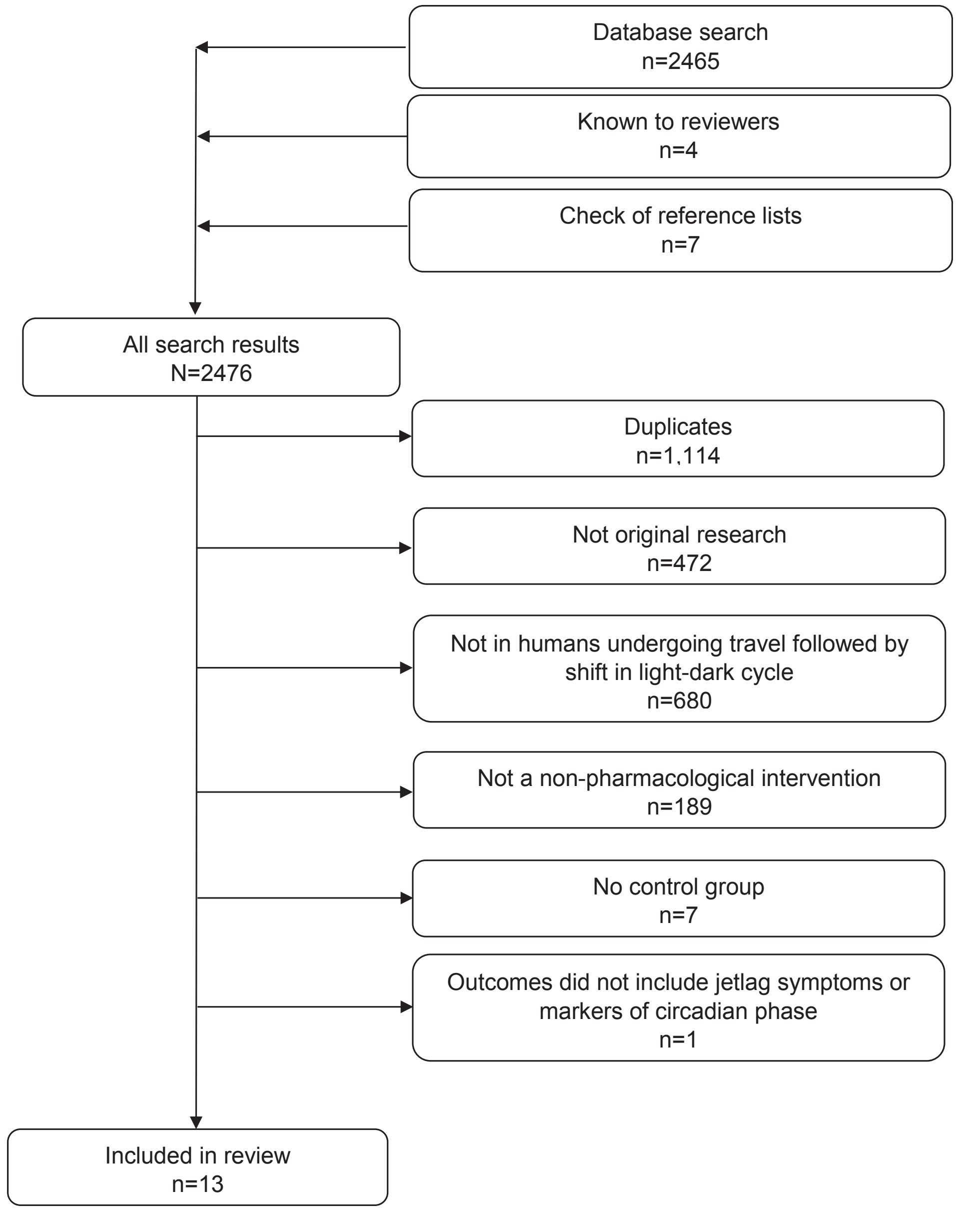

Fig. 1. Flowchart showing study selection.

soldiers. Other participants were healthy volunteers from the general community (35%), professional or elite athletes (9%), and the remainder (6%) were flight crew.

Five studies assessed only one outcome, while the other eight studies examined two to seven outcomes. Outcomes included: sleep assessed via self-report, sleep diary, actigraphy or polysomnography (n = 9 studies), self-reported jetlag symptoms (n = 8), mood (n = 5), melatonin rhythm (n = 2), physical performance (n = 2), psychomotor performance (n = 2), self-reported sleepiness (n = 2), core body temperature rhythm (n = 1), self-reported fatigue (n = 1), and trait anxiety (n = 1). Outcome data were collected for up to a week after travel, although the interventions tended to be administered for only 1–4 d after travel.

Light interventions

Light applied to the eyes was the most common intervention with nine of 13 studies using either light alone or in combination with other strategies to counteract jetlag. Fig. 2 illustrates the timing of scheduled bright light exposure at destination relative to estimated body clock time in the six studies that reported the times of light exposure. Two of these studies scheduled light to achieve phase advances of +5 h, +6 h, and +8 h [13,15]. The others scheduled light to achieve phase delays of −6 h, +8 h (−16 h), and +10 h (−14 h) [12,14,18,19]. Notably, the large phase advances of +8 h and +10 h were treated via phase delay rather than phase advance of the body clock.

Study appraisal

Risk of bias within studies

Study appraisal is summarised in Table 2. Of the 13 studies, nine revealed no significant effect of the interventions, three revealed mixed results depending on the outcome, and only one showed a significant positive impact of the intervention. We note that our

Table 1
Jetlag intervention studies by type of intervention and study setting/design (N = 13).

Study (Year) (Ref)	Study setting/ design	Sample (N, age, gender)	Travel details (phase shift)	Intervention (group size)	Control (group size)	Outcomes (outcome measure)
Thompson (2013) [13]	Field/RCT with parallel groups	N = 20 professional female soccer players (mean age 26, SD 4 y)	Flight from east coast USA to Portugal (+5 h), or 12 h flight from west coast USA to Portugal (+8 h)	**Bright light** Polychromatic light at 2500 lx for 45–60 min starting at 15:30 on day one and advancing an hour per day for 4 d; included subjects from both east and west coast flights (n = 11)	**Usual activity** in hotel room including reading, socialising, watching television; included subjects from both east and west coast flights (n = 9)	**No significant differences in** - Jetlag symptoms (Liverpool scale) - Temperature (intra-aural) - Grip strength
Cole (1989) [11] *Abstract only*	Field/RCT stratified by usual bedtime (before/after 23:00) and number of time zones crossed	N = 19 volunteers (mean age 37, SD 10 y, seven females)	Flight to San Diego from various locations with no layovers (+6.5 to +10.0 h)	**Bright light** Polychromatic white light of 2000 lx self-administered on days 1–3 for 2–3 h starting "as soon as possible after you wake from your main sleep period" (n = 11)	**Red light** (<100 lx), self-administered in same fashion as the intervention (n = 8)	**No significant differences on** - Sleep (sleep diary): total 24 h sleep, percent night-time sleep, percent daytime sleep
Boulos (2002) [12]	Field/RCT 2-day baseline, travel day, and 2-day follow-up	N = 20 healthy volunteers (aged 21–34 y, 12 females)	Flight from Zurich to New York (−6 h)	**Bright light** White light visor with a peak at blue-green wavelengths; 3000 lx applied from 19:00 to 22:00 on day 0 and from 20:30–23:30 on day 1. Otherwise, exposure to ambient 100 lx, and allowed to go outside from 10:00 to16:00 on day 1 (n = 10)	**Red LED visor** (10 lx) at the same schedule as the intervention (n = 10)	**Significant changes due to intervention in** - Melatonin (saliva DLMO): larger phase delay for bright compared to dim light (2.6 h vs. 1.6 h) **No significant differences in** - Jetlag symptoms (Columbia Scale) - Sleep (actigraphy, Leeds Questionnaire) - Psychomotor performance (memory and search test, choice reaction time) - Subjective sleepiness (visual analogue scale) - Mood (Profile of Mood States questionnaire)
Suhner (2001) [15] *Abstract only*	Field/Controlled trial	N = 9 volunteers (mean age 29 y, five females)	Flight from New York to Zurich (+6 h)	**Bright light** Polychromatic light at 2500 lx for 1.5 h after participants' T_{min} (determined pre-flight) on days 0–2, dark sunglasses for **light avoidance** at pre-defined times (times not reported) (n = 5)	**Dim red light** (<20 lx) scheduled as for the bright light condition, without light avoidance (n = 4)	**No significant differences in** - Melatonin (saliva DLMO) - Sleep (actigraphy) - Sleep quality, vigor, and mood (questionnaire): Overall jetlag rating did not differ between groups but bright light perceived to be significantly more effective than control condition
Sasaki (1989) [14] *Abstract only*	Field/Controlled trial 2-day baseline, travel, 5-day follow-up	N = 4 healthy males (aged 29–35 y)	Flight from Tokyo to San Francisco (+8 h)	**Bright light** Polychromatic light of 3000 lx from 11:00 to 14:00 on days 1–3; light exposure at other times not reported (n = 2)	**"Dim" light** i.e., illuminance maintained at <500 lx at the same schedule as the intervention (n = 2)	**Changes due to intervention in** - Sleep (PSG): sleep efficiency higher in intervention (86–97%) vs. control (51–77%) across the four nights after travel; mean wake after sleep onset lower in intervention group (110 min vs. 201 min)
Lahti (2007) [16]	Field/Observational study	N = 15 flight crew (mean age 42, SD 10 y, 14 females)	Flight of ≥3-time zones with ≥3 d at one of eight destinations (±3 h minimum)	**Bright light** Portable fluorescent lamp at 5000 lx; treatment schedule tailored to destinations for use at home/hotel and in crew briefing areas; sunlight if available (times not reported) (n = 20 flights)	**No bright light** treatment (n = 8 flights)	**No significant differences in** - Jetlag symptoms (Columbia scale)
Jurveilin (2015) [23]	Field/RCT 1-week pre-travel, minimum 1 wk at destination, and 1 wk after return flight. Day 0 is the day of the return flight.	N = 55 males (mean age 39, SD 7 y)	Flight from Finland to various locations in North America and return; ≥1 wk before return to Finland (+8 to +10 h)	**Transcranial bright light** White LEDs (peak spectrum at 448 nm) hidden in earmuffs; 9100 lx for 12 min every 2 h from 08:00 to 14:00 on day 0 and from 10:00 to 16:00 on days 1–6 (n = 25)	**Earmuffs with inactive LEDs** administered on same schedule as the intervention (n = 30)	**Significant changes due to intervention in** - Jetlag symptoms (visual analogue scale) - Subjective sleepiness (Karolinska Sleepiness Scale) - Mood (Profile of Mood States questionnaire): fatigue, inertia, and forgetfulness subscales **No significant differences in**

Table 1 (*continued*)

Study (Year) (Ref)	Study setting/ design	Sample (N, age, gender)	Travel details (phase shift)	Intervention (group size)	Control (group size)	Outcomes (outcome measure)
						- Sleep (sleep diary) - State-Trait Anxiety Inventory
Klein (1974) [17]	Field/Controlled trial Baseline days −3 to −1, travel day 0, follow-up on day 1, 3, 5, 8, and 13	N = 8 students (age and gender not reported)	Flight between Germany and USA (±6 h)	**Outdoor and indoor activity** Participants allowed to leave test facility on post-flight days 2, 4, 6, and 7 (n = unknown)	**Indoor activity** with participants kept inside for 7 days after flight (n = unknown)	**Changes due to intervention in** - Psychomotor performance rhythm: speed of re-entrainment faster in group with intermittent outdoor activity
Shiota (1996) [18]	Field/Observational Baseline on days −4 and −2, travel on days 0–1, exercise scheduled on day 2, and return flight on day 3, recovery – days 4–7	N = 10 male flight crew (mean age 47, SD 7 y in intervention group; mean age 47, SD 2 y in control group)	Flight from Tokyo to Los Angeles (+8 h)	**Outdoor exercise** Golf or ocean swim during 09:30–14:30 on day 2 (in Los Angeles) under sunlight (n = 5)	**Sedentary indoors activity** or shopping if rainy or cloudy weather (n = 5)	**Significant changes due to intervention in** - 17-hydroxy-corticosteroids (urine): Acrophase advanced in outdoor exercise compared to indoor activity group (day 3) - Fatigue (self-report): Significantly higher fatigue after exercise on day 3 **No significant differences in** - Sleep time and depth (self-report)
Montaruli (2009) [20]	Field/Observational study	N = 18 male volunteers (age unknown)	Flight from Milan to New York (−6 h)	**Morning or evening training** Runners who trained for marathon 3 times a week for 1 mo and daily in the 5 d before travel during either 07:00–09:00 (n = 6) or 19:00–21:00 (n = 6)	Participants who did physical activity recreationally but did no physical activity the week before travel (n = 6)	**Significant changes between the groups in** - Movement and fragmentation index during sleep (actigraphy): lower movement and fragmentation in the evening exercise group compared to morning and control (1st night post travel). **No significant differences in** - Jetlag symptoms (questionnaire); - Sleep (actigraphy): No differences on sleep efficiency, sleep time, or sleep latency were seen.
Reynolds (2002) [21]	Field/Observational study	N = 186 soldiers (mean age 33 y, 96% male)	Flights from USA to Korea (+15 h), and/or Korea to USA (−9 h)	**Argonne diet** Alternate days of feasting (high-protein breakfast and lunch; high-carbohydrate dinner) and fasting (800 Cal daily) beginning 4 d before travel (n = 95 USA to Korea, n = 34 Korea to USA)	**Diet as usual** (n = 91 USA to Korea, n = 127 Korea to USA)	**Significant differences in** - Jetlag symptoms (questionnaire): On deployment, soldiers who did not use the diet were 7.5 times more likely to report jetlag than those who did. On return home, those who did not use the diet were 33.3 times more likely to report jetlag
Straub (2001) [22]	Field/RCT 19-day trial, unclear day of travel, 4 d follow-up for each leg of return trip	N = 15 track and field athletes (mean age 18 y, three females)	Flight from Helsinki to Marietta, Georgia, USA (−7 h) and back (+7 h)	**Chiropractic adjustment** Chiropractic care from licensed chiropractors as needed (n = 5)	**Sham adjustment** Sham adjustment from licensed chiropractor daily (n = 5) **Control** No chiropractic care (n = 5)	**No significant differences in** - Jetlag symptoms (10-point rating scale) - Mood (Profile of Mood States questionnaire) - Heart rate (Polar monitor) - Sleep (actigraphy)
Fowler (2015) [19]	Laboratory/ Randomised cross-over trial with 1 wk between conditions Baseline on day −1, travel on day 0, follow-up days 1–3	N = 13 healthy males (mean age 24 y)	Simulated 24 h flight from Sydney to London with normobaric hypoxic room, noise, meals and lighting schedule according to typical flight with 2 h stopover in Hong Kong, London lighting schedule, and meal delivery upon "arrival" (+10 h)	**Multi-strategy intervention** Noise cancelling headphones and neck cushion with advice to sleep during "flight"; Light-emitting glasses (Re-Timer^{TM}) used from 02:00 to 05:00 and sunglasses used 05:00 to 08:00 for 2 days post-flight; Sleep hygiene on reducing screen time and quiet and dark conditions prior to bed (n = 13)	No assistance or advice given during flight and instructed to maintain normal behaviour (n = 13)	**No significant differences in** - Jetlag symptoms (Liverpool questionnaire) - Physical performance (Maximal sprint, countermovement jump, Yo–Yo intermittent recovery test) - Sleep (actigraphy) - Mood (Brunel Mood Scale)

Note: (i) for consistency across the studies we use day 0 for day of travel or phase shift, day n for the nth day post-travel and day −n is the nth day pre-travel; (ii) In all studies the reported clocktime of interventions refers to the local time zone of participant at the time of the intervention; i.e., the destination time zone for the field jetlag experiments and time zone of the laboratory for the simulated study; (iii) SD stands for standard deviation; (iv) T_{min} = core body temperature minimum; (v) DLMO = dim light melatonin onset; (v) RCT = randomized controlled trial.

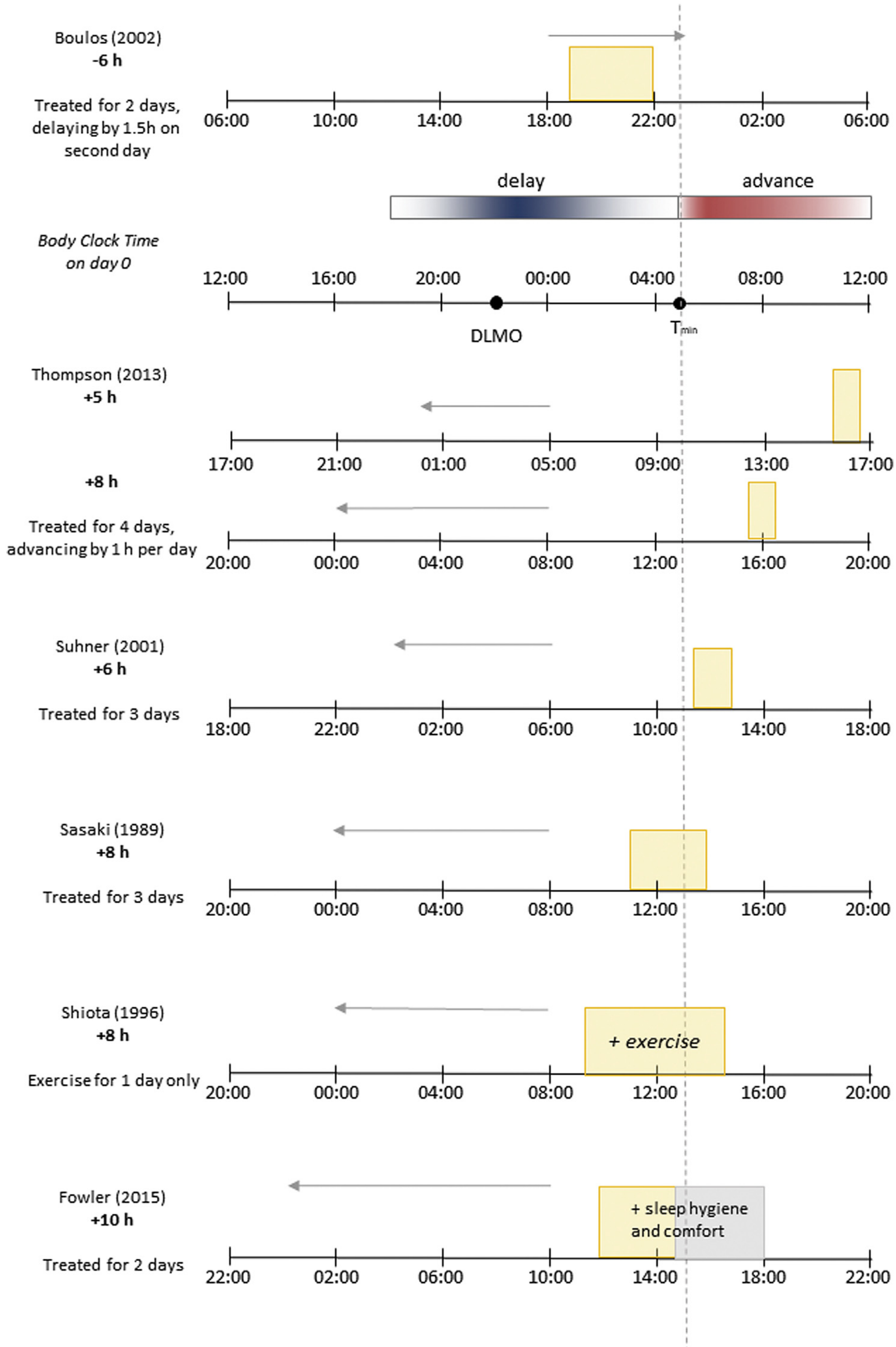

Fig. 2. Timing of light treatment across studies of light intervention, by size of phase shift. Note: Only the studies using light as a part of the intervention and reporting the times of light exposure are shown (six from 13 studies in Table 1). For studies that reported participants travelling to/from different destinations, the time differences are shown separately. Times of light exposure are indicated with yellow rectangles and light avoidance with grey. Arrows show the direction and amplitude of body clock time change required for re-entrainment (regardless of intervention protocol). Indicative times of advance and delay relative to body clock time of light onset are shown at the top based on the phase response curves for 1 h and 6.7 h light exposure in St Hilaire et al. [30]. Gradient indicates the magnitude of expected phase change with darker colour referring to a larger change. The times of DLMO and T_{min} are indicative only, as there is large individual variability. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

definition of an overall positive result depended on the number of outcomes assessed by the study; we considered results positive if all outcomes assessed were significantly influenced by the intervention and this is clearly easier to achieve if only one outcome was considered. However, given that primary outcomes were not stipulated in any of the studies and tests of statistical significance were not conducted in studies with small numbers of participants, this was the most straightforward and conservative way to assess the findings.

Table 2
Risk of bias assessment for included studies of jetlag interventions (N = 13).

Study	Intervention type	Phase shift	Estimated travel duration[a]	Overall effectiveness[b]	Risk of selection bias	Risk of information bias (exposure)	Risk of information bias (outcomes)	Generalizability
Thompson (2013) [13]	Light	+5 or +8 h	7 h	Negative	Low – RCT	High – participants and researchers not blinded	Moderate – Temperature rhythm is masked under normal light	Moderate – female athletes only
Cole (1989) [11]	Light	+6.5 to +10.0 h	Various	Negative	Low – RCT	High – participants and researchers not blinded	High – only one subjective outcome	High – volunteers from community
Boulos (2002) [12]	Light	−6 h	8 h	Mixed	Low - RCT	High – participants and researchers not blinded	Low – combination of objective and subjective outcomes	Moderate – young adults only
Suhner (2001) [15]	Light	+6 h	8 h	Negative	Moderate – groups allocated, but no randomization	High – participants and researchers not blinded	Low – combination of objective and subjective outcomes	Moderate – young adults only
Sasaki (1989) [14]	Light	+8 h	9 h	Negative	Moderate – groups allocated, but no randomization	High – participants and researchers not blinded	Moderate – only one objective outcome	Moderate – males only
Lahti (2007) [16]	Light	±3 h minimum	Various	Negative	High – groups not allocated	High – participants and researchers not blinded	High – only one subjective outcome	Moderate – experienced fliers only
Jurveilin (2015) [23]	Transcranial light	+8 to +10 h	10–15 h	Mixed	Low – RCT	Moderate – participants blinded, researchers not blinded	Low – combination of objective and subjective outcomes	Moderate – males only
Klein (1974) [17]	Outdoor activity	±6 h	9–11 h	Negative	Moderate – groups allocated, but no randomization	High – participants and researchers not blinded	Moderate – only one objective outcome	Low – participant characteristics unknown
Shiota (1996) [18]	Physical activity	+8	10 h	Mixed	High – groups not allocated	High – participants and researchers not blinded	Low – combination of objective and subjective outcomes	Moderate – males only
Montaruli (2009) [20]	Physical activity	−6 h	10 h	Negative	High – groups not allocated	High – participants and researchers not blinded	Low – combination of objective and subjective outcomes	Moderate – males only
Reynolds (2002) [21]	Diet	−9 or +15	13–15 h	Positive	High – groups not allocated	High – participants and researchers not blinded	High – only one subjective outcome	Moderate – mostly male soldiers only
Straub (2001) [22]	Chiropractic treatment	±7 h	10 h	Negative	Low – RCT	Moderate – sham control and inactive controls, researchers not blinded	Low – combination of objective and subjective outcomes	Moderate – teenage athletes only
Fowler (2015) [19]	Light, sleep hygiene, comfort, and noise reduction combined	+10 h	24 h	Negative	Low – randomised cross-over with washout	Moderate – cross-over, researchers not blinded	Low – combination of objective and subjective outcomes	Low – simulated travel in males only

[a] Assuming direct flights with no layover, based on present-day flight times.
[b] Overall effectiveness was positive if the intervention improved the outcome/s relative to the control group and this difference was statistically significant.

The risk of selection bias was high for the four observational studies but otherwise moderate as most other studies allocated participants into the intervention/control groups and many involved randomization into these groups. The greatest risk of bias came from the lack of blinding of participants and researchers across the majority of studies. Potential bias in the measurement of the outcome was generally low as a range of objective and subjective outcomes were assessed in the majority of studies. Generalisability of the results was moderate: all but one study involved actual travel, although only one study included participants who were likely representative of travellers at large.

Risk of bias across studies

Publication bias does not appear to be an important factor in this review given that only one of 13 studies reported results significantly in favour of the intervention (Table 2).

Discussion

Summary

There is limited evidence for the effectiveness of interventions for jetlag. This systematic review found 13 studies on jetlag interventions that met our selection criteria: nine of these found no significant impact of the interventions, three studies found mixed results, and only one reported an overall benefit of the intervention on jetlag. However, the study that found an overall positive result was also an observational study and therefore at high risk of biased results that require replication. Of the studies considered here, two involved interventions before the flight, nine applied interventions after the flight and two applied interventions both before and after the flight. There were no published studies of interventions during the flight itself. We discuss the different types of interventions below and discuss reasons for their possible failure to improve jetlag when applied to travellers.

Light exposure and avoidance

We found nine studies using light exposure via the eyes as a part of a jetlag intervention: six investigated the impact of standalone bright light exposure [11–16], one combined light with strategies to improve sleep [19], one combined exercise with light [18] and one provided participants with opportunities for outdoor activity [17].

Guidelines for treating jetlag recommend appropriately timed light to facilitate the re-entrainment of circadian rhythms to a new time zone [2,24–26]. Phase- and dose-response curves (PRCs and DRCs) have been developed to characterise how changing the timing, duration, illuminance, and spectrum of light affects circadian phase [27–32]. Application of these principles in controlled laboratory settings has shown that properly scheduled light is successful in re-entraining the circadian clock and improving alertness after a shift in light/dark and sleep/wake cycles [33–37]. Thus, there is a strong scientific basis for the use of scheduled bright light and darkness to shift circadian rhythms. Despite this, we found that of the nine light intervention studies, only two suggested a beneficial impact of light on sleep efficiency [14] and psychomotor performance [17]. Both were small studies with only four and eight participants respectively and were underpowered to detect statistically significant results.

In addition to small sample sizes, the reasons for the lack of effectiveness of light may also include 1) inefficient timing of light exposure, 2) lack of control over ambient light, and 3) large individual variability in circadian phase. First, as seen in Fig. 2, many studies did not take advantage of the maximum effect of light on circadian phase. The timing of the maximum effect depends on light duration but generally the greatest phase delay is achieved when light starts near the dim light melatonin onset (DLMO, ~22:00) and maximum phase advance is expected when light exposure is 7–8 h after DLMO; i.e., near the core body temperature minimum (T_{min}) [29,30]. For instance, Thompson and colleagues scheduled light exposure approximately 2.5 h and 5.5 h after T_{min} when earlier lighting would have resulted in a stronger phase shift [13]. All the phase delay studies positioned their light treatment to start 3–5 h after DLMO, which should have had a strong phase-delaying effect, especially for shorter light exposure durations. Notably, three studies chose to phase delay the body clock to treat a large advance in clock time [14,18,19]. This is justified because a larger phase delay can be achieved in one day than a phase advance and re-entrainment can occur more quickly [29]. However, this may also lead to an initial worsening of jetlag symptoms as the body clock moves farther away from local clock time and this may appear in the results as a negligible impact of the intervention.

Second, ambient light exposure likely influenced circadian dynamics and jetlag symptoms: five of nine studies did not fully report light levels outside of treatment schedules and indicated that participants were free to go on with their activities. Six of the studies did not schedule periods of light avoidance. Both of these factors could have led to ambient light counteracting the intervention if exposure appeared at the opposing part of the PRC. Thus, scheduling light avoidance is as important as scheduling light exposure for jetlag management. According to the DRC for polychromatic light [31], half of the maximal phase-delaying response is achieved at illuminance as low as 100 lx, with 550 lx allowing for 95% of the maximal response. This indicates that even exposure to room light at inappropriate times may impede circadian adaptation. Admittedly, PRCs and DRCs were developed under controlled laboratory settings with dim light (<15 lx) present at all times outside the times of scheduled light exposure, so it is difficult to apply the PRCs and DRCs directly to scheduling light for jetlag treatment under conditions where ambient light is present. To design light treatment under such dynamic conditions, it is necessary to use mathematical models of the circadian clock that account for the effects of ambient light. Such models exist for the circadian pacemaker alone [38–40] or integrated with the sleep-wake switch [41–43]. An important practical point is that scheduling light avoidance (darkness) may be achieved by scheduling sleep in darkness. Thus, light interventions should ideally be combined with tailored sleep schedules to facilitate optimal light/dark exposure.

A third reason for the null findings could be due to large individual differences in circadian phase. For example, Sletten and colleagues showed that DLMO time varies between 19:00 and 01:00 in individuals entrained to the same time zone [44]. This poses considerable difficulties for scheduling efficient light exposure without information about an individual's circadian phase. Phase shifts in the wrong direction are likely, especially when light is scheduled near an expected T_{min}. Only one of the nine light intervention studies measured individual circadian phase before the flight and scheduled light accordingly. Compounding this problem is the difficulty of ascertaining circadian phase: measuring DLMO in blood/saliva or rectal body temperature is not easy in applied settings. Measuring the acrophase of sulphatoxymelatonin (aMT6s) in urine is a promising way to estimate circadian phase that does not require dim light conditions [45]. New techniques based on mechanism-based modelling to predict melatonin and aMT6s dynamics [46] or the use of artificial neural networks to predict circadian phase from wearable data; e.g., light and skin temperature, are also being developed and hold potential for real-world applications [47]. The latter, however, still need to be validated under conditions of circadian misalignment. A practical alternative to reducing the impact of individual variability is to adopt strategies that partly take into account an individual's rhythm. Using an existing sleep schedule as the starting point allows interventions to be better tailored to individuals without the need to more precisely measure underlying circadian parameters.

Lastly, the light interventions focused on the period after travel. When light–dark interventions only begin after arrival at the destination, travellers will experience the maximum amount of circadian misalignment, thereby limiting the scope for minimising jetlag symptoms. In contrast, appropriate light exposure and avoidance before [48,49], and during the flight could significantly reduce the degree of circadian misalignment and the time required to adapt to a new time zone. The aircraft cabin may provide a more controlled environment in which to deliver the same intervention to groups of travellers, especially if the flight is long. Changing the characteristics and schedule of lighting during a long-haul flight for instance could be trialled as a novel strategy for counteracting jetlag.

Physical activity/exercise

We found two observational studies of physical activity, which provided little evidence that physical activity prior to travel reduced susceptibility to jetlag [20] or that physical activity after travel improved jetlag symptoms [18]. Being observational studies, these were poorly controlled with exercise self-selected by the participants. The results could be strongly confounded by unexplored differences between the exercise and comparison groups.

There is however some experimental evidence to suggest that physical activity affects circadian rhythms. Buxton and colleagues showed that one hour of high intensity cycling before DLMO advances the melatonin rhythm by 30 min, compared to a 25 min phase delay seen in control participants who did not exercise. This difference of an hour with a single session of exercise is comparable in size to a single dose of bright light [50,51]. Like light, the timing of exercise appears to be critical in producing a phase advance or delay; exercise later in the evening after DLMO and closer to bedtime appears to lead to a phase advance. However, there have also been failures of exercise to produce a phase shift beyond that induced by bright light alone [52]. Thus, the effects of physical activity on circadian phase and on jetlag symptoms needs to be further explored.

Diet

We found one study which examined use of the Argonne diet and subjective jetlag symptoms in an observational study of US soldiers and this was the only significant positive finding of this review [21]. The Argonne diet recommends alternating days of feasting and fasting beginning 4 d prior to travel. Soldiers who partook in the diet reported reduced symptoms of jetlag compared to those who ate as usual [21]. Caffeine was only allowed during certain times and no alcohol was allowed in transit. Soldiers who had not used the diet were 16.2 times more likely to report jetlag than those who had dieted, but since soldiers were not randomised to the diet, this may have been confounded by predisposition to jetlag, sedentary jobs (with reduced natural light exposure), and other unmeasured factors. The rules around the use of alcohol and caffeine may have also contributed to the effect. Whether a placebo effect was responsible is unclear since the only outcome examined was self-reported jetlag. Selection bias is an issue for the study as soldiers who did not use the diet could have been those who perceived it was not effective. The Argonne diet recommends high protein breakfasts/lunches and high carbohydrate dinners on feast days and it is unknown whether the composition of the diet is as important for alleviating symptoms as the relative timing and size of the meals.

While causal conclusions cannot be drawn from this observational study, the findings suggest that there may be value in investigating diet and meal timing further [21]. Experimental studies in non-human animals have shown that feeding contributes to the regulation of clock genes in various organs and therefore to circadian rhythmicity [53]. Research on meal timing and its potential circadian effects in humans is very preliminary and suggest a role for feeding and meal-timing on some circadian oscillators but not the suprachiasmatic nucleus [54,55]. Dietary interventions for jetlag would be relatively inexpensive, have few side effects, be easier to implement and potentially more acceptable to travellers than other interventions, but further study is required to understand how they might work and to determine if they are efficacious.

Other interventions

We found two studies that examined unexpected interventions for jetlag: one which made use of light exposure via the ear canal [23] and one that investigated the effect of chiropractic treatment before and after travel [22]. The first of these administered bright blue-enriched light through light-emitting diodes (LEDs) hidden in earmuffs to alleviate jetlag and was compared to earmuffs with LEDs that did not emit light [23]. This was the only light intervention study reporting a significant improvement in jetlag symptoms including reduced subjective sleepiness but there were no significant changes in sleep. The study cannot rule out an unforeseen placebo effect given that participants could have been unblinded by the heat emitted by the LEDs in the intervention. However, the biological basis for effects of in-ear light exposure is unclear.

The study of chiropractic treatment found no significant effect on self-reported mood and jetlag, or objectively assessed sleep and heart rate compared with sham chiropractic adjustment or no care. It is unclear why the authors believed chiropractic treatment could mitigate jetlag but the results of this study suggest chiropractic therapy is neither useful nor harmful for jetlag.

Sleep

Surprisingly, we found no studies that specifically examined the impact of sleep interventions on jetlag. One of the light interventions did combine light exposure with strategies to reduce sleep deprivation and fatigue [19]. Participants in this study underwent a simulated 24-hour flight and were given the use of noise-cancelling headphones and neck cushions during the flight, light-emitting glasses and sunglasses for 2 d post-flight, and advice on scheduling sleep and light exposure [19]. Despite the comprehensive and multifaceted intervention, the study revealed no impact of these strategies on physical performance, jetlag, or mood, only a tendency towards longer sleep during the flight relative to controls who were told to behave as they normally would during travel [19].

A commonly recommended method of counteracting jetlag is to shift bedtimes in the days before travel to be more closely in line with sleep times at the destination, but we found no studies examining the impact of shifting sleep schedules on jetlag symptoms. A previous study has reported that advancing bedtimes by 1-hour a day for three successive days is a feasible strategy, although that study did not examine if these advances improved jetlag or sleep after travel [56]. The sleep period provides travellers with a major opportunity to avoid light. Thus, future interventions should consider the combination of sleep and light, and emphasise to travellers the importance of remaining in darkness even when sleep is not possible after travel, while light-focused interventions should consider sleep time as an expedient period for light avoidance.

Sleep disturbances are thought to be a symptom arising from the circadian misalignment associated with jetlag, but the sleep deprivation that arises from travel itself was largely neglected as a potential cause of jetlag symptoms. Symptoms of fatigue are the most powerful predictor of jetlag, suggesting that the sleep deprivation contributes considerably to perceived jetlag [57,58]. Further, long-haul air travel in a north-south direction, which does not cross any time zones, is also associated with significant fatigue, which improves with sleep and rest. Sleep deprivation may have also contributed to the negative findings of this review as the need for sleep may have led to better, rather than worse, sleep on the nights immediately following travel.

Methodological issues

Measurement of outcomes

Only three of 13 reviewed studies reported outcomes for circadian phase assessment. Of these, two used salivary DLMO as the marker [12,15] and one used intra-aural temperature [13]. However, in ambulatory settings core body temperature is masked by sleep, food, locomotion and other activities [59], and care must be taken to collect salivary DLMO under dim light conditions. The alternative is to use urine sulfatoxymelatonin acrophase in field studies as it has the advantage of not requiring collection under dim light [45].

For jetlag symptoms, the two questionnaires used were the Columbia Jet Lag Scale [60] and the Liverpool Jet Lag Questionnaire [58], although as many studies devised their own ratings or surveys of jetlag symptoms. Standardising the measurement of jetlag and using previously validated questionnaires would be useful for comparing different interventions, for comparing the severity of jetlag symptoms across travel conditions and travellers, and for combining results across studies in future meta-analyses. Timing is also an important consideration in the assessment of jetlag symptoms which are rated differently at different times of day [58]. Intervention studies need to assess subjective outcomes at appropriate times so that benefits of the intervention are not inadvertently concealed and collecting appropriate objective markers of circadian timing would help to achieve this.

Tolerability and acceptability of interventions

The tolerability or acceptance of the interventions to participants was only mentioned in one study: Boulos and colleagues [12] found that at least three participants in an intervention group of 10 who wore a light-emitting visor complained of discomfort, suggesting that higher illumination to produce a greater phase shift may be counterproductive if travellers look away from the light. In general, artificial bright light is much brighter than room lighting and perceived as harsher than natural light. Thus, as with any intervention, it is important to know if the treatment is well tolerated and if side effects can occur. Headache, eye strain, irritability, and nausea have been reported as side effects of bright light therapy, but a study in 213 healthy adults comparing 30-minute sessions of bright white light to an equivalent session of dim red light found that eye strain and blurred vision were reported in both groups [61]. The properties of light that combine effectiveness and acceptability are yet to be determined.

Related to the acceptability of interventions is the issue of inter-individual variability or individual differences in the experience of jetlag and responses to interventions. Jetlag symptoms vary greatly between individuals, but the characteristics that contribute to this variability have not been well studied. Jetlag also comprises a range of symptoms with individuals experiencing different symptoms and attaching varying degrees of importance to each symptom [62]. Age is the only factor that has been examined as a potential contributor to individual differences but results vary on whether older age predisposes to, or protects against jetlag [63,64]. Similarly, chronotype is thought to be associated with jetlag, with evening types thought to accommodate phase delays easier but being more impaired by phase advances compared to morning or intermediate types, but this remains to be demonstrated in travellers [65].

In the reviewed studies, selection bias may be a considerable issue. People who do not tolerate jetlag (or disruptions of sleep) are less likely to participate in studies that call for transmeridian flight or studies that require sleeping in the laboratory. If only participants who tolerate jetlag are included, then any effect of the interventions will be minimised. Alternatively, travellers who suffer severe jetlag may be more motivated to participate but they may also be more resistant to common strategies used to counteract jetlag, again contributing to negative findings.

Strengths and limitations of this review

The current review found a small number of studies for each type of jetlag intervention and as such, we cannot meaningfully synthesise the results in a meta-analysis, nor can we draw strong conclusions about the effectiveness or lack thereof for each type of intervention. We cannot rule out a small risk of bias in the review since our search strategy included only studies published in English and we may have missed studies published in other languages. However, the systematic searching across multiple databases and in reference lists suggests that the results are comprehensive. We do not believe publication bias is a significant issue given that the majority of studies provided negative results.

The quality of the included studies was low to moderate, with selection bias, lack of blinding, and the limited representativeness of travellers being the main drawbacks. We note that information from three of the studies were based on abstracts only as the studies were not published as full manuscripts and the corresponding lack of detail may have resulted in lower quality ratings for these studies. The risk of selection bias was concentrated in the observational studies and the associated interventions (physical activity and diet) need to be tested with more stringent experimental studies in future. The lack of blinding of both participants and researchers occurred across most studies, although we acknowledge that blinding participants to interventions is not always possible in applied settings or for these types of interventions. The lack of participant blinding suggests however that the conclusions from this review have good ecological validity.

Blinding of the study authors remains an important issue. While we have tried to mitigate this by including only the results of direct comparisons between the intervention and control groups in our summary table and excluding post hoc and subgroup analyses, future studies must stipulate the main outcomes and plan the analyses to avoid selective reporting. The generalisability of the findings is moderate given that all bar one study was conducted under conditions of real travel, but participants were not representative of travellers at large. Professional athletes and flight crew comprised a minority of study participants but their responses to interventions may have been very different to that of the average traveller; athletes have high levels of physical fitness which may protect them from the rigours of travel, while flight crew are experienced travellers who may be in their job partly because they cope well with jetlag. The majority of participants were healthy young male adults and future studies will need investigate the effectiveness of interventions beyond this demographic.

We must emphasise that this review focused on *effectiveness* rather than *efficacy*. *Efficacy* refers to whether an intervention works under ideal or selected conditions such as in the laboratory-based studies, whereas *effectiveness* refers to whether an intervention works under real-life conditions and in terms that matter to patients/participants, or in the case of jetlag, to travellers. While light exposure and avoidance has the ability to shift circadian rhythms, that is, it is efficacious for circadian misalignment, we refer to the lack of *effectiveness* of jetlag interventions to convey the idea that the usefulness of circadian interventions have not been demonstrated under conditions of air travel. This is important because effectiveness considers factors such as poor implementation and low acceptance/adherence of jetlag strategies by participants, resulting in highly efficacious strategies being less useful in practice. This may also lead to highly efficacious strategies being less useful than strategies that are of low efficacy, but which may be more easily implemented in practice and more acceptable to travellers. At this point in time, it is unclear what strategies are effective, although the circadian science shows that light exposure and avoidance, and along with it, sleep scheduling, should be the most efficacious.

Implications for future studies

"After a flight in a westward or eastward direction, all zeitgebers one can think of work together to shift the circadian system" [66]. Interventions may not be able to facilitate the achievement of re-entrainment any faster than the combination of all the zeitgebers that a traveller is exposed to upon arrival at their destination and this might explain why many of the field studies found that interventions had negligible effects on jetlag. Further, there is a general assumption that the mismatch between circadian rhythms and the light–dark cycle of the new time zone is responsible for all jetlag symptoms and that re-entrainment of circadian rhythms is all that is required for optimal functioning. However, in addition to a change in time zone, travellers are subject to stressors prior to, during, and after travel which results in travel fatigue. The symptoms of jetlag and those of travel fatigue are not easily disentangled in practice. Whilst scientists pinpoint jetlag as resulting directly from circadian misalignment and travel fatigue as a broader term which encompasses all stressors related to travel, travellers do not make this distinction. Those who travel in a north-south direction do not experience jetlag, but still experience considerable travel fatigue [67]. It is unclear if fatigue contributes significantly to the experience of jetlag or affects the ability of the body to adapt to a new time zone.

During a flight, passengers are exposed to an extended period of acceleration, vibration, noise, lowered barometric pressure, and variations in temperature and humidity – all of which are known to contribute to fatigue [68]. Experimental studies show that exposure to reduced air pressure and associated oxygen levels for 8 h changes the pattern of cortisol expression [69], depresses peak plasma melatonin [70], and delays the evening decline in core body temperature [71], suggesting that air quality and pressure contribute to jetlag symptoms [72]. Providing a flight cabin environment with air pressure and oxygen levels closer to those at sea level might help to reduce discomfort and fatigue. The cabin environment also affects a traveller's ability to sleep, thus contributing to sleep deprivation. Several studies indicate that sitting upright impairs sleep and that sleep quality is improved when sleeping position is closer to the horizontal [73–75]. Cabin pressurisation and seat pitch is outside the control of passengers and requires collaboration with the aviation industry to ameliorate. Cabin noise may be a more controllable factor to target in interventions: environmental noise disrupts sleep [76,77] and integrating interventions such as earplugs with an appropriate lighting and sleep schedule may mitigate some of the sleep deprivation that occurs on long-haul flights, which in turn should reduce fatigue, and may contribute to reduced jetlag.

Travellers may also be subjected to sudden changes in ambient temperature, humidity, air pollution, altitude, and food quality on arrival at their destination. All of these will contribute to feelings of discomfort [78]. While some of these factors may not be modifiable, consideration of strategies and interventions that also target these other causes of jetlag symptoms is warranted. It is unclear if reducing travel fatigue can also help to reduce the severity or duration of circadian-based jetlag symptoms, and this is a question for future research. It is possible that interventions to improve sleep and reduce fatigue may have stronger effects on wellbeing after transmeridian travel than circadian alignment per se. Thus, future studies should explore the relative importance of circadian misalignment, mild hypoxia, sleep deprivation, fatigue, and other factors to tease apart the contributors to a traveller's experience of jetlag and to help to develop effective interventions.

Conclusions

Light exposure and sleep scheduling are commonly suggested remedies for jetlag, however, we found limited evidence for the effectiveness of these and other strategies for reducing jetlag in travellers. Existing studies were few, often underpowered, and not always well designed to maximise the impact of strategies known to be efficacious, such as scheduled periods of light and dark, including the scheduling of sleep as a period of darkness. Neither were studies well controlled enough to evaluate effectiveness under real-world conditions. More well-designed studies are required to systematically test a range of jetlag interventions, especially those which have been shown to be efficacious under laboratory conditions. Study is also required of strategies that have been little explored, but which show promise as interventions such as diet and meal timing. Strategies that reduce sleep deprivation and fatigue, altering the characteristics of the in-flight environment as well as the behaviours of individual passengers, and administering interventions before, during and after flight are important elements that have thus far been neglected in jetlag interventions. Although our review focuses only on non-pharmacological interventions, research on approaches combining pharmacological solutions such as melatonin and caffeine with non-pharmacological strategies may be useful as controlled studies suggest these have greater effects together than each alone [79,80]. Continued growth in transmeridian travel should be supported by strategies to counteract jetlag to ensure the wellbeing of travellers, to mitigate the adverse consequences of jetlag on health and performance, and to aid in the sustainability of long-haul flights as a mode of transport.

Practice Points

- There is currently a lack of evidence on the use of supplemental bright light, sleep scheduling, exercise, and meal timing as interventions for jetlag under conditions of real travel. High quality studies are needed to translate circadian principles into effective jetlag interventions in air passengers.
- Following appropriately timed schedules of light exposure and avoidance before, during, and after flight to reduce circadian misalignment should reduce jetlag symptoms.
- Minimising environmental and individual stressors before, during, and after travel may help to reduce the travel fatigue associated with jetlag.

Research Agenda

Future studies should:

- Separate the role of factors which cause the circadian misalignment of jetlag from factors which cause the travel fatigue component of jetlag e.g., environmental conditions of temperature, noise, humidity, air pressure, and reduced oxygenation experienced during flight.
- Identify travellers predisposed to jetlag, assess circadian phase to inform the timing of circadian interventions, and address how individual behaviours such as meal timing and composition, and physical activity may help to reduce jetlag.
- Enhance the effect of light through the use of dynamic models to optimise timing of light exposure, incorporate active light avoidance, and take into account effects of ambient light.
- Use more stringent study designs with appropriate circadian markers, target participants representative of real travellers, and note the acceptability of interventions to passengers, including any undesirable side effects.

Conflicts of interest

PAC holds an endowed academic chair at the University of Sydney that was funded by ResMed Inc. He has received research and/or equipment support from ResMed Inc, SomnoMed Ltd, Zephyr Sleep technologies, and Exploramed Inc. He has acted as consultant/advisor for Zephr Sleep Technologies, NovoNordisk, and Fisher & Paykel Healthcare.

SP is a Theme Leader at the Cooperative Research Centre for Alertness, Safety and Productivity. All authors are affiliated with the Charles Perkins Centre, which has a research partnership with Qantas Airways.

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Appendix A. Supplementary data

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