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Caffeine for the prevention of injuries and errors in shift workers (Review)

Ker K, Edwards PJ, Felix LM, Blackhall K, Roberts I

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[Intervention Review]

Caffeine for the prevention of injuries and errors in shift workers

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ABSTRACT

Background

Sleepiness leads to a deterioration in performance and attention, and is associated with an increased risk of injury. Jet lag and shift work disorder are circadian rhythm sleep disorders which result in sleepiness and can elevate injury risk. They create a need for individuals to operate at times which are different to those dictated by their circadian rhythms. Consequently there is also a need for interventions to help ensure that these persons can do so safely. Caffeine has a potential role in promoting alertness during times of desired wakefulness in persons with jet lag or shift work disorder, however its effects on injury and error are unclear.

Objectives

To assess the effects of caffeine for preventing injuries caused by impaired alertness in persons with jet lag or shift work disorder.

Search methods

We searched the Cochrane Injuries Group Specialised Register, CENTRAL (*The Cochrane Library*), MEDLINE, EMBASE, PsycINFO, CINAHL, TRANSPORT (to July 2008); and PubMed databases (to April 2010). We also searched the Internet and checked reference lists of relevant papers.

Selection criteria

Randomised controlled trials investigating the effects of caffeine on injury, error or cognitive performance in people with jet lag or shift work disorder.

Data collection and analysis

Two authors independently screened search results and assessed full texts for inclusion. Data were extracted and risk of bias was assessed. Estimates of treatment effect (odds ratio and standardised mean difference (SMD)) and 95% confidence intervals (CI) were calculated and pooled using the fixed-effect model.

Main results

Thirteen trials were included. None measured an injury outcome. Two trials measured error, and the remaining trials used neuropsychological tests to assess cognitive performance. The trials assessing the impact on errors found that caffeine significantly reduced the number of errors compared to placebo. The pooled effect estimates on performance by cognitive domain suggest that, when compared to placebo, caffeine improved concept formation and reasoning (SMD -0.41; 95% CI -1.04 to 0.23), memory (SMD -1.08; 95% CI -2.07 to -0.09), orientation and attention (SMD -0.55; 95% CI -0.83 to -0.27) and perception (SMD -0.77; 95% CI -1.73 to 0.20); although there was no beneficial effect on verbal functioning and language skills (SMD 0.18; 95% CI -0.50 to 0.87). One trial comparing the effects of caffeine with a nap found that there were significantly less errors made in the caffeine group. Other trials comparing caffeine with other active interven-

tions (for example nap, bright light, modafinil) found no significant differences. There is a high risk of bias for the adequacy of allocation concealment and presence of selective outcome reporting amongst the trials.

Authors' conclusions

Caffeine may be an effective intervention for improving performance in shift workers however, there are no trials from which we can assess its effect on injuries. The results largely originate from studies involving young participants under simulated conditions, and the extent to which the findings are generalisable to older workers and real world shift work is unclear. Based on the current evidence, there is no reason for healthy individuals who already use caffeine within recommended levels to improve their alertness to stop doing so. The assessment of the relative effects of caffeine to other potential countermeasures should be a focus of future research.

PLAIN LANGUAGE SUMMARY

Caffeine for preventing injuries and errors in shift workers

Sleepiness leads to a deterioration in performance and is associated with an increased risk of error and injury. Shift work is an major cause of sleepiness as it requires workers to be awake at times which are different to those dictated by their 'body clock'. This in turn can compromise the safety of themselves and of others - sleepiness is a risk factor for events such as traffic crashes, occupational injuries and medical errors.

The identification of interventions which can reduce the risk of error and injury is necessary to help ensure that those who are required to work through the night, can do so safely. Caffeine has been proposed as one such intervention, although how effective it is in shift workers is unknown.

For this systematic review, the authors searched for randomised controlled trials which investigated the effects of caffeine on injury, error and cognitive performance in shift workers. They found 13 trials - none of the trials looked at the effect on injury, two trials measured error, while the remaining trials used neuropsychological tests to assess cognitive performance.

The results of the trials suggest that compared to no intervention, caffeine can reduce the number of errors and improve cognitive performance in shift workers. No difference in effect was found by the trials comparing caffeine with other interventions (such as nap, bright light and modafinil). However, due to some methodological weaknesses of the trials, some caution is required when interpreting the results.

The authors of the systematic review conclude that caffeine may be an effective intervention for improving performance in shift workers however, there are no trials from which they could assess its effect on injuries. Based on the current evidence, the review authors judge that there is no reason for healthy shift workers who already use caffeine within recommended levels to improve their alertness, to stop doing so. They go on to suggest that it would be useful for further trials to be undertaken to assess the effects of caffeine against other potential countermeasures.

BACKGROUND

Description of the condition

Medical errors and the contribution of sleepiness

Injuries to patients arising from medical errors are an important cause of avoidable mortality and morbidity, and are a great concern for clinicians, hospital managers and the public. In the UK, it is estimated that there are in excess of 850,000 incidents (constituting approximately 10% of admissions) which either harm or nearly harm a NHS patient every year, incurring £2 billion direct costs in additional hospital days alone (DoH 2000). In the USA, an estimated 44,000 to 98,000 deaths every year are caused by medical errors. Even when using the lowest estimate, this makes medical errors the eighth leading cause of death, exceeding the death toll from motor vehicle crashes, breast cancer and AIDS (Kohn 1999).

There are numerous risk factors that can contribute to the occurrence of medical errors, although the sleepiness of healthcare providers has been identified as being of concern (Gaba 2002; Jha 2001; Kohn 1999) and studies have found evidence for an association between medical errors and lack of sleep. Clinicians are required to have good attention, good judgment and quick reaction times, sometimes in highly pressurised, emergency situations; all of these can be compromised by sleepiness (Jha 2001). A meta-analysis of studies by Philibert 2005 explored the effects of sleep deprivation on performance in both physicians and non-physicians, and found that sleep deprivation of 24 to 30 hours reduced overall performance by one standard deviation (SD) and clinical performance by 1.5 SD. Other studies of laparoscopic performance suggest a poorer performance after night shifts than with daytime shifts (Eastridge 2003; Grantcharov 2001). Similarly, analysis of survey data from a cohort of interns in the USA found that needle-stick injuries were more frequent during night shifts than during the day (odds ratio (OR) 2.04; 95% CI 1.98 to 2.11) (Ayas 2006).

Wider implications of sleepiness

The impairment of alertness associated with sleepiness leads to a deterioration of performance, attention and motivation, and diminishment of mental concentration and intellectual capacity (WHO 2004). A meta-analysis by Pilcher 1996 showed that the performance of sleep-deprived individuals was 1.37 SD lower than that of those with adequate sleep, and that partial sleep deprivation (< 5 hours of sleep in a 24 hour period) had a greater negative effect on cognition than short or long term sleep deprivation (continuous time without sleep ≤ 45 hours, and > 45 hours respectively). It is also believed that relatively moderate levels of sleepiness impair performance to an extent that is equivalent to, or greater than, that currently acceptable for alcohol intoxication (Dawson 1997).

The harmful effects of errors caused by impaired alertness are not limited to the medical setting, they pose an important health risk in a number of sectors and industries. Their possible consequences vary enormously. A number of high profile human catastrophes and environmental disasters have been caused, at least in part, by human error attributed to sleepiness. These include the Three Mile Island nuclear plant incident, the Chernobyl explosion (Mitler 1988) and the space shuttle Challenger explosion (Wilson 2005).

Occupational injuries as a whole present an important public health issue and the effects of sleepiness are believed to be a significant risk factor. A systematic review of epidemiological studies found that sleepiness consistently increased risk of occupational injury (Robb 2008). The cohort study conducted in the Netherlands found a greater risk of injuries amongst workers with the highest fatigue score compared to those with the lowest score (relative risk 1.29; 95% CI 1.03 to 2.78), after adjustment for potential confounders (Swaen 2003). Likewise the findings from a case-control study involving railway workers in France suggested a raised risk of injury in workers with a 'sleep disorder' (defined as < six hours sleep per day or regular consumption of sleeping pills, or both) (adjusted OR 1.30; 95% CI 1.08 to 1.57) (Chau 2004).

There is also evidence for an association between sleepiness and transportation injuries. A case-control study of drivers in New Zealand by Connor 2002 et al found that, after adjustment for potential confounders, the traffic crash risk was greater among drivers who had slept five hours or less in the previous 24 hours than those who had slept more than five hours (OR 2.7; 95% CI 1.4 to 5.4). The risk was also higher among those driving between 2.00 am and 5.00 am compared to other times of day (OR 5.6; 95% CI 1.4 to 22.7). Similarly, a case-control study by Stutts 2003 et al found that drivers who on average slept less than five hours per night were over four times more likely to be in a crash than drivers who slept at least eight hours per night (adjusted OR 4.64; 95% CI 2.54 to 8.45). Further evidence originates from the GAZEL cohort study in France where adjusted rate ratios indicated that road traffic crashes were more common in those who reported driving while sleepy 'once a month or more often' in the previous 12 months than for those who reported not driving while sleepy (rate ratio 2.9; 95% CI 1.3 to 6.3) (Nabi 2006). Such evidence has increased awareness of sleepiness as a risk factor for transportation injuries. A consensus statement endorsed by an international group of sleep experts states that "fatigue (sleepiness, tiredness) is the largest identifiable and preventable cause of accidents in transport operations (between 15% and 20% of all accidents), surpassing that of alcohol or drug related incidents in all modes of transportation. Official statistics often underestimate this contribution" (Akerstedt 2000). Specifically in the field of aviation, the reduction of aircraft crashes and incidents caused by human sleepiness is listed as one of the 'most wanted' transportation safety improvements by the USA's National Transportation Safety Board (NTSB 2008).

It should be noted that inadequate sleep is a risk factor for a number of health problems. Total sleep deprivation is fatal in some animal species (Rechtschaffen 1989; WHO 2004) and short sleepers (< six hours) have a higher overall mortality rate (Wingard 1983). Insufficient sleep is also associated with an increased risk of obesity, type-2 diabetes, heart problems and dementia (Wilson 2005). Of particular interest to this systematic review is the diminished alertness and cognitive performance associated with sleep deprivation (Thomas 2000), including the adverse impact on vigilance (Franzen 2008; Gillberg 1998), speech (Harrison 1997), decision making (Harrison 2000; Killgore 2006), divergent and flexible thinking (Harrison 1999; Horne 1988) and increased distractibility (Anderson 2006). Yet the extent of these negative impacts depends on other factors such as age, individual variability and lifestyle factors such as alcohol consumption.

Circadian rhythm sleep disorders

Circadian rhythm sleep disorders (CRSDs) explain some of the sleepiness and associated impaired alertness that is prevalent in the population. The circadian rhythm describes the cyclical changes involving body temperature, hormone levels and sleep oc-

curring over a 24 hour period, which are driven by our biological clocks. This cycle is synchronised by rhythmic environmental cues, known as 'zeitgebers'. The main zeitgebers are known to be the environmental light-dark cycle and the secretion of melatonin, both of which can be manipulated to induce a phase shift in an individual's circadian rhythm (Waterhouse 2007). The circadian rhythm dictates the times at which we feel the typical urge to sleep at night and wake in the morning. CRSDs occur when there is a misalignment between a person's sleep pattern and the sleep pattern desired (AASM 2001), which results in symptoms of sleepiness and insomnia.

Time zone change syndrome (that is jet lag) and shift work disorder are two types of CRSD which can impair performance of workers in the healthcare and transportation industries, and are the focus of this review. These disorders can be considered distinct from the other CRSDs as sufferers of these conditions have circadian systems which function normally under usual circumstances (Sack 2007).

Time zone change syndrome (jet lag)

The American Academy of Sleep Medicine (AASM) describes jet lag as consisting "of varying degrees of difficulties in initiating or maintaining sleep, excessive sleepiness, decrements in subjective daytime alertness and performance, and somatic symptoms…following rapid travel across multiple timezones" (AASM 2001). Jet lag results from the misalignment between the circadian rhythm and the sleep-wake schedule in the new time zone. The severity of the symptoms of the disorder depend on the age of the traveller (severity increases with age), number of time zones crossed, direction of travel (eastward journeys are associated with more profound effects), time of travel and the individual's susceptibility (Waterhouse 2007). Symptoms are alleviated as the body clock adjusts to the new time zone. This adjustment takes a number of days, the number of which corresponds to approximately two-thirds of the number of time zones crossed (Waterhouse 2007). The detrimental effects of jet lag on alertness can have serious implications for those who do not have the opportunity to adjust to the new time zone and are required to be sufficiently alert to perform tasks accurately and safely, such as aircrew and military personnel.

Shift work disorder

Shift work disorder (SWD) is described by the AASM as consisting "of symptoms of insomnia or excessive sleepiness that occur as transient phenomena in relation to work schedules". It mainly affects those persons whose working hours are scheduled during the habitual hours of sleep. The main complaint of sufferers is the inability to maintain a normal sleep duration when the major sleep episode is begun in the morning after a night shift. Workers engaged in early morning (starting between 04.00 and 07.00) or evening shift work may also experience sleep difficulties associated with their working hours (AASM 2001). Excessive sleepiness often occurs during the shift work, thus impairing alertness. Over time improvement in symptoms is observed, however they tend to persist to some degree for the duration of the shift work, only alleviating once a regular daytime shift pattern is resumed (AASM 2001).

The number of people engaged in shift work has increased in response to the demands of a 24 hour global society. It is currently estimated that 15% to 20% of all workers are engaged in night or shift work in most industrialised countries (Bonneford 2004). A survey of workers in Detroit, USA, estimated that 10% of the night and rotating shift workers suffered from SWD (Drake 2004). Both the healthcare and transportation sectors employ a high proportion of shift workers, in comparison to other industries (Beers 2000), as round the clock provision of services is required. Thus it is likely that SWD is an important cause of impaired alertness in these individuals.

Description of the intervention

Adequate, quality natural sleep is the most effective and safe measure for preventing the detrimental effects of lack of sleep, including injury. However, there will always be a need for individuals to sleep or be alert at times which are different to those dictated by their circadian rhythm. Consequently there is a need for interventions which can safely alleviate the impairment of alertness associated with jet lag and SWD. Effective interventions to prevent and treat jet lag and SWD have the potential to reduce the number of errors resulting from impaired alertness, thus preventing the occurrence of injury to themselves and to others that may result.

Interventions may aim to address the adverse effect on alertness arising from jet lag and SWD in two related, but distinct, ways. First, there are interventions which aim to promote alertness during times of desired wakefulness (for example pharmacological stimulants) or which aim to treat the insomnia symptom and facilitate sleep during the desired times (for example pharmacological sedatives). Second, interventions may be employed to directly help the circadian rhythm to adjust to the new sleep-wake schedule (for example administration of bright light). A third type of interventions that might be employed are those which do not aim to treat an individual's symptoms, instead they attempt to directly prevent the occurrence of an error (for example alarm systems). The focus of this systematic review is on an intervention that comes under the first of these types, caffeine as a pharmacological stimulant.

Caffeine is the most widely used psychoactive drug (Nelson 2007; Roehrs 2008), promoting wakefulness by stimulating the neurons involved in maintaining arousal and inhibiting those involved in promoting sleep (Boutrel 2004). It is found naturally in coffee and tea, is an active ingredient in 'stimulant drinks', or can been administered orally in capsule or tablet form. Caffeine-containing food and drinks are likely to be some of the most commonly used interventions for alleviating the symptoms of jet lag and SWD and for promoting alertness. Furthermore, caffeine is recommended as the "compound of choice for counteracting cognitive deficits" during military operations (CMNR 2001). It is, however, associated with some negative side-effects, including anxiety, stress and subsequent sleep disruption, if too much is consumed. There is particular concern over the potential negative effects of stimulant drinks, the market for which is unregulated in many countries (including the UK) (Finigan 2003).

Why it is important to do this review

As described above, the impaired alertness associated with the symptoms of jet lag and SWD is an important cause of injury and constitutes a significant threat to public safety.

The main focus of this review is on the prevention of medical errors and the identification of effective interventions of relevance to the healthcare industry. However, the scope of the review will be broadened to include evidence from all sectors for a number of reasons. First, there is a dearth of quality intervention research about ways to reduce medical errors and improve patient safety (Ioannidis 2001). Other fields such as aviation and road safety have a

more developed research tradition in prioritising public safety and risk management. There is, therefore, potential for development of strategies aimed at preventing medical errors to be informed by research from other industries. Second, the issue of impaired alertness resulting from jet lag and SWD is not a concern of just one sector. By reviewing all relevant evidence this review will serve as a resource for all sectors which seek to address the burden of injuries resulting from impaired alertness. This broad perspective accounts for the inclusion of jet lag, which we recognise is unlikely to be an important cause of medical error but is a potentially important cause of injury in other occupations, such as the military and aviation. Furthermore, there are similarities between the two disorders in terms of aetiology (that is circadian desynchronisation) and symptoms (that is insomnia and sleepiness), thus we suggest that evidence regarding the effects of interventions for jet lag will have relevance to SWD, and vice versa.

To the best of our knowledge this is the first systematic review and meta-analysis aimed at assessing the effects of caffeine administered to sufferers of jet lag and SWD on risk of injury.

OBJECTIVES

To assess the effects of caffeine for the prevention of injuries caused by impaired alertness in persons with jet lag or shift work disorder.

METHODS

Criteria for considering studies for this review

Types of studies

- Randomised controlled trials
- Randomised cross-over trials

Types of participants

Persons of any age suffering from jet lag, or engaged in shift work, and who are otherwise healthy.

Eligible shift workers may or may not have a formal diagnosis of SWD and could be engaged in early morning, late evening or night shift work.

The onset of jet lag or SWD may be real or induced (for example a simulated night shift in a laboratory setting).

Types of interventions

Caffeine administered in any form (for example coffee, capsule) at any dosage.

Studies comparing the effects of caffeine with placebo or another active intervention were eligible.

Types of outcome measures

Primary outcomes

- Occurrence of injury
- Occurrence of error (error as defined by the individual trial)

Secondary outcomes

Tests of cognitive performance.

The included studies used a variety of tests to measure cognitive performance. We therefore categorised the tests according to the underlying cognitive construct being assessed. We referred to Lezak 2004 to classify the tests into the following domains:

- construction,
- concept formation and reasoning,
- executive function and motor performance,
- memory,
- orientation and attention,
- perception,
- verbal functioning and language skills.

See Table 1 for the lists of neuropsychological tests classified according to cognitive domain.

Adverse events

We also planned to collect data on the following potential adverse effects:

- subsequent impairment of sleep architecture;
- risk of dependence;
- headache.

Search methods for identification of studies

The searches for this review were part of wider searches performed to identify trials assessing the effects of any intervention for the prevention of injuries caused by impaired alertness in individuals with jet lag or shift work disorder.

Electronic searches

We searched the following electronic databases:

- CENTRAL, DARE (*The Cochrane Library* Issue 2, 2008);
- MEDLINE (Ovid MEDLINE(R), 1950 to July Week 1 2008);
- EMBASE (Ovid EMBASE, EMBASE Classic, 1980 to July Week 27 2008);
- PsycINFO (SilverPlatter, 1806 to 2008/07 Week 2);
- CINAHL (1982 to July 2008);
- TRANSPORT (SilverPlatter, pre-1988 to 2007/06);
- PubMed (searched July 2008 to April 2010).

The search strategies used in each database are presented in Appendix 1. To further refine the results a further search was undertaken to identify irrelevant records for deletion. Details of this search strategy can be found in Appendix 2.

Searching other resources

We searched the publication catalogues on the following websites using keywords selected from the database strategies:

- CRISP,
- Current Controlled Trials,
- Defense Technical Information Center,
- Monash Accident Research Centre,
- NASA Technical Reports Server,
- National Highway Traffic Safety Administration,
- National Institute for Occupational Safety and Health (NIOSH),

- National Technical Information Service,
- NTL Integrated Search,
- SPECTR,
- Swedish National Road and Transport Research Institute (VTI),
- SWOV,
- Transportation Research Board,
- Transportation Research Library.

We screened the electronic abstracts and proceedings of the following meetings:

- 18th Congress of the European Sleep Research Society, Innsbruck, Austria 2006,
- 17th Congress of the European Sleep Research Society, Prague 2004,
- 16th Congress of the European Sleep Research Society, Reykjavik 2002,
- 15th Annual Meeting of the Associated Professional Sleep Societies, 5-10 June, 2001. Chicago, Illinois, USA,
- 14th Annual Meeting of the Associated Professional Sleep Societies, 17-22 June, 2000. Las Vegas, USA.

Data collection and analysis

Selection of studies

Two authors independently examined titles, abstracts and keywords of electronic records for eligibility. We obtained the full text of all potentially relevant reports of trials and two authors independently assessed whether each met the pre-defined inclusion criteria. We resolved disagreement through discussion.

Data extraction and management

One author (KK) extracted data on the characteristics each trial, which were then checked by a second author (LF). Results data were extracted by one author. Data were extracted on the following:

- study design;
- participant characteristics;
- intervention characteristics;
- outcome measures;
- statistical analysis.

Assessment of risk of bias in included studies

The risk of bias in the included trials was assessed using the Cochrane Collaboration's recommended tool, described in Higgins 2008. This tool assesses the following six domains:

- sequence generation (was the allocation sequence adequately generated?);
- allocation concealment (was allocation adequately concealed?);
- blinding (was knowledge of the allocated intervention adequately prevented during the study?);
- incomplete outcome data (were incomplete outcome data adequately addressed?);
- selective outcome reporting (are reports of the study free of suggestion of selective outcome reporting?);
- other issues (was the study apparently free of other problems that could put it at a high risk of bias?).

Risk of bias tables were completed based on the above criteria. These incorporated the review authors' judgement ('Yes' for low risk of bias; 'No' for high risk of bias; or 'Unclear') and description of the design, conduct or observations that underlie the judgement, for each domain in each included trial.

Measures of treatment effect

Trial results were presented using a combination of dichotomous and continuous data.

For dichotomous outcomes we calculated relative risks (RR) and 95% confidence intervals (CIs).

For continuous data, as these were measured using different scales or different versions of the same scale we calculated the standardised mean difference (SMD) and 95% CI. The SMD expresses the size of the estimated intervention effect in each study relative to the variability in that study. By using this method we were able to standardise study results to a uniform scale to enable them to be pooled (Higgins 2008).

All data were entered into RevMan so that higher mean values represented poorer performance. For continuous data in which a higher value indicated better performance the mean values and 95% CIs were multiplied by -1.

Where studies made repeated measurements of performance during the study period, the means and SDs of these were pooled to provide an average post-intervention summary estimate.

Unit of analysis issues

We identified a number of randomised cross-over studies which were eligible for inclusion. Where sufficient data were presented, we analysed data from all experimental periods according to the methods described in Elbourne 2002. For dichotomous data we calculated an odds ratio (OR) specific to a two-treatment, two-period cross-over trial by Becker and Balagtas. For continuous data from a two period, two-intervention cross-over trial, we planned to perform a paired t-test. Where there were insufficient data presented to allow such analyses the results from both periods of the cross-over trials were analysed as if they had originated from a parallel design. Whilst such an approach leads to a unit of analysis error, causing the CIs to be too wide and the trial to receive too little weight, the subsequent error leads to conservative estimates and we judged that the inclusion of conservative estimates was preferable to omitting all such data from the analysis.

Dealing with missing data

We contacted the investigators to obtain any missing data required for the analyses.

Where data were only presented graphically, individual values were read from graphs. In such cases where individual means or SDs could not be distinguished, we imputed the average value as calculated from the available figures.

Assessment of heterogeneity

We examined trial characteristics in terms of participants, interventions and outcomes for evidence of clinical heterogeneity. Statisti-

cal heterogeneity was examined by the I^2 and Chi^2 statistics. The I^2 statistic describes the percentage of total variation across trials due to heterogeneity rather than chance. A value of 0% indicates no observed heterogeneity, and larger values show increasing heterogeneity; substantial heterogeneity is considered to exist with I^2 > 50%. For the Chi^2 statistic, a P value < 0.10 was used to indicate the presence of statistically significant heterogeneity.

Assessment of reporting biases

There were insufficient data to investigate the presence of reporting bias using funnel plots.

Data synthesis

We judged that the trials were sufficiently homogenous in terms of types of participants, interventions and outcomes to pool the results using the fixed-effect model.

A large number of neuropsychological tests were used in the included studies to measure cognitive performance. For the pooled analyses, we classified each test according to the underlying cognitive construct being measured. As a number of the included trials used multiple tests, and outcome variables measuring the same cognitive construct, we randomly selected one variable to include in the pooled analysis (using the RANDBETWEEN command in MS Excel) to avoid multiple representation of such studies.

Subgroup analysis and investigation of heterogeneity

There were insufficient data to perform the following planned subgroup analyses:

- age - persons aged > 60 years versus persons aged 18 to 60 years versus children aged <18 years;
- environment - simulated, transportation, clinical, military;
- allocation concealment - adequate versus inadequate.

RESULTS

Description of studies

Results of the search

The combined database search identified 3616 records (CENTRAL 907, DARE 8, MEDLINE 710, EMBASE 632, PsycINFO 857, CINAHL 338, TRANSPORT 164). After de-duplication (n = 963) and deletion of irrelevant records identified by searching within the ProCite database (n = 366), a total of 2285 records remained for the scanning process.

Two hundred (9%) of the 2285 records were judged to be potentially eligible studies based on title and abstract. Of these 200, we were able to obtain the full reports of 185 (93%). We retrieved a further 80 reports which had been identified by the other search methods.

After the full text review of these 280 reports, 100 reports describing 73 trials were found to meet the inclusion criteria. Thirteen of these 73 trials assessed the effects of caffeine and are included in this review.

Included studies

Full details of each trial are presented in the Characteristics of included studies table; a summary is given below.

Design

Four of the trials were randomised, parallel group trials and nine were randomised cross-over trials.

Participants

The number of participants in each trial ranged from six to 68. One trial examined female participants only, four studies males only, and eight included both male and female participants. All were adults: the minimum and maximum eligible ages were 18 and 65, respectively.

One trial investigated the effects of caffeine in workers engaged in night shifts; one involved participants who were required to undertake night-time driving; and in one trial participants took an eastward international flight, crossing seven time zones to induce jet lag. The remaining trials involved participants exposed to conditions to lead to circadian disruption (e.g. simulated night shifts in a sleep laboratory). No trial participants were reported as having a confirmed diagnosis of shift work disorder.

Interventions

Caffeine was administered in a variety of forms:

- tablet or capsule in eight trials, 1 x dose of 200 mg (n = 3), 1 x dose 300 mg (n = 3), 1 x dose 4 mg/kg (n = 1), hourly doses of 0.3 mg/kg (n = 1);
- coffee in two trials, 1 x dose of 200 mg (n = 1) and 1 x dose of 2 mg/kg (n = 1);
- caffeinated food in two trials, 2 x dose of 200 mg (n = 1) and 1 x dose of 200 mg (n = 1);
- caffeinated energy drink in one trial, 2 x dose of 80 mg.

Caffeine intervention was compared to modafinil, bright and dim light, a chewing intervention and naps.

Outcomes

None of the trials collected outcome data on the occurrence of injuries. Two trials collected data on the occurrence of error: one based on actual driving performance, and one based on simulated flying performance.

Ten studies used neuropsychological tests of cognitive performance.

Excluded studies

A number of trials identified by the searches were eligible in terms of design, participants and intervention but did not have any eligible outcome measures. Most of these studies limited their outcomes to measures of sleepiness using tools such as the Multiple Sleep Latency test, Stanford Sleepiness Scale and Epworth Sleepiness Scale. As these tools do not attempt to measure performance they were excluded from the review. A full list of these studies is available from the review authors.

Risk of bias in included studies

The review authors' judgement of the risk of bias, and description of the design, conduct or observations that underlie the judgement, for each domain in each included trial are presented in the risk of bias tables. A summary of the information in the tables is given below. Additionally, a visual summary of judgements about

each methodological quality item for each included trial is shown in Figure 1.

Figure 1. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.

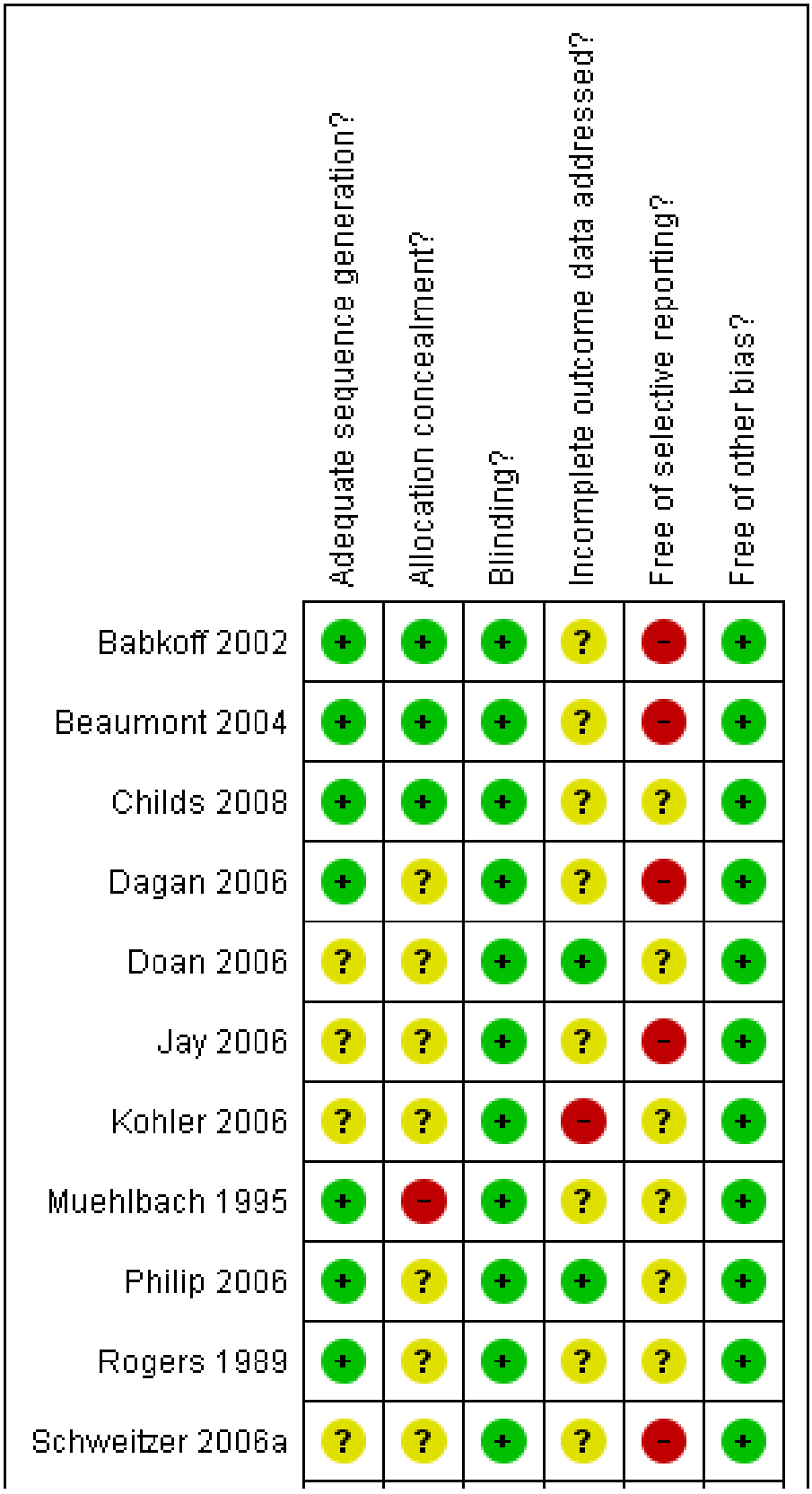
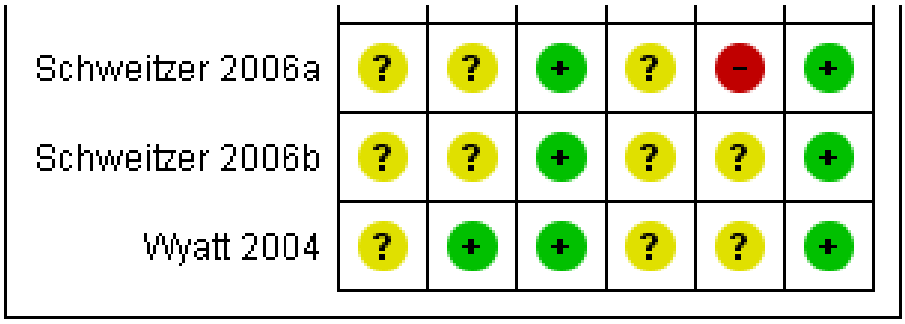


Figure 1. (Continued)



Allocation

Sequence generation

None of the trials were judged to be at high risk of bias for this domain. Seven studies used an adequate method of sequence generation (table of random numbers and computerised randomisation). The remaining six were rated as unclear due to no information being presented in the report or being available from the study author(s).

Allocation concealment

Three trials used pharmacy-controlled randomisation and one used central randomisation, all four studies were judged to be at low risk of bias. Of the remaining nine trials, the adequacy of allocation concealment was unclear for eight and inadequate for one.

Blinding

Nine trials were reported as being 'double-blinded'. Three trials could not be fully blinded due to the nature of the intervention and one trial did not report any information on blinding. However, the review authors judged that the outcome and the outcome measurement were not likely to be influenced by lack of blinding, thus all 13 trials have been rated as being at low risk of bias for this domain.

Incomplete outcome data

We judged two trials to be at low risk of bias for this domain: there were no missing data in one trial, while the other used appropriate methods for imputing missing data. There was insufficient information available to judge risk of bias for the remaining 11 trials, which have been classified as unclear for this domain.

Selective reporting

We were unable to obtain the trial protocols for any of the included trials and we were not able to confidently ascertain the pre-specified outcome measures, thus none of the trials were judged to be at low risk of bias for selective reporting. It was judged that there was evidence of selective outcome reporting affecting five trials, and it was clear that three of these only presented statistically significant results. The remaining trials were judged to be unclear, although in all eight of these all of the outcomes described in the methods section were reported in the results of the trial reports.

Other potential sources of bias

All of the included trials were judged to be at low risk of bias for this domain.

Effects of interventions

Ten of the 13 included trials presented sufficient data to enable inclusion in the analyses for this review.

Caffeine versus placebo

Occurrence of error

Two trials (Dagan 2006 and Philip 2006) measured errors.

In the cross-over trial by Philip 2006, night-time driving performance was assessed; an error was defined as an inappropriate line crossing. The OR was 0.14 (95% CI 0.05 to 0.41, P = 0.0003) (Analysis 1.1) suggesting a reduction in errors in the caffeine group.

In the cross-over trial by Dagan 2006, a flight simulator was used to assess performance; errors were measured as deviation from altitude and velocity flight envelopes. For deviations from altitude, the SMD was -1.30 (95% CI -1.93 to -0.68, P < 0.0001). For deviations from velocity, the SMD was -1.18 (95% CI -1.79 to -0.56, P = 0.0002) (Analysis 1.2).

Cognitive performance

All outcome data from the neuropsychological tests comparing caffeine with placebo are listed in Table 2. The pooled analysis is presented in Analysis 1.3.

Concept formation and reasoning

Two trials (Kohler 2006; Rogers 1989) involving three outcome variables used neuropsychological tests to assess the effect of caffeine on 'concept formation and reasoning'. The point estimates for all three variables were consistent with better performance in the caffeine group; however, none of these estimates were statistically significant at the 5% level.

With the multiple outcomes removed, the pooled SMD was -0.41 (95% CI -1.04 to 0.23, P = 0.21). There was no evidence of statistically significant heterogeneity (Chi^2 = 0.63, df = 1, P = 0.43; I^2 = 0%).

Memory

Two trials (Doan 2006; Rogers 1989) involving three outcome variables used neuropsychological tests to assess the effect of caffeine on 'memory'. All of the point estimates were consistent with better performance in the caffeine group; none of these estimates were statistically significant at the 5% level.

With the multiple outcomes from single trials removed (Analysis 1.3.2), the pooled SMD was -1.08 (95% CI -2.07 to -0.09, P = 0.03). There was no evidence of statistically significant heterogeneity (Chi^2 = 0.40, df = 1, P = 0.53; I^2 = 0%).

Orientation and attention

Six trials (Childs 2008; Doan 2006; Kohler 2006; Muehlbach 1995; Rogers 1989; Schweitzer 2006a) involving 22 outcome variables used neuropsychological tests to assess the effects on the cognitive domain of 'orientation and attention'. The point estimates of 19 of the 22 variables were consistent with better performance in the caffeine group; two of these estimates were statistically significant at the 5% level.

With the multiple outcomes from single trials removed (Analysis 1.3.3), the pooled SMD was -0.55 (95% CI -0.83 to -0.27, P ≤ 0.0001). There was some suggestion of statistically significant heterogeneity (Chi^2 = 9.82, df = 5, P = 0.08; I^2 = 49%).

Perception

Two trials (Doan 2006; Rogers 1989) involving two outcome variables used neuropsychological tests to assess the effects on 'perception'. The pooled SMD was -0.77 (95% CI -1.73 to 0.20, P = 0.12). There was no evidence of statistically significant heterogeneity (Chi^2 = 1.36, df = 1, P = 0.24; I^2 = 27%).

Verbal functioning and language skills

One trial (Schweitzer 2006a) involving three outcome variables used neuropsychological tests to assess the effect of caffeine on 'verbal functioning and language skills'. The point estimates of two

of these three variables were consistent with better performance in the caffeine group, with the third consistent with better performance in the placebo group; none of the estimates were statistically significant at the 5% level.

With the multiple outcomes removed, the SMD was 0.18 (95% CI -0.50 to 0.87, P = 0.60).

Caffeine versus nap

Occurrence of error

One trial (Philip 2006) measured subsequent performance errors during a night-time driving session; an error was defined as an inappropriate line crossing. The OR was 0.71 (95% CI 0.56 to 0.90, P = 0.005) (Analysis 2.1), suggesting a reduction in errors in the caffeine group.

Cognitive performance

All outcome data from the neuropsychological tests comparing caffeine with a nap condition are listed in Table 3. The pooled analysis is presented in Analysis 2.2.

Concept formation and reasoning

One trial (Rogers 1989) with one outcome variable used neuropsychological tests to assess the effect of caffeine compared to naps on 'concept formation and reasoning'. The SMD was -0.45 (95% CI -1.61 to 0.70, P = 0.44).

Memory

One trial (Rogers 1989) involving two outcome variables used neuropsychological tests to assess the effect on 'memory'. Both point estimates were consistent with better performance in the caffeine group; none of these estimates were statistically significant at the 5% level.

With the multiple outcome from the single trial removed, the SMD was -0.80 (95% CI -2.00 to 0.40, P = 0.19).

Orientation and attention

Two trials (Rogers 1989; Schweitzer 2006a) involving eight outcome variables used neuropsychological tests to assess the effects on 'orientation and attention'. Seven of the point estimates were consistent with better performance in the caffeine group; none of the estimates were statistically significant at the 5% level.

With the multiple outcomes from single trials removed, the pooled SMD was -0.14 (95% CI -0.72 to 0.45, P = 0.65). There was no evidence of statistically significant heterogeneity ($Chi^2 = 0.78$, df = 1, P = 0.38; $I^2 = 0\%$).

Perception

One trial (Rogers 1989) with one outcome variable assessed the effect on 'perception'. The SMD was -0.57 (95% CI -1.74 to 0.59, P = 0.33).

Verbal functioning and language skills

One trial (Schweitzer 2006a) involving three outcome variables used neuropsychological tests to assess 'verbal functioning and language skills'. The point estimates of two of these three variables were consistent with better performance in the caffeine group, with the third consistent with better performance in the nap group; none of the estimates were statistically significant at the 5% level.

With the multiple outcomes removed, the SMD was -0.26 (95% CI -0.94 to 0.41, P = 0.45).

Caffeine versus modafinil

Occurrence of error

One trial compared the effects of caffeine to modafinil on the occurrence of errors during a simulated flight. For deviations from altitude, the SMD was -0.25 (95% CI -0.81 to 0.32, P = 0.40). For deviations from velocity, SMD was 0.60 (95% CI 0.02 to 1.18, P = 0.04) (Analysis 3.1).

Caffeine versus chewing intervention

Cognitive performance

All outcome data from the neuropsychological tests comparing caffeine with a chewing intervention are listed in Table 4. The pooled analysis is presented in Analysis 4.1.

Concept formation and reasoning

One trial (Kohler 2006) involved three outcome variables to assess the effect of caffeine compared to a chewing intervention on 'concept formation and reasoning'. One point estimate was consistent with better performance in the caffeine group, one indicated better performance in the chewing group and one indicated no effect; none of these estimates were statistically significant at the 5% level.

With the multiple outcomes removed, the SMD was -0.33 (95% CI -1.07 to 0.42, P = 0.39).

Orientation and attention

One trial (Kohler 2006) involved two outcome variables to assess the effect of caffeine compared to a chewing intervention on 'orientation and attention'. Both point estimates were consistent with better performance in the caffeine group; none of these were statistically significant at the 5% level.

With the multiple outcome removed, the SMD was -0.33 (95% CI -1.08 to 0.42, P = 0.39).

Caffeine plus nap versus placebo

Cognitive performance

All outcome data from the neuropsychological tests used to compare caffeine plus nap with placebo are listed in Table 5. The pooled analysis is presented in Analysis 5.1.

Orientation and attention

Two trials (Schweitzer 2006a; Schweitzer 2006b) involving two outcome variables used neuropsychological tests to compare the effect of caffeine plus nap with placebo on 'orientation and attention'. The pooled SMD was -0.31 (95% CI -0.68 to 0.07, P = 0.11). There was no evidence of statistically significant heterogeneity ($Chi^2 = 1.67$, df = 1, P = 0.20; $I^2 = 40\%$).

Verbal functioning and language skills

One trial (Schweitzer 2006a) involving three outcome variables used neuropsychological tests to assess 'verbal functioning and

language skills'. The point estimates of all these variables were consistent with better performance in the caffeine plus nap group; none of the estimates were statistically significant at the 5% level.

With the multiple outcomes removed, the SMD was -0.77 (95% CI -1.48 to -0.06, P = 0.03).

Caffeine plus dim light versus placebo plus dim light

Cognitive performance

All outcome data from the neuropsychological tests used to compare caffeine plus dim light with placebo plus dim light are listed in Table 6. The pooled analysis is presented in Analysis 6.1.

Memory

One trial (Babkoff 2002) used four outcome variables to assess the effect of caffeine plus dim light with placebo plus dim light on 'memory'. Three of the point estimates were consistent with better performance in the caffeine plus dim light group and one indicated better performance in the placebo plus dim light group; none of the estimates were statistically significant at the 5% level.

With the multiple variables removed, the SMD was -0.41 (95% CI -1.25 to 0.44, P=0.35).

Orientation and attention

One trial (Babkoff 2002) measured six outcome variables to assess the effect of caffeine plus dim light with placebo plus dim light on 'orientation and attention'. All point estimates were consistent with better performance in the caffeine plus dim light group; none were statistical significant at the 5% level.

With the multiple variables removed the SMD was -0.14 (95% CI -0.97 to 0.70, P = 0.75).

Caffeine plus bright light versus placebo plus bright light

Cognitive performance

All outcome data from the neuropsychological tests used to compare caffeine plus bright light with placebo plus bright light are listed in Table 7. The pooled analysis is presented in Analysis 7.1.

Memory

One trial (Babkoff 2002) used four outcome variables to assess the effect of caffeine plus bright light with placebo plus bright light on 'memory'. All four point estimates were consistent with better performance in the caffeine plus bright light group; none of the estimates were statistically significant at the 5% level.

With the multiple variables removed the SMD was -0.23 (95% CI -1.07 to 0.61, P = 0.59).

Orientation and attention

One trial (Babkoff 2002) measured six outcome variables to assess the effect of caffeine plus bright light with placebo plus bright light on 'orientation and attention'. Five of the point estimates were consistent with better performance in the caffeine plus bright light group and one indicated better performance in the placebo plus bright light group; none were statistically significant at the 5% level.

With the multiple variables removed the SMD was -0.16 (95% CI -1.00 to 0.68, P=0.71).

Adverse events

Six studies reported the occurrence of an adverse event of interest to this review.

Disruption to subsequent sleep

The study by Beaumont 2004 observed that in the caffeine group there was an adverse effect on recovery sleep in jet lagged participants, with increased wakefulness, less overall sleep and more awakenings amongst these participants.

Rogers 1989 found a statistically significant difference (P < 0.05) in daytime sleep between the caffeine and control (nap) groups, with the caffeine group associated with a shorter total sleep time. Muehlbach 1995 and Schweitzer 2006b found no evidence for a difference in the duration of daytime sleep between groups.

Risk for dependence

Participants in the trial by Childs 2008 completed a drug effects questionnaire. Compared to placebo, the caffeine group's ratings for 'drug liking', 'want more drug' and 'feel drug' were significantly higher than the placebo group's ratings.

Headache

Doan 2006 looked at the occurrence of headache: one participant in the caffeine group and no participants in the placebo group reported having a headache.

DISCUSSION

Summary of main results

There are currently no randomised controlled trials and consequently no reliable evidence that caffeine is effective in preventing injuries caused by impaired alertness in shift workers. The two studies measuring error both observed a beneficial effect associated with caffeine, however the small sample size of both studies and the clear selective outcome reporting in one, limit our confidence in this finding.

There is some evidence to suggest that caffeine can improve cognitive performance compared to placebo, with effect estimates being largely consistent with a favourable intervention effect. However, caution is required when interpreting this finding due to the lack of adequate allocation concealment and the presence of selective outcome reporting amongst the included studies.

There are too few data available with which to ascertain relative effects of caffeine and other potential countermeasures, such as naps, modafinil and bright light.

Overall completeness and applicability of evidence

The objective of this review was to assess the effects of caffeine for preventing injuries in persons with shift work disorder or jet lag. Ten included studies involved participants under simulated conditions (circadian disruption induced in a sleep laboratory). The remaining three trials were conducted in ‘real world’ settings, specifically a long haul transnational flight, workers engaged in night work and night-time driving. Whilst sleep laboratory studies have the advantage of maintaining a consistent environment throughout the study, and maximising compliance and follow up, the extent to which we can accurately generalise findings from these trials to the

real world environment is questionable. Furthermore, it is notable that none of the trials involved participants with a diagnosis of shift work disorder (SWD). SWD is considered to be distinct and more severe than the typical sleep disturbances associated with shift work (Culpepper 2010). It cannot be assumed that interventions will have the same effect in both conditions.

The participants in the included trials were comparatively young workers, with the average age in many trials being between 20 and 30 years. The effects of shift work on the circadian rhythm are thought to vary with age; workers aged 40 to 50 years and over are understood to have a lower tolerance to shift work than their younger counterparts (Costa 2005). The lack of trial data on older participants means that we are unable to assess whether the effects of caffeine vary with the age of the shift workers.

A further issue relating to the indirectness of the evidence concerns the outcome measures. None of the studies measured an injury outcome and most studies relied on neuropsychological tests to measure effects on cognitive performance. The absence of trials with injury outcomes may be expected, given the relatively large study sizes that would be required to observe sufficient injury events. The use of neuropsychological tests in the included trials provide some evidence of caffeine's impact on performance, but the degree to which this might reduce injury risk is unknown. It is reasonable to assume that higher performance levels are associated with fewer injuries, however we cannot quantify the magnitude of such a reduction. Furthermore, a total of 19 neuropsychological tests with 47 outcome variables were used to assess cognitive performance. It would be useful if there was greater consistency in the number and types of tests administered; which might improve reproducibility of results and assist with the pooling of data in future analyses.

Quality of the evidence

Poor reporting within the trial reports limited some aspects of our assessment of risk of bias in the included studies. We judged there to be 'high' or 'unclear' risk of bias for the adequacy of allocation concealment, incomplete outcome data and selective outcome reporting. As there is evidence that the quality of allocation concealment particularly affects the results of studies (Schulz 1995), the small number of studies rated as at 'low' risk of bias for this criterion is an important consideration. Selective outcome reporting also appears to be a particular concern, affecting the included studies. There was clear evidence of selective outcome reporting in four studies, with selective reporting of statistically significant findings being explicit in the report or confirmed by contact with trial authors. Selective outcome reporting poses a major threat to the validity of systematic reviews and meta-analyses, possibly leading to the over-estimation of intervention effects.

Potential biases in the review process

This systematic review addresses a focused research question using pre-defined inclusion criteria and methodology to select and appraise eligible studies. As with all systematic reviews, the possibility of publication bias should be considered as a potential threat to validity. However, in light of our extensive and sensitive searching, we believe that the risk of such a bias affecting the results is minimal.

Most of the included studies used a cross-over design. Such studies can usually give more precise results than parallel trials, as variation in repeated responses within an individual is generally less than between different individuals (Elbourne 2002). However, in order to benefit from this correlation, an appropriate paired analysis is required. Unfortunately only one cross-over trial reported sufficient data to enable us to appropriately analyse the data. Instead, data from the remaining cross-over trials were analysed as if they had originated from parallel trials. A unit-of-analysis error arises from this approach, which causes confidence intervals to be too wide and the study receiving too little weight in the meta-analysis. However, as such a unit-of-analysis error is conservative in that it leads to studies receiving too little weight (Higgins 2008), we judged that their inclusion in this way was preferable to their complete omission from the pooled analysis.

The quality of reporting of outcome data was variable. In many cases outcome data were only presented graphically in the trial report, and so we were required to read each individual value from figures. Such a technique is obviously susceptible to a degree of inaccuracy, however we judged it to be preferable to the exclusion of such data from the review.

As previously mentioned, a large number of neuropsychological tests were used to assess cognitive performance. For our synthesis, we classified each test according to the underlying cognitive domain under study; however, such categorisation of tests is somewhat arbitrary. Furthermore, where there were multiple outcome variables for a cognitive domain originating from a single study, we selected one outcome for entry in the meta-analysis to avoid multiple representation of trials. Although the selection of outcomes was random, and made independently of the outcome data, such an approach is not ideal. However, all results for each outcome variable are presented in the additional tables for completeness.

Our decision to only include studies with eligible outcome measures may have introduced a bias into the review process. If it was not explicit in the report that eligible outcome measures had not been measured, we contacted the trial author(s) for clarification. Trials for which we did not receive a response from the authors remain excluded from the review, however we cannot be certain whether these trials did measure eligible outcomes and simply omitted the results from the final report.

Agreements and disagreements with other studies or reviews

We have not identified any other systematic reviews or meta-analyses specifically investigating the effects of caffeine in this population. However, the findings of our review in terms of caffeine's beneficial effects on cognitive performance are largely consistent with those from other literature reviews of countermeasures for impaired alertness associated with sleepiness (Caldwell 2008; Caldwell 2009; CMNR 2001).

AUTHORS' CONCLUSIONS

Implications for practice

The results of this systematic review suggest that caffeine may be effective in improving performance in persons engaged in shift work or suffering from jet lag, although it may not be possible to confidently translate such an improvement in performance to a

reduced injury risk. The current evidence arises largely from trials conducted under simulated conditions thus caution is required when extrapolating the findings to real world shift work environments. Furthermore, the lack of trials involving persons aged 40 years and over, who are particularly vulnerable to the adverse effects of shift work, limits the ability to draw confident conclusions regarding the effects of caffeine in this group.

We judge that shift workers who currently use caffeine as a countermeasure to sleepiness can continue to do so with the knowledge that their risk of error should not increase as a result, and they may experience improvement in cognitive performance.

Implications for research

Future research in this area should focus on:

1. identifying the most effective method for the administration of caffeine as an alertness management intervention, and
2. exploring the relative effects of caffeine against other potential countermeasures.

The review authors are currently working on a number of systematic reviews investigating the effects of other interventions for preventing injuries in shift workers. On the completion of the reviews we will be able to identify the interventions which, according to the existing evidence, are the most effective.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Babkoff 2002

Methods	Design: Randomised cross-over trial (4 periods) Setting: USA
Participants	N=12, healthy males and females, aged 19-36 years Simulated night shift from 17.30 to 10.00
Interventions	• Dim light (20-50 lux) + placebo • Bright light (3000 lux) + placebo • Dim light (20-50 lux) + caffeine (200mg tablets, No Doz®) • Bright light (3000 lux) + caffeine (200mg tablets, No Doz®) Placebo and caffeine capsules were identical in appearance. Light exposure between 01.30-02.30, caffeine/placebo administered at 01.40. Each experimental condition separated by at least one week.
Outcomes	Performance measures - reaction time, spatial discrimination, letter cancellation task, logical reasoning, team performance task, air traffic-control task.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Report states that the "order of the four experimental conditions was randomized across the groups of three participants each over the 4 test weeks". Author correspondence confirmed that sequence was generated with use of a table of random numbers.
Allocation concealment?	Low risk	Correspondence with author - the pharmacy had control of randomisation.
Blinding? All outcomes	Low risk	Investigators and participants could not be blinded to the bright/dim light conditions, however were blind to the caffeine/placebo conditions. Review authors judge that the outcome and the outcome measurement are not likely to be influenced by lack of blinding.

Babkoff 2002 *(Continued)*

Incomplete outcome data addressed? All outcomes	Unclear risk	Report states that "of the 12 participants who began the experiment, 11 successfully completed the 4 wk of testing" and "one subject chose to terminate his participation after the first week". 11 were included in the analyses.
Free of selective reporting?	High risk	Outcome data for the team performance task and air traffic-control task are not reported.
Free of other bias?	Low risk	The study appears to be free of other sources of bias.

Beaumont 2004

Methods	Design: Randomised parallel group trial Setting: USA/France
Participants	N=27, healthy male and female volunteers, aged 19 to 47 years, from an US Air Force Reserve Unit Jet lag (eastwards travel): flown from USA to France. Flight at 15.00, across 7 time zones. Arrived in France at 06.00 local time. Prohibited from sleeping during flight, overall were awake for period of 33 hours.
Interventions	• Melatonin (n=9), 5mg melatonin, administered day 1 (17.00), day 0 (16.00) day 1 to 3 (23.00) • Caffeine (n=9), 300mg slow release caffeine, administered day 1 to 5 at 08.00. • Placebo (n=9), lactose capsules, administered day 1 (17.00), day 0 (16.00) day 1 to 3 (23.00)
Outcomes	Seven tests of the NATO STRES Battery, the attention level from a paper/pencil test (Signs barrage), central fatigue from a Critical Fusion Frequency test.
Notes	Funding: Nestec S.A., Lausanne, Switzerland

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Correspondence with author - sequence was generated using a table of random numbers.
Allocation concealment?	Low risk	Correspondence with author - "a pharmacist allocated each group to one of the 3 medications then put in blisters, subject by subject, the appropriate number of blinded capsules (same size, same colour, containing the medication in powder) of the given treatment. The pharmacist also prepared 27 sealed envelopes, each labelled with the subject code number in which the name of the medication was. Envelopes were kept in a safe. If any serious adverse event occurred, the envelope labelled with the appropriate subject number would have been opened by the main investigator in front of 2 witnesses".
Blinding? All outcomes	Low risk	Double-blind, placebo-controlled.
Incomplete outcome data addressed? All outcomes	Unclear risk	Insufficient reporting of attrition/exclusions to permit judgement of 'Yes' or 'No'.
Free of selective reporting?	High risk	Correspondence with author - cognitive performance outcome measures were not published because they were not statistically significant.

Beaumont 2004 *(Continued)*

Free of other bias?	Low risk	The study appears to be free of other sources of bias.

Childs 2008

Methods	Design: Randomised cross-over trial (2 periods) Setting: USA
Participants	N=35, healthy males and females, aged 18-35 years Participants remained awake throughout overnight sessions between 17.00 and 05.00 Experimental sessions were at least one week apart
Interventions	• Caffeine (200mg) containing food supplement • Placebo Drugs were identical in appearance Caffeine/placebo capsules were consumed at 03.30
Outcomes	Simple reaction-time task, two-choice reaction-time task performed at 03.00, 04.00 and 05.00
Notes	Funded by a grant from Atlas Labs, USA and by National Institute on Drug Abuse, USA.

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Correspondence with author - computer generated randomisation.
Allocation concealment?	Low risk	Central allocation.
Blinding? All outcomes	Low risk	Double-blind.
Incomplete outcome data addressed? All outcomes	Unclear risk	Insufficient reporting of attrition/exclusions to permit judgement of 'Yes' or 'No'.
Free of selective reporting?	Unclear risk	All outcomes described in Methods section are reported in the Results.
Free of other bias?	Low risk	The study appears to be free of other sources of bias.

Dagan 2006

Methods	Design: Randomised cross-over trial (3 periods) Setting: Israel
Participants	N=24, male students, aged 25-31 years Participants remained awake during the night, undertook performance testing throughout

Dagan 2006 *(Continued)*

	Each experimental session separated by two weeks
Interventions	• Modafinil, 200mg • Caffeine, 200mg • Placebo, 200mg starch All drugs were identical in appearance. Drugs were administered once a day at 23.00.
Outcomes	Pilot Evaluation System (a cockpit-type simulator) used to evaluate vigilance and cognitive performance.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Correspondence with author - table of random numbers.
Allocation concealment?	Unclear risk	No information.
Blinding? All outcomes	Low risk	Double-blind.
Incomplete outcome data addressed? All outcomes	Unclear risk	Insufficient reporting of attrition/exclusions to permit judgement of 'Yes' or 'No'.
Free of selective reporting?	High risk	Appears from report that only significant results are presented.
Free of other bias?	Low risk	The study appears to be free of other sources of bias.

Doan 2006

Methods	Design: Randomised cross-over trial (2 periods) Setting: USA
Participants	N=12, healthy male pilots in the US Air Force volunteered to participate. Aged 26-45 years.
Interventions	• Caffeinated (200mg) tube food • Placebo tube food Consumed at 00.00 and 04.00
Outcomes	Performance (desktop flight simulator task, scanning visual vigilance test, adaptive tracking task, code substitution task, match-to-sample task, gauge-monitoring task, Nova Scan complex task), wrist activity monitors, symptom questionnaire.
Notes	

Risk of bias

Doan 2006 *(Continued)*

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	No information.
Allocation concealment?	Unclear risk	No information.
Blinding? All outcomes	Low risk	Double-blind.
Incomplete outcome data addressed? All outcomes	Low risk	Report states that "All 12 participants completed the study. Due to occasional technical problems, a small amount of data were lost (<2%). Prior to analysis, we estimated each missing point based on the average percent change of the other data available for that same drug condition and time point".
Free of selective reporting?	Unclear risk	All outcomes described in Methods section are reported in the Results.
Free of other bias?	Low risk	The study appears to be free of other sources of bias.

Jay 2006

Methods	Design: Randomised cross-over trial (2 periods) Setting: Australia
Participants	N=21, healthy male and females aged 22±2 and 23.5±4.7 (mean±SD) years, respectively Laboratory-based simulated night shift
Interventions	• Caffeinated functional energy drink, 250ml (ingredients include; taurine (1000mg), glucoronolactone (600mg), caffeine (80mg), glucose (5.25mg), sucrose (21.5mg), B vitamins and flavours) • Non-functional energy drink Administered at 01.30 and 05.30, consumed within a 10 min time period Two treatment periods were at least one week apart.
Outcomes	Psychomotor vigilance test and a 30min battery of tasks
Notes	Funded: Queen Elizabeth Hospital Research Foundation.

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	No information.
Allocation concealment?	Unclear risk	No information.
Blinding? All outcomes	Low risk	No information.

Jay 2006 *(Continued)*

Incomplete outcome data addressed? All outcomes	Unclear risk	Final analysis based on 15 participants -3 participants withdraw from the study prior to completion and 3 participants not included in analysis due to substantial data loss.
Free of selective reporting?	High risk	Only outcome data from PVT are presented, other data from the 30min battery of tasks are not reported.
Free of other bias?	Low risk	The study appears to be free of other sources of bias.

Kohler 2006

Methods	Design: Randomised cross-over trial (3 periods) Setting: Australia
Participants	N=15, healthy male and females, aged 18-36 years Remained awake throughout one night, testing occurred between 21.30 and 06.30 Experimental sessions were separated by 7 days
Interventions	• Caffeine, 200mg • Chewing, Parafilm (sheet form of paraffin wax) • Placebo Capsules administered at 24.00. Participants in the chewing group were required to chew continuously for 15 minutes each hour prior to testing.
Outcomes	Grammatical reasoning, psychomotor vigilance task, tracking task
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Report states that participants received all conditions in a "randomized crossover fashion". No other details presented.
Allocation concealment?	Unclear risk	No information.
Blinding? All outcomes	Low risk	Double-blind.
Incomplete outcome data addressed? All outcomes	High risk	1/15 withdrew before completing all the sessions, not included in analyses.
Free of selective reporting?	Unclear risk	All outcomes described in Methods section are reported in the Results.
Free of other bias?	Low risk	The study appears to be free of other sources of bias.

Muehlbach 1995

Methods	Design: Randomised parallel group trial Setting: USA
Participants	N=30, male and female, healthy, adult volunteers aged 19-30 years Laboratory-based simulated night shift schedule for 5 consecutive nights
Interventions	• Caffeine (n=15), 2mg/kg • Placebo (n=15) All participants received 300ml of decaffeinated coffee between 22.20 and 22.50 and again between 01.20 and 01.50 hours on each of the 5 nights. For participants in the caffeine group, caffeine was added to the coffee for the first 3 nights.
Outcomes	SALT performance measure (measured every 2 hours throughout the shift)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Correspondence with author - table of random numbers.
Allocation concealment?	High risk	Correspondence with author - allocation was not concealed.
Blinding? All outcomes	Low risk	Participants and laboratory-based personnel were blind to allocation status.
Incomplete outcome data addressed? All outcomes	Unclear risk	Insufficient reporting of attrition/exclusions to permit judgement of 'Yes' or 'No'.
Free of selective reporting?	Unclear risk	All outcomes described in Methods section are reported in the Results.
Free of other bias?	Low risk	The study appears to be free of other sources of bias.

Philip 2006

Methods	Design: Randomised cross-over trial (3 periods) Setting: France
Participants	N=12, males, aged 21.3±1.8 (mean±SD) years. Participants had held a driving licence for at least 2 years, but were not professional drivers. Participated in three night driving sessions (02.00 to 03.30) on open highway
Interventions	• Caffeine, 125ml of coffee containing 200mg of caffeine. Consumed 30 minutes before the driving session • Placebo, 125ml decaffeinated coffee containing 15ml of caffeine. Consumed 30 minutes before the driving session • Napping, 30 minutes, started at one hour before driving session

Philip 2006 *(Continued)*

	At least one week between each treatment period.
Outcomes	Inappropriate line crossings (i.e. when the car crossed a lateral highway lane marker). Assessed using video footage.
Notes	Funded: French Ministry of Research & Laboratoire d'Accidentologie et de Bio Méchanique.

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Correspondence with author - table of random numbers.
Allocation concealment?	Unclear risk	Correspondence with author - "one of our research assistants had a code to select our patients independently of the investigators".
Blinding? All outcomes	Low risk	Double-blind. Investigator marking video was blind to allocation.
Incomplete outcome data addressed? All outcomes	Low risk	No missing data - no protocol deviations occurred and all participants completed.
Free of selective reporting?	Unclear risk	All outcomes described in Methods section are reported in the Results.
Free of other bias?	Low risk	The study appears to be free of other sources of bias.

Rogers 1989

Methods	Design: Randomised cross-over trial (3 periods) Setting: UK
Participants	N=6, females aged 20-32 years Each experimental session lasted 17.5 hours and was preceded by a 4 hour rest period Participants remained awake over night
Interventions	• Nap, 1 hour, at 02.00 • No nap+caffeine, 300mg • No nap+placebo Placebo/caffeine administered at 23.15, were identical in appearance administered in a double-blind manner.
Outcomes	Sustained attention, auditory vigilance & tracking, complex vigilance, short-term memory, visual vigilance, two-letter cancellation, digit symbol substitution, logic. Measured at 17.00, 19.15, 21.30, 23.45,02.00, 04.15, 06.30 and 08.45.
Notes	

Risk of bias

Rogers 1989 *(Continued)*

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Correspondence with author - random number generator.
Allocation concealment?	Unclear risk	No information.
Blinding? All outcomes	Low risk	Double-blind.
Incomplete outcome data addressed? All outcomes	Unclear risk	Insufficient reporting of attrition/exclusions to permit judgement of 'Yes' or 'No'.
Free of selective reporting?	Unclear risk	All outcomes described in Methods section are reported in the Results.
Free of other bias?	Low risk	The study appears to be free of other sources of bias.

Schweitzer 2006a

Methods	Design: Randomised parallel group trial Setting: USA
Participants	N=68, males and females aged 19-65 years Laboratory-based simulated night shifts. Remained awake from 23.00 to 07.30, performed a variety of assessments
Interventions	• 2.5 hour nap plus placebo (n=17) • caffeine (n=17) • 2.5 hour nap opportunity plus caffeine (n=17) • placebo and no nap opportunity (n=16) Naps were taken between 19.30 and 22.00 during the first 2 of the 4 consecutive night shifts. 4mg/kg caffeine was taken 30 minutes prior to all 4 night shifts.
Outcomes	Psychomotor vigilance test, digit symbol substitution test (administered at 2-hour intervals, total of 4 times during night shift), the Torrence test of creative thinking-verbal (performed on night 1), the Wisconsin card sorting test, Thurstone's word fluency test, the anagram task (performed on night 2), Torrence test of creative thinking - figural (performed on night 3), the category test, letter-numbering sequencing, sentence completion test (night 4).
Notes	Trial reported in same publication as Schweitzer 2006b.

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	No information.
Allocation concealment?	Unclear risk	No information.

Schweitzer 2006a *(Continued)*

Blinding? All outcomes	Low risk	Not feasible to blind participants to nap status due to nature of intervention, however review authors judge that the outcome and the outcome measurement are not likely to be influenced by lack of blinding. Participants were blinded to caffeine and placebo. All data were scored without knowledge of allocation.
Incomplete outcome data addressed? All outcomes	Unclear risk	4 participants withdrew from the study for personnel reasons, 3 placebo participants from a separate study were included. Final sample n=67.
Free of selective reporting?	High risk	Only outcome measures with statistically significant findings are reported.
Free of other bias?	Low risk	The study appears to be free of other sources of bias.

Schweitzer 2006b

Methods	Design: Randomised cross-over trial (2 periods) Setting: USA
Participants	N=53, male and female shift-workers, 18-65 years Continued with their usual jobs - experimental period of 4 consecutive night shifts
Interventions	• Caffeine (300mg) taken on all four nights plus 2 hour evening nap on first 2 nights • Placebo taken on all four nights and no nap opportunity Caffeine/placebo taken at start of each night shift. Naps taken at home in the evening prior to the night shift (3-4 hours before start of shift) Experimental periods separated by 3-24 days
Outcomes	Psychomotor vigilance test (performed 3 times each night shift)
Notes	Trial reported in same publication as Schweitzer 2006a. 6 persons did not complete the study, 8 were excluded for technical failures and protocol violations. N=39 completed both study arms.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	No information.
Allocation concealment?	Unclear risk	No information.
Blinding? All outcomes	Low risk	Not feasible to blind participants to nap status due to nature of intervention, however review authors judge that the outcome and the outcome measurement are not likely to be influenced by lack of blinding. Participants were blinded to caffeine and placebo.

Schweitzer 2006b *(Continued)*

Incomplete outcome data addressed? All outcomes	Unclear risk	6 persons did not complete the study, 8 were excluded for technical failures and protocol violations. N=39 completed both study arms and are included in the analysis.
Free of selective reporting?	Unclear risk	All outcomes described in Methods section are reported in the Results.
Free of other bias?	Low risk	The study appears to be free of other sources of bias.

Wyatt 2004

Methods	Design: Randomised parallel controlled trial Setting: USA
Participants	N=16, healthy males, aged 18-30 years Underwent a forced desynchrony paradigm in which participants adopted a 42.85 hour cycle (28.57 hours awake, 14.28 hours asleep) occurring over 25x 24 hour days.
Interventions	• Caffeine capsules (n=8), 0.3mg per kg • Placebo capsules (n=8) Taken each waking hour
Outcomes	Assessed each 2 hours with a 30 minute test battery consisting of the probed recall memory task, psychomotor vigilance task, addition task and the digit symbol substitution task.
Notes	Funded by the US Air Force Office of Scientific Research and the National Center for Research Resources.

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Correspondence with author - could not recall method used to generate sequence.
Allocation concealment?	Low risk	Correspondence with author - pharmacy-controlled randomisation.
Blinding? All outcomes	Low risk	Double-blind.
Incomplete outcome data addressed? All outcomes	Unclear risk	One participant was excluded from the analysis for the digit symbol substitution task because of missing baseline data.
Free of selective reporting?	Unclear risk	All outcomes described in Methods section are reported in the Results, however the presented data are not suitable for meta-analysis.
Free of other bias?	Low risk	The study appears to be free of other sources of bias.

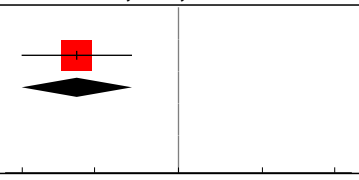
DATA AND ANALYSES

Comparison 1. Caffeine versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Error	1		Odds Ratio (Fixed, 95% CI)	Subtotals only
1.1 ≥ inappropriate line crossings	1		Odds Ratio (Fixed, 95% CI)	0.14 [0.05, 0.41]
2 Error	1		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.1 Deviation from altitude	1	48	Std. Mean Difference (IV, Fixed, 95% CI)	-1.30 [-1.93, -0.68]
2.2 Deviation from velocity	1	48	Std. Mean Difference (IV, Fixed, 95% CI)	-1.18 [-1.79, -0.56]
3 Cognitive performance	6		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.1 Concept formation & reasoning	2	40	Std. Mean Difference (IV, Fixed, 95% CI)	-0.41 [-1.04, 0.23]
3.2 Memory	2	20	Std. Mean Difference (IV, Fixed, 95% CI)	-1.08 [-2.07, -0.09]
3.3 Orientation & attention	6	211	Std. Mean Difference (IV, Fixed, 95% CI)	-0.55 [-0.83, -0.27]
3.4 Perception	2	20	Std. Mean Difference (IV, Fixed, 95% CI)	-0.77 [-1.73, 0.20]
3.5 Verbal functioning & language skills	1	33	Std. Mean Difference (IV, Fixed, 95% CI)	0.18 [-0.50, 0.87]

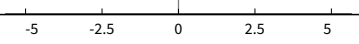
Analysis 1.1. Comparison 1 Caffeine versus placebo, Outcome 1 Error.

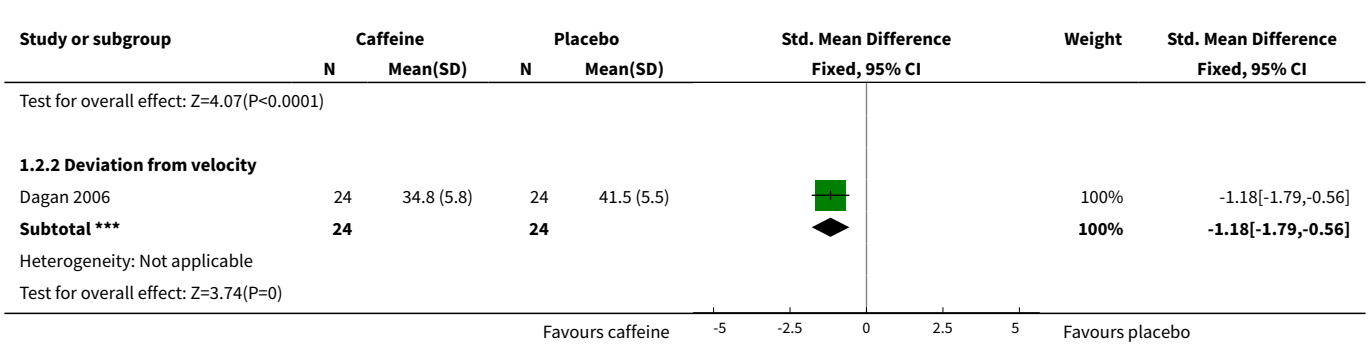
Study or subgroup	Favours caffeine N	Placebo N	log[Odds Ratio] (SE)	Odds Ratio IV, Fixed, 95% CI	Weight	Odds Ratio IV, Fixed, 95% CI
1.1.1 ≥ inappropriate line crossings						
Philip 2006	0	0	-1.9 (0.54)		100%	0.14[0.05,0.41]
Subtotal (95% CI)					**100%**	**0.14[0.05,0.41]**
Heterogeneity: Not applicable						
Test for overall effect: Z=3.61(P=0)						



Analysis 1.2. Comparison 1 Caffeine versus placebo, Outcome 2 Error.

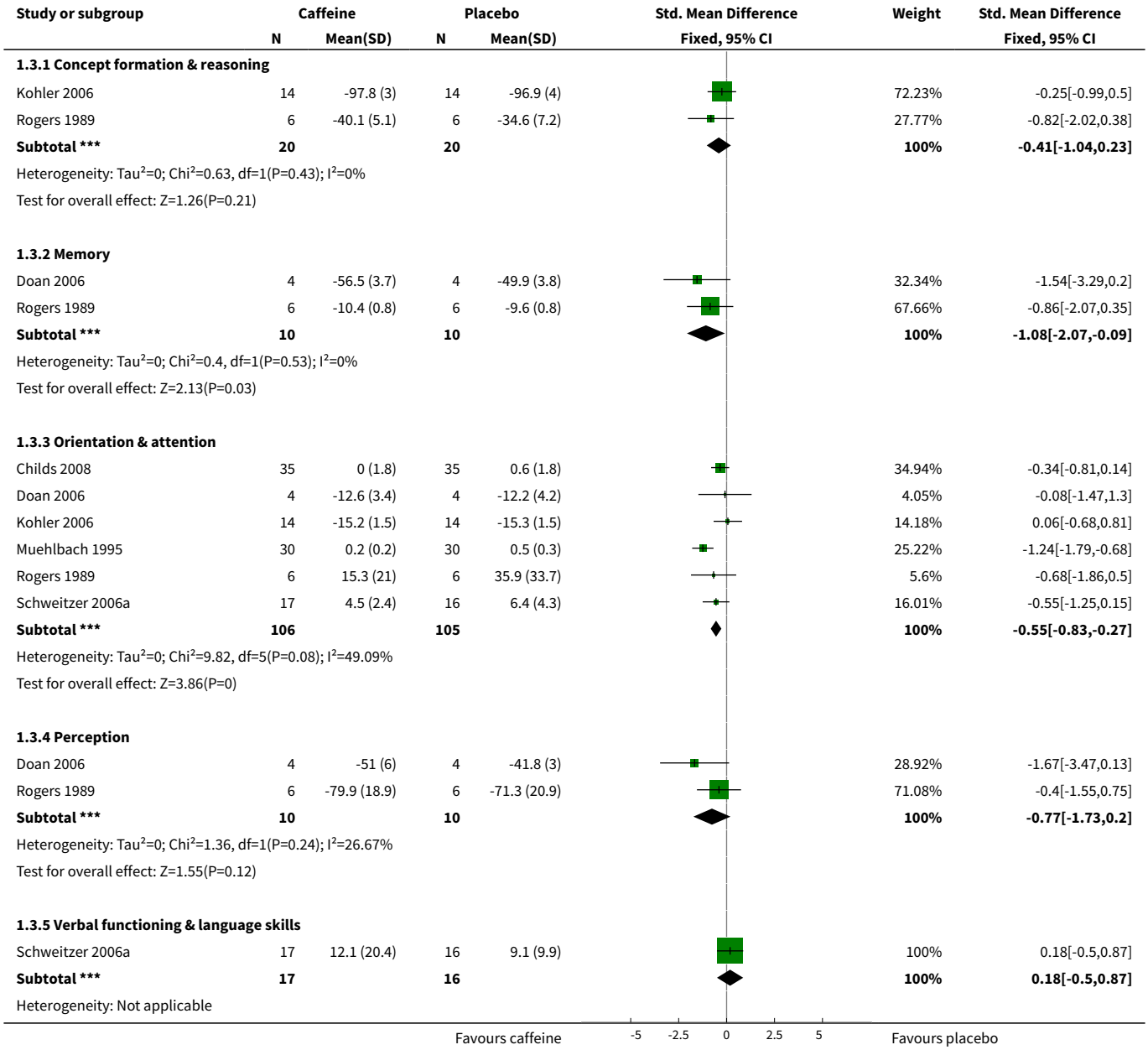
Study or subgroup	Caffeine N	Caffeine Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
1.2.1 Deviation from altitude							
Dagan 2006	24	560 (40)	24	620 (50)		100%	-1.3[-1.93,-0.68]
Subtotal ***	**24**		**24**			**100%**	**-1.3[-1.93,-0.68]**
Heterogeneity: Not applicable							





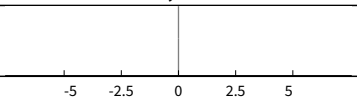
Study or subgroup	Caffeine N	Caffeine Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
Test for overall effect: Z=4.07(P<0.0001)							
1.2.2 Deviation from velocity							
Dagan 2006	24	34.8 (5.8)	24	41.5 (5.5)		100%	-1.18[-1.79,-0.56]
Subtotal ***	**24**		**24**			**100%**	**-1.18[-1.79,-0.56]**
Heterogeneity: Not applicable							
Test for overall effect: Z=3.74(P=0)							

Analysis 1.3. Comparison 1 Caffeine versus placebo, Outcome 3 Cognitive performance.



Study or subgroup	Caffeine N	Caffeine Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
1.3.1 Concept formation & reasoning							
Kohler 2006	14	-97.8 (3)	14	-96.9 (4)		72.23%	-0.25[-0.99,0.5]
Rogers 1989	6	-40.1 (5.1)	6	-34.6 (7.2)		27.77%	-0.82[-2.02,0.38]
Subtotal ***	**20**		**20**			**100%**	**-0.41[-1.04,0.23]**
Heterogeneity: Tau^2=0; Chi^2=0.63, df=1(P=0.43); I^2=0%							
Test for overall effect: Z=1.26(P=0.21)							
1.3.2 Memory							
Doan 2006	4	-56.5 (3.7)	4	-49.9 (3.8)		32.34%	-1.54[-3.29,0.2]
Rogers 1989	6	-10.4 (0.8)	6	-9.6 (0.8)		67.66%	-0.86[-2.07,0.35]
Subtotal ***	**10**		**10**			**100%**	**-1.08[-2.07,-0.09]**
Heterogeneity: Tau^2=0; Chi^2=0.4, df=1(P=0.53); I^2=0%							
Test for overall effect: Z=2.13(P=0.03)							
1.3.3 Orientation & attention							
Childs 2008	35	0 (1.8)	35	0.6 (1.8)		34.94%	-0.34[-0.81,0.14]
Doan 2006	4	-12.6 (3.4)	4	-12.2 (4.2)		4.05%	-0.08[-1.47,1.3]
Kohler 2006	14	-15.2 (1.5)	14	-15.3 (1.5)		14.18%	0.06[-0.68,0.81]
Muehlbach 1995	30	0.2 (0.2)	30	0.5 (0.3)		25.22%	-1.24[-1.79,-0.68]
Rogers 1989	6	15.3 (21)	6	35.9 (33.7)		5.6%	-0.68[-1.86,0.5]
Schweitzer 2006a	17	4.5 (2.4)	16	6.4 (4.3)		16.01%	-0.55[-1.25,0.15]
Subtotal ***	**106**		**105**			**100%**	**-0.55[-0.83,-0.27]**
Heterogeneity: Tau^2=0; Chi^2=9.82, df=5(P=0.08); I^2=49.09%							
Test for overall effect: Z=3.86(P=0)							
1.3.4 Perception							
Doan 2006	4	-51 (6)	4	-41.8 (3)		28.92%	-1.67[-3.47,0.13]
Rogers 1989	6	-79.9 (18.9)	6	-71.3 (20.9)		71.08%	-0.4[-1.55,0.75]
Subtotal ***	**10**		**10**			**100%**	**-0.77[-1.73,0.2]**
Heterogeneity: Tau^2=0; Chi^2=1.36, df=1(P=0.24); I^2=26.67%							
Test for overall effect: Z=1.55(P=0.12)							
1.3.5 Verbal functioning & language skills							
Schweitzer 2006a	17	12.1 (20.4)	16	9.1 (9.9)		100%	0.18[-0.5,0.87]
Subtotal ***	**17**		**16**			**100%**	**0.18[-0.5,0.87]**
Heterogeneity: Not applicable							

Study or subgroup	Caffeine N	Caffeine Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
Test for overall effect: Z=0.52(P=0.6)							
Test for subgroup differences: Chi²=5.61, df=1 (P=0.23), I²=28.76%							

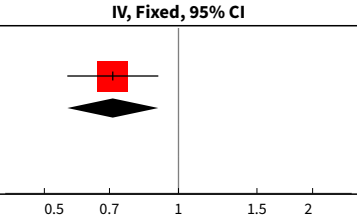


Comparison 2. Caffeine versus nap

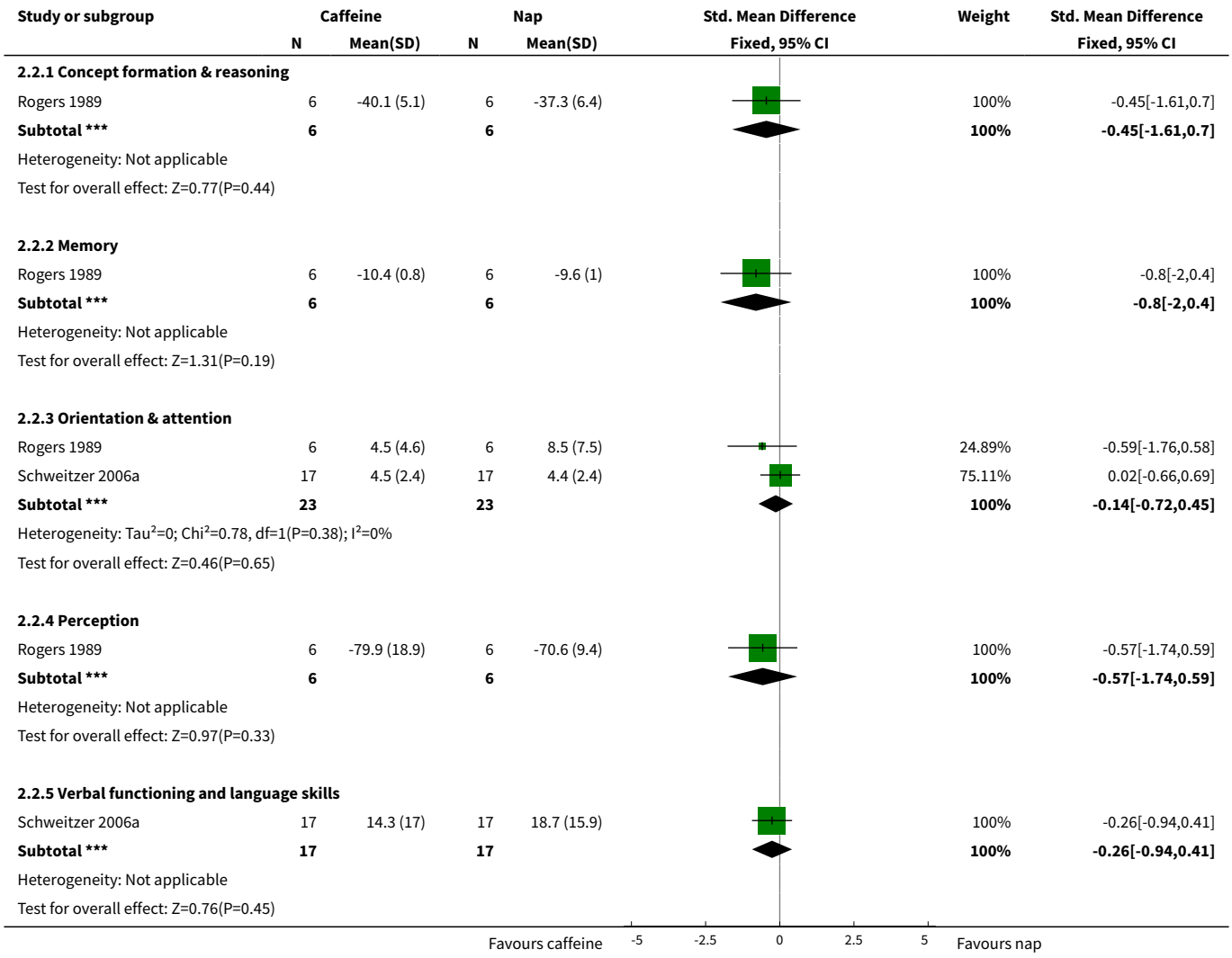
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Error	1		Odds Ratio (Fixed, 95% CI)	Subtotals only
1.1 ≥1 inappropriate line crossings	1		Odds Ratio (Fixed, 95% CI)	0.71 [0.56, 0.90]
2 Cognitive performance	2		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.1 Concept formation & reasoning	1	12	Std. Mean Difference (IV, Fixed, 95% CI)	-0.45 [-1.61, 0.70]
2.2 Memory	1	12	Std. Mean Difference (IV, Fixed, 95% CI)	-0.80 [0.00, 0.40]
2.3 Orientation & attention	2	46	Std. Mean Difference (IV, Fixed, 95% CI)	-0.14 [-0.72, 0.45]
2.4 Perception	1	12	Std. Mean Difference (IV, Fixed, 95% CI)	-0.57 [-1.74, 0.59]
2.5 Verbal functioning and language skills	1	34	Std. Mean Difference (IV, Fixed, 95% CI)	-0.26 [-0.94, 0.41]

Analysis 2.1. Comparison 2 Caffeine versus nap, Outcome 1 Error.

Study or subgroup	Caffeine N	Nap N	log[Odds Ratio] (SE)	Odds Ratio IV, Fixed, 95% CI	Weight	Odds Ratio IV, Fixed, 95% CI
2.1.1 ≥1 inappropriate line crossings						
Philip 2006	0	0	-0.3 (0.12)		100%	0.71[0.56,0.9]
Subtotal (95% CI)					**100%**	**0.71[0.56,0.9]**
Heterogeneity: Not applicable						
Test for overall effect: Z=2.83(P=0)						



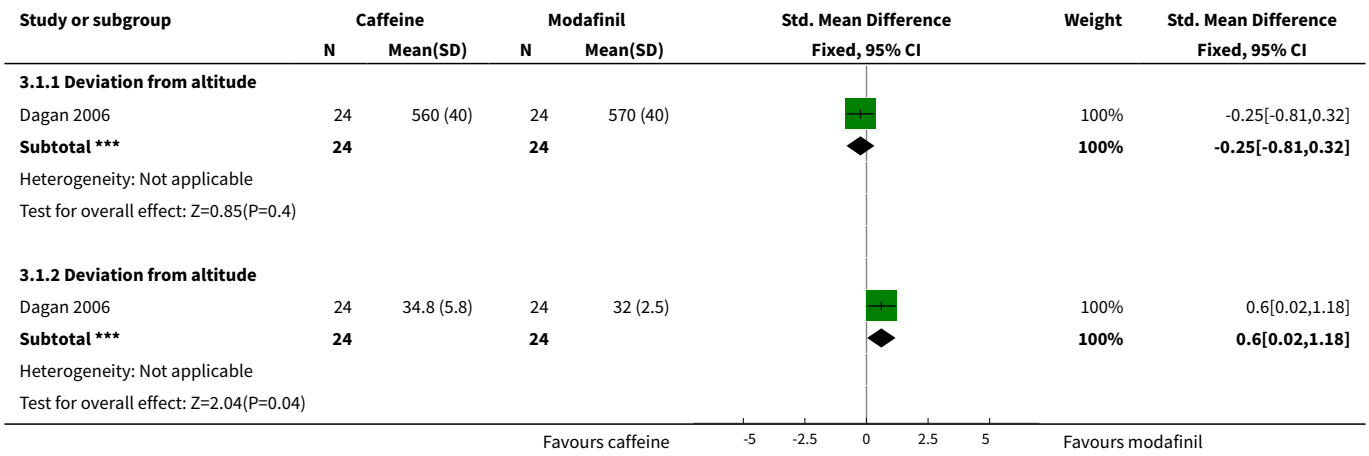
Analysis 2.2. Comparison 2 Caffeine versus nap, Outcome 2 Cognitive performance.



Comparison 3. Caffeine versus modafinil

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Error	1		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 Deviation from altitude	1	48	Std. Mean Difference (IV, Fixed, 95% CI)	-0.25 [-0.81, 0.32]
1.2 Deviation from altitude	1	48	Std. Mean Difference (IV, Fixed, 95% CI)	0.60 [0.02, 1.18]

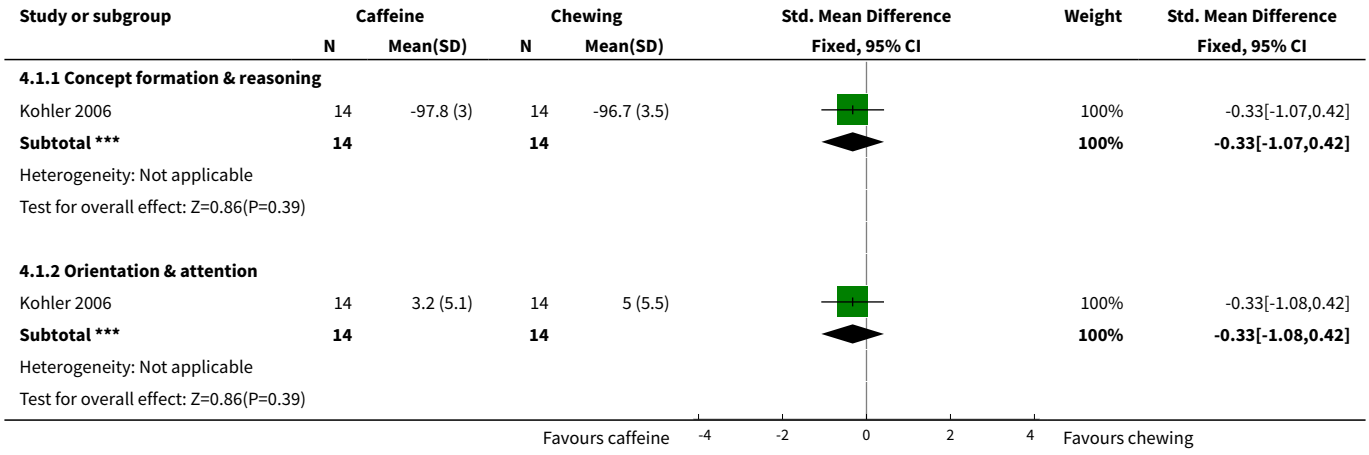
Analysis 3.1. Comparison 3 Caffeine versus modafinil, Outcome 1 Error.



Comparison 4. Caffeine versus chewing intervention

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Cognitive performance	1		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 Concept formation & reasoning	1	28	Std. Mean Difference (IV, Fixed, 95% CI)	-0.33 [-1.07, 0.42]
1.2 Orientation & attention	1	28	Std. Mean Difference (IV, Fixed, 95% CI)	-0.33 [-1.08, 0.42]

Analysis 4.1. Comparison 4 Caffeine versus chewing intervention, Outcome 1 Cognitive performance.

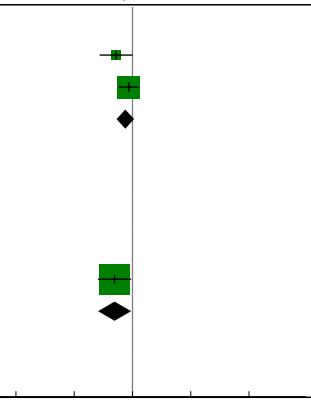


Comparison 5. Caffeine+nap versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cognitive performance	2		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 Orienation & attention	2	111	Std. Mean Difference (IV, Fixed, 95% CI)	-0.31 [-0.68, 0.07]
1.2 Verbal functioning & language skills	1	33	Std. Mean Difference (IV, Fixed, 95% CI)	-0.77 [-1.48, -0.06]

Analysis 5.1. Comparison 5 Caffeine+nap versus placebo, Outcome 1 Cognitive performance.

Study or subgroup	Caffeine+nap N	Caffeine+nap Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
5.1.1 Orienation & attention							
Schweitzer 2006a	17	3.9 (2.6)	16	6.4 (4.3)		28.38%	-0.7[-1.41,0]
Schweitzer 2006b	39	-2.4 (0.8)	39	-2.3 (0.8)		71.62%	-0.15[-0.6,0.29]
Subtotal ***	**56**		**55**			**100%**	**-0.31[-0.68,0.07]**
Heterogeneity: Tau^2=0; Chi^2=1.67, df=1(P=0.2); I^2=40.1%							
Test for overall effect: Z=1.61(P=0.11)							
5.1.2 Verbal functioning & language skills							
Schweitzer 2006a	17	-0.8 (13.6)	16	8.3 (8.8)		100%	-0.77[-1.48,-0.06]
Subtotal ***	**17**		**16**			**100%**	**-0.77[-1.48,-0.06]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.12(P=0.03)							

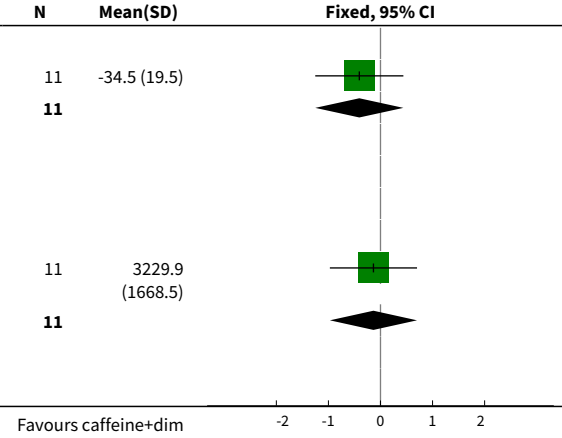


Comparison 6. Caffeine+dim light versus placebo+dim light

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cognitive performance	1		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 Memory	1	22	Std. Mean Difference (IV, Fixed, 95% CI)	-0.41 [-1.25, 0.44]
1.2 Orientation & attention	1	22	Std. Mean Difference (IV, Fixed, 95% CI)	-0.14 [-0.97, 0.70]

Analysis 6.1. Comparison 6 Caffeine+dim light versus placebo+dim light, Outcome 1 Cognitive performance.

Study or subgroup	Caffeine+dim light N	Caffeine+dim light Mean(SD)	Placebo+dim light N	Placebo+dim light Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
6.1.1 Memory							
Babkoff 2002	11	-41.9 (15.2)	11	-34.5 (19.5)		100%	-0.41[-1.25,0.44]
Subtotal ***	**11**		**11**			**100%**	**-0.41[-1.25,0.44]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.94(P=0.35)							
6.1.2 Orientation & attention							
Babkoff 2002	11	3004.5 (1534.9)	11	3229.9 (1668.5)		100%	-0.14[-0.97,0.7]
Subtotal ***	**11**		**11**			**100%**	**-0.14[-0.97,0.7]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.32(P=0.75)							

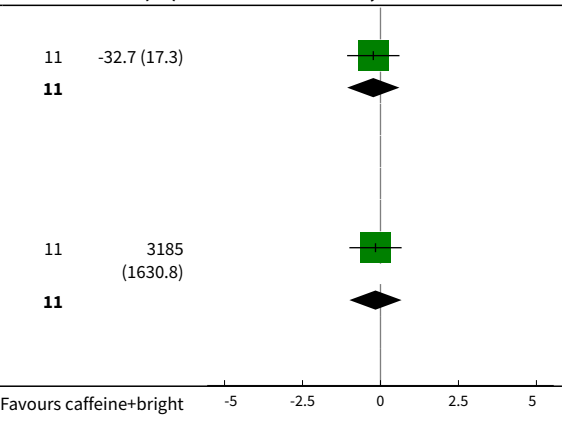


Comparison 7. Caffeine+bright light versus placebo+bright light

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cognitive performance	1		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 Memory	1	22	Std. Mean Difference (IV, Fixed, 95% CI)	-0.23 [-1.07, 0.61]
1.2 Orientation & attention	1	22	Std. Mean Difference (IV, Fixed, 95% CI)	-0.16 [1.00, 0.68]

Analysis 7.1. Comparison 7 Caffeine+bright light versus placebo+bright light, Outcome 1 Cognitive performance.

Study or subgroup	Caffeine+bright light N	Caffeine+bright light Mean(SD)	Placebo+bright light N	Placebo+bright light Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
7.1.1 Memory							
Babkoff 2002	11	-36.8 (17.5)	11	-32.7 (17.3)		100%	-0.23[-1.07,0.61]
Subtotal ***	**11**		**11**			**100%**	**-0.23[-1.07,0.61]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.54(P=0.59)							
7.1.2 Orientation & attention							
Babkoff 2002	11	2925.2 (1493.5)	11	3185 (1630.8)		100%	-0.16[-1,0.68]
Subtotal ***	**11**		**11**			**100%**	**-0.16[-1,0.68]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.37(P=0.71)							



ADDITIONAL TABLES

Table 1. Neuropsychological tests classified according cognitive domain

Concept formation & reasoning	Construction	Executive function & motor performance	Memory	Orientation & attention	Perception	Verbal functioning & language skills
Kohler 2006 - Grammatical reasoning test (adapted from Baddeley 1968). **Rogers 1989** - Logic test.	n/a	n/a	**Babkoff 2002** - Working memory. **Doan 2006** - Code substitution test. **Rogers 1989** - Short term memory test.	**Babkoff 2002** - Choice reaction time, spatial discrimination task. **Childs 2008** - Two-choice reaction time test, simple reaction time. **Doan 2006** - Nova Scan™ complex task, adaptive tracking, scanning visual vigilance. **Kohler 2006** - Psychomotor vigilance task (Dinges & Powel 1985), Tracking task (OSPAT version 4). **Muehlbach 1995** - Simulated assembly line task. **Rogers 1989** - auditory tracking, sustained attention (adapted from Rosvold 1956), digit-symbol substitution, visual vigilance, complex attention **Schweitzer 2006a** - Psychomotor vigilance task (Dinges & Powel 1985). **Schweitzer 2006b** - Psychomotor vigilance task (Dinges & Powel 1985).	**Doan 2006** - Match-to-sample test. **Rogers 1989** - Two-letter cancellation task.	**Schweitzer 2006a** - Torrance test of creative thinking-verbal (Torrance 1990).

Table 2. Caffeine versus placebo - all outcome data from neuropsychological tests

	Caffeine			Placebo			
Subgroup/study	**mean**	**sd**	**n**	**mean**	**sd**	**n**	**SMD (95% CIs)**
Concept formation and reasoning							
Kohler - grammatical reasoning, accuracy %	-97.8	3	14	-96.9	4	14	-0.25 (-0.99 to 0.50)
Kohler - grammatical reasoning, response time, s	2.2	0.6	14	2.4	0.7	14	-0.30 (-1.04 to 0.45)
Rogers - logic	-40.1	5.05	6	-34.6	7.18	6	-0.82 (-2.02 to 0.38)
Memory							
Doan - code substitution, throughput	-56.55	3.72	4	-49.88	3.8	4	-1.54 (-3.29 to 0.20)
Rogers - short term memory, av. no. correct	-10.38	0.83	6	-9.64	0.76	6	-0.86 (-2.07 to 0.35)
Rogers - short term memory, av. no. correct in correct sequence	-8.74	1.07	6	-7.58	1.2	6	-0.94 (-2.16 to 0.28)
Orientation and attention							
Childs - simple reaction time, ms	12	29.58	35	26.4	26.62	35	-0.51 (-0.98 to -0.03)
Childs - simple reaction time, no. lapses	-0.1	0.59	35	0.3	2.37	35	-0.26 (-0.70 to 0.24)
Childs - two-choice reaction time, ms	11.2	69.22	35	52.7	53.84	35	-0.66 (-1.14 to -0.18)
Childs - two-choice reaction time, no. lapses	0	1.77	35	0.6	1.77	35	-0.34 (-0.81 to 0.14)
Doan - adaptive tracking task	59.48	22.02	4	77.11	13.16	4	-0.85 (-2.35 to 0.66)

Table 2. Caffeine versus placebo - all outcome data from neuropsychological tests *(Continued)*

Doan - Nova Scan complex task, mean response time	1839.25	88.08	4	1994.5	63.5	4	-1.76 (-3.60 to 0.08)
Doan - scanning visual vigilance test	-12.56	3.4	4	-12.19	4.16	4	-0.08 (-1.47 to 1.30)
Kohler - PVT, no. lapses	3.2	5.1	14	3.6	6.7	14	-0.07 (-0.81 to 0.68)
Kohler - PVT, response speed, ms	4.1	0.7	14	4.1	0.8	14	0.00 (-0.74 to 0.74)
Kohler - tracking task, score	-15.2	1.5	14	-15.3	1.5	14	0.06 (-0.68 to 0.81)
Muehlbach - SALT, correct responses %	-92.84	8	30	-92.55	5.8	30	-0.04 (-0.55 to 0.47)
Muehlbach - SALT, correction time (sec)	6.6	2.17	30	6.61	2.14	30	0.00 (-0.51 to 0.50)
Muehlbach - SALT, empty items %	0.12	0.23	30	0.23	0.36	30	-0.36 (-0.87 to 0.15)
Muehlbach - SALT, non-faulty item %	0.16	0.2	30	0.48	0.3	30	-1.12 (-1.79 to -0.68)
Rogers - auditory tracking and vigilance, error score	879.32	898.25	6	1305.24	1284.73	6	-0.35 (-1.50 to 0.79)
Rogers - auditory tracking and vigilance, missed responses %	28.1	42.38	6	45.86	62.68	6	-0.31 (-1.45 to 0.84)
Rogers - complex attention, missed responses %	15.28	21.02	6	35.88	33.66	6	-0.68 (-1.86 to 0.50)
Rogers - digit symbol substitution, no. substitutions	-113.94	8.79	6	-103.98	12.64	6	-0.84 (-2.05 to 0.36)
Rogers - sustained attention, missed responses %	4.46	4.55	6	10.74	16	6	-0.49 (-1.65 to 0.66)
Rogers - visual vigilance, mean RT for correct responses	0.6	0.03	6	0.62	0.05	6	-0.45 (-1.60 to 0.70)
Rogers - visual vigilance, missed responses %	24.56	35.98	6	62.72	42.57	6	-0.89 (-2.11 to 0.32)

Table 2. Caffeine versus placebo - all outcome data from neuropsychological tests *(Continued)*

Schweitzer a - PVT, no. lapses	4.47	2.44	17	6.42	4.28	16	-0.55 (-1.25 to 0.15)
Perception							
Doan - match-to-sample task	-50.98	6.02	4	-41.85	3	4	-1.67 (-3.47 to 0.13)
Rogers - two-letter cancellation, no. correct	-79.92	18.89	6	-71.34	20.92	6	-0.40 (-1.55 to 0.75)
Verbal functioning and language skills							
Schweitzer a - Torrance test of creative thinking (verbal), flexibility	14.3	17.03	17	15.68	13.2	16	-0.09 (-0.77 to 0.60)
Schweitzer a - Torrance test of creative thinking (verbal), fluency	4.68	10.23	17	8.25	8.8	16	-0.36 (-1.05 to 0.32)
Schweitzer a - Torrance test of creative thinking (verbal), originality	12.1	20.41	17	9.08	9.92	16	0.18 (-0.50 to 0.87)

Table 3. Caffeine versus nap - all outcome data from neuropsychological tests

	Caffeine			Nap			
Subgroup/study	**mean**	**sd**	**n**	**mean**	**sd**	**n**	**SMD (95% CIs)**
Concept formation and reasoning							
Rogers - logic	-40.1	5.05	6	-37.28	6.37	6	-0.45 (-1.61 to 0.70)
Memory							
Rogers - short term memory, av. no. correct	-10.38	0.83	6	-9.6	0.96	6	-0.80 (-2.00 to 0.40)
Rogers - short term memory, av. no. correct in correct sequence	-8.74	1.07	6	-7.4	1.81	6	-0.83 (-2.03 to 0.37)
Orientation and attention							

Table 3. Caffeine versus nap - all outcome data from neuropsychological tests *(Continued)*

Rogers - auditory tracking and vigilance, error score	879.32	898.25	6	1460	1993.27	6	-0.35 (-1.49 to 0.80)
Rogers - auditory tracking and vigilance, missed responses %	28.1	42.38	6	44.95	42.3	6	-0.37 (-1.51 to 0.78)
Rogers - complex attention, missed responses %	15.28	21.02	6	32.75	19.23	6	-0.80 (-2.00 to 0.40)
Rogers - digit symbol substitution, no. substitutions	-113.94	8.79	6	-108.6	3.55	6	-0.74 (-1.92 to 0.45)
Rogers - sustained attention, missed responses %	4.46	4.55	6	8.45	7.52	6	-0.59 (-1.76 to 0.58)
Rogers - visual vigilance, mean RT for correct responses	0.6	0.03	6	0.62	0.02	6	-0.72 (-1.91 to 0.46)
Rogers - visual vigilance, missed responses %	24.56	35.98	6	55.98	45	6	-0.71 (-1.90 to 0.47)
Schweitzer a - PVT, no. lapses	4.47	2.44	17	4.43	2.44	17	0.02 (-0.66 to 0.69)
Perception							
Rogers - two-letter cancellation, no. correct	-79.92	18.89	6	-70.63	9.39	6	-0.57 (-1.74 to 0.59)
Verbal functioning and language skills							
Schweitzer a - Torrance test of creative thinking (verbal), flexibility	14.3	17.03	17	18.7	15.87	17	-0.26 (-0.94 to 0.41)
Schweitzer a - Torrance test of creative thinking (verbal), fluency	4.68	10.23	17	9.08	11.34	17	-0.40 (-1.08 to 0.28)
Schweitzer a - Torrance test of creative thinking (verbal), originality	12.1	20.41	17	10.45	6.8	17	0.11 (-0.57 to 0.78)

Table 4. Caffeine versus chewing intervention - all outcome data from neuropsychological tests

	Caffeine			Chewing intervention			
Subgroup/study	**mean**	**sd**	**n**	**mean**	**sd**	**n**	**SMD (95% CI)**
Concept formation and reasoning							
Kohler - grammatical reasoning, accuracy %	-97.8	3	14	-96.7	3.5	14	-0.33 (-1.07 to 0.42)
Kohler - grammatical reasoning, response time, s	2.2	0.6	14	2.5	0.8	14	-0.41 (-1.16 to 0.34)
Orientation and attention							
Kohler - PVT, no. lapses	3.2	5.1	14	5	5.5	14	-0.33 (-1.08 to 0.42)
Kohler - PVT, response speed, ms	4.1	0.7	14	3.8	0.6	14	0.45 (-0.30 to 1.20)
Kohler - tracking task, score	-15.2	1.5	14	-15.2	1.3	14	0.00 (-0.74 to 0.74)

Table 5. Caffeine+nap versus placebo - all outcome data from neuropsychological tests

	Caffeine+nap			Placebo			
Subgroup/study	**mean**	**sd**	**n**	**mean**	**sd**	**n**	**SMD (95% CIs)**
Orientation and Attention							
Schweitzer a - PVT, no. lapses	3.89	2.6	17	6.42	4.28	16	-0.70 (-1.41 to 0.00)
Schweitzer b - PVT, slowest 10%	-2.41	0.81	39	-2.29	0.75	39	-0.15 (-0.60 to 0.29)
Verbal functioning and language skills							
Schweitzer a - Torrance test of creative thinking (verbal), flexibility	3.85	17.03	17	15.68	13.2	16	-0.75 (-1.46 to -0.04)
Schweitzer a - Torrance test of creative thinking (verbal), fluency	-0.83	13.61	17	8.25	8.8	16	-0.77 (-1.48 to -0.06)

Table 5. Caffeine+nap versus placebo - all outcome data from neuropsychological tests *(Continued)*

Schweitzer a - Torrance test of creative thinking (verbal), originality	4.68	15.87	17	9.08	9.92	16	-0.32 (-1.01 to 0.37)

Table 6. Caffeine+dim light versus placebo+dim light - all outcome data from neuropsychological tests

	Caffeine+dim light			Placebo+dim light			
Subgroup/study	**mean**	**sd**	**n**	**mean**	**sd**	**n**	**SMD (95% CIs)**
Memory							
Babkoff - working memory #3, false alarms	30.58	16.54	11	33.61	19.46	11	-0.41 (-1.25 to 0.44)
Babkoff - working memory #3, hits	-41.92	15.17	11	-34.54	19.49	11	-0.16 (-1.00 to 0.68)
Babkoff - working memory #5, false alarms	35.59	15.18	11	34.88	18.69	11	-0.03 (-0.87 to 0.80)
Babkoff - working memory #5, hits	-19.98	12.75	11	-19.48	15.23	11	0.04 (-0.80 to 0.88)
Orientation and attention							
Babkoff - choice reaction, lift time	493.45	165.82	11	608.02	258.2	11	-0.47 (-1.32 to 0.38)
Babkoff - choice reaction, total time	684.36	185.74	11	807.74	300.81	11	-0.51 (-1.36 to 0.34)
Babkoff - spatial discrimination task #20, lift time	3239.37	1686.87	11	3406.01	1765.73	11	-0.09 (-0.93 to 0.74)
Babkoff - spatial discrimination task #20, total time	3447.95	1696.51	11	3615.13	1779.63	11	-0.09 (-0.93 to 0.74)
Babkoff - spatial discrimination task #50, lift time	3004.54	1534.94	11	3229.85	1668.85	11	-0.14 (-0.97 to 0.70)
Babkoff - spatial discrimination task #50, total time	3213.71	1539.49	11	3440.06	1681.27	11	-0.14 (-0.97 to 0.70)

Table 7. Caffeine+bright light versus placebo+bright light - all outcome data from neuropsychological tests

	Caffeine+bright light			Placebo+bright light			
Subgroup/study	**mean**	**sd**	**n**	**mean**	**sd**	**n**	**SMD (95% CIs)**
Memory							
Babkoff - working memory #3, false alarms	28.89	18.64	11	33.72	15.21	11	-0.23 (-1.07 to 0.61)
Babkoff - working memory #3, hits	-36.83	17.54	11	-32.66	17.29	11	-0.27 (-1.11 to 0.57)
Babkoff - working memory #5, false alarms	33.96	17.77	11	42.79	13.83	11	-0.21 (-1.04 to 0.63)
Babkoff - working memory #5, hits	-20.26	14.99	11	-17.25	13.12	11	-0.53 (-1.39 to 0.32)
Orientation & attention							
Babkoff - choice reaction, lift time	506.83	194.45	11	510.09	147.42	11	0.50 (-0.36 to 1.35)
Babkoff - choice reaction, total time	689.89	207.06	11	595.99	153.72	11	-0.02 (-0.85 to 0.82)
Babkoff - spatial discrimination task #20, lift time	3215.49	1692.27	11	3386.48	1704.72	11	-0.11 (-0.95 to 0.72)
Babkoff - spatial discrimination task #20, total time	3424.03	1698.27	11	3624.44	1719.9	11	-0.10 (-0.93 to 0.74)
Babkoff - spatial discrimination task #50, lift time	2925.15	1493.52	11	3185.04	1630.8	11	-0.19 (-1.03 to 0.65)
Babkoff - spatial discrimination task #50, total time	3119.9	1502.32	11	3428.54	1641.4	11	-0.16 (-1.00 to 0.68)

APPENDICES

Appendix 1. Search strategies

CENTRAL (hits = 907) and DARE (hits = 8) (The Cochrane Library Issue 2, 2008)

#1 MeSH descriptor Jet Lag Syndrome explode all trees
#2 MeSH descriptor Sleep Disorders, Circadian Rhythm explode all trees
#3 MeSH descriptor Work Schedule Tolerance explode all trees
#4 MeSH descriptor Aerospace Medicine explode all trees
#5 (work* near3 schedule*):ab,ti
#6 ((sleep-wake or time-zone) near3 (disorder* or syndrome*)):ab,ti
#7 circadian near2 (dysrythmi* or disrupt* or disturb* or disorder*):ab,ti
#8 jet-lag* or jetlag* or shift-lag* or shiftlag:ab,ti
#9 (shift* near3 work*) or shiftwork* or (night* near3 shift*) or nightshift* or (night* near3 work*) or nightwork* or (rotat* near3 shift*):ab,ti
#10 aviation or airtravel or (air near1 travel):ti,ab
#11 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10)

MEDLINE (Ovid MEDLINE(R) 1950 to July Week 1 2008) hits = 710

1 exp Jet Lag Syndrome/
2 exp Sleep Disorders, Circadian Rhythm/
3 exp Work Schedule Tolerance/
4 exp Aerospace Medicine/
5 (work* adj3 schedule* adj3 tolerance).ab,ti.
6 ((sleep-wake or time-zone) adj3 (disorder* or syndrome*)).ab,ti.
7 (circadian adj2 (dysrhythmi* or disrupt* or disturb* or disorder*)).ab,ti.
8 (jet-lag* or jetlag* or shift-lag* or shiftlag).ab,ti.
9 ((shift* adj3 work*) or shiftwork* or (night* adj3 shift*) or nightshift* or (night* adj3 work*) or nightwork* or (rotat* adj3 shift*)).ab,ti.
10 exp Accidents, Aviation/pc [Prevention & Control]
11 (aviation or airtravel or (air adj1 travel)).ti,ab.
12 or/1-11
13 randomi?ed.ab.
14 randomized controlled trial.pt.
15 controlled clinical trial.pt.
16 placebo.ab.
17 clinical trials as topic.sh.
18 randomly.ab.
19 trial.ti.
20 or/13-19
21 humans.sh.
22 20 and 21
23 12 and 22

EMBASE (OVID EMBASE, EMBASE Classic, 1980 to July Week 27 2008) hits = 632

1 exp jet lag/
2 exp Circadian Rhythm Sleep Disorder/
3 exp work schedule/
4 exp shift worker/
5 exp night work/
6 (work* adj3 schedule* adj3 tolerance*).ab,ti.
7 ((sleep-wake or time-zone) adj3 (disorder* or syndrome*)).ab,ti.
8 (circadian adj2 (dysrythmi* or disrupt* or disturb* or disorder*)).ab,ti.
9 (jet-lag* or jetlag* or shift-lag* or shiftlag).ab,ti.
10 ((shift* adj3 work*) or shiftwork* or (night* adj3 shift*) or nightshift* or (night* adj3 work*) or nightwork* or (rotat* adj3 shift*)).ab,ti.
11 (aviation or airtravel or (air adj1 travel)).ti,ab.
12 or/1-12
13 random*.tw.
14 placebo*.mp.
15 double-blind*.tw.
16 or/13-15
17 12 and 16

PsycINFO (SilverPlatter 1806 to 2008/07 Week 2) hits = 857

#1 explode "Aviation-+" in MJ,MN
#2 explode "Work-Scheduling" in MJ,MN
#3 explode "Workday-Shifts" in MJ,MN
#4 explode "Sleep-Wake-Cycle" in MJ,MN
#5 (((work* near3 schedule*)) in AB)or(((work* near3 schedule*)) in TI)
#6 (((sleep-wake or time-zone) near3 (disorder* or syndrome*)) in AB)or(((sleep-wake or time-zone) near3 (disorder* or syndrome*)) in TI)
#7 ((circadian near2 (dysrythmi* or disrupt* or disturb* or disorder*)) in AB)or((circadian near2 (dysrhythmi* or disrupt* or disturb* or disorder*)) in TI)
#8 ((jet-lag* or jetlag* or shift-lag* or shiftlag) in AB)or((jet-lag* or jetlag* or shift-lag* or shiftlag) in TI)
#9 (((shift* near3 work*) or shiftwork* or (night* near3 shift*) or nightshift* or (night* near3 work*) or nightwork* or (rotat* near3 shift*)) in AB)or(((shift* near3 work*) or shiftwork* or (night* near3 shift*) or nightshift* or (night* near3 work*) or nightwork* or (rotat* near3 shift*)) in TI)
#10 ((aviation or airtravel or (air near1 travel)) in AB)or((aviation or airtravel or (air near1 travel)) in TI)
#11 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10
#12 (randomi* or randomly or random order or random sequence or random allocation or randomly allocated or at random or controlled clinical trial*) in KC
#13 (investigat* or experiment* or crossover* or (cross* near1 over) or evaluat* or effective* or comparative or efficacy or placebo or prospective or followup or (follow* near1 up) or trial*) in TI
#14 (clin* or control* or compar* or evaluat* or prospectiv*) near (trial* or studi* or study)
#15 (((singl* or doubl* or trebl* or tripl*) near3 (blind* or dummy or mask*)) in AB)or(((singl* or doubl* or trebl* or tripl*) near3 (blind* or dummy or mask*)) in TI)
#16 explode "Placebo-" in MJ,MN
#17 explode "Experimental-Design" in MJ,MN
#18 explode "Treatment-Effectiveness-Evaluation" in MJ,MN
#19 #12 or #13 or #14 or #15 or #16 or #17 or #18
#20 #11 and #19
#21 (clin* or control* or compar* or evaluat* or prospectiv*) near3 (trial* or studi* or study)
#22 #12 or #13 or #21 or #15 or #16 or #17 or #18
#23 #11 and #22

CINAHL (1982 to July 2008) hits = 338

S1 (MH “Jet Lag Syndrome”)
S2 (MH “Sleep Disorders, Circadian Rhythm+”)
S3 (MH “Personal Staffing and Scheduling”+)
S4 (MH “Shift Workers”) or (MH “Shiftwork”)
S5 AB (work* N3 schedule*) or TI (work* N3 schedule*)
S6 AB (sleep-wake N3 disorder*) or TI (sleep-wake N3 disorder*)
S7 AB (sleep-wake N3 syndrome*) or TI (sleep-wake N3 syndrome*)
S8 AB (time-zone N3 disorder*) or TI (time-zone N3 disorder*)
S9 AB (time-zone N3 syndrome*) or TI (time-zone N3 syndrome*)
S10 AB (circadian N2 disorder*) or TI (circadian N2 disorder*)
S11 AB (circadian N2 dysrhythmi*) or TI (circadian N2 dysrhythmi*)
S12 AB (circadian N2 disrupt*) or TI (circadian N2 disrupt*)
S13 AB (circadian N2 disturb*) or TI (circadian N2 disturb*)
S14 AB (jet-lag* or jetlag* or shift-lag* or shiftlag*) or TI (jet-lag* or jetlag* or shift-lag* or shiftlag*)
S15 AB ((shift* N3 work*) or shiftwork* or (night* N3 shift*) or nightshift* or (night* N3 work*) or nightwork* or (rotat* N3 shift*)) or TI ((shift* N3 work*) or shiftwork* or (night* N3 shift*) or nightshift* or (night* N3 work*) or nightwork* or (rotat* N3 shift*))
S16 AB (aviation or airtravel or air travel) or TI (aviation or airtravel or air travel)
S17 S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16
S18 (MH “Clinical Trials+”) or (MH “Experimental Studies”+) or (MH “Random Assignment”)
S19 (MH “Double-Blind Studies”) or (MH “Single-Blind Studies”) or(MH “Triple-Blind Studies”)
S20 AB placebo
S21 TI trial
S22 AB random* or TI random*
S23 S18 or S19 or S20 or S21 or S22
S24 S17 and S23

TRANSPORT (SilverPlatter, pre-1988 to 2007/06) hits = 164

#1 jet-lag* or jet lag*

#2 work* near schedule*
#3 sleep* near (disorder* or syndrome*)
#4 time near (disorder* or syndrome*)
#5 circadian*
#6 shift-lag* or shift lag* or shiftlag*
#7 night* near work*
#8 shift* near work*
#9 night* near shift*
#10 rotat* near shift*
#11 aviation
#12 air travel
#13 night* near driv*
#14 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12
#15 randomi* or randomly
#16 controlled near (trial or trials or study or studies or experiment*)
#17 (singl* or doubl* or trebl* or tripl*) and (mask* or blind*)
#18 research design or comparative study or evaluation studies or follow-up studies or prospective studies
#19 #15 or #16 or #17 or #18
#20 #14 and #19

PubMed (searched on 16th July 2008 for records added during the previous 90 days) hits = 18*[*browsed – not added to ProCite database]

#1 "Jet Lag Syndrome"[Mesh] OR "Sleep Disorders, Circadian Rhythm"[Mesh] OR "Work Schedule Tolerance"[Mesh]) OR "Aerospace Medicine"[Mesh]
#2 (work* AND schedul*[tiab]) OR (circadian AND dysrhythmi*[tiab]) OR (circadian AND disrupt*[tiab]) OR (circadian AND disturb*[tiab]) OR (circadian AND disorder*[tiab]) OR (shift-work* OR "shift work*" OR shiftwork*[tiab]) OR (jet-lag* OR "jet lag*" OR jetlag*[tiab]) OR (shift-lag* OR "shift lag*" OR shiftlag*[tiab]) OR (night-work* OR "night* work*" OR nightwork*[tiab]) OR ("night* shift*"[tiab]) OR (aviation OR "air travel"[tiab]))
#3 #1 OR #2
#4 "Randomized Controlled Trial "[Publication Type] OR "Controlled Clinical Trial "[Publication Type] OR random*[tiab] OR placebo[tiab] OR trial[ti]
#5 #3 AND #4 Limits: added to PubMed in the last 90 days

Appendix 2. ProCite search

ProCite searching - 'NOT' words. Records identified by the following terms were deleted from the ProCite database (hits = 366) #04 = title field

(#04 = attention) AND (#04 = deficit*)
(#04 = obstructive) AND (#04 = disease*)
(#04 = chronic*) AND (#04 = fatigu*)
(#04 = heart*) AND (#04 = disease*)
(#04 = vascular*) AND (#04 = disease*)
(#04 = heart*) AND (#04 = failure*)
(#04 = coronary) AND (#04 = disease*)
(#04 = coronary) AND (#04 = syndrome*)
(#04 = cardiovascular) AND (#04 = disease*)
(#04 = sleep) AND (#04 = apnea)
(#04 = sleep) AND (#04 = apnoea)
(#04 = depress*)
(#04 = common) AND (#04 = cold)
(#04 = brain) AND (#04 = injur*)
(#04 = drug*) AND (#04 = user*)
(#04 = restless) AND (#04 = leg*)
(#04 = cystic) AND (#04 = fibrosis)
(#04 = chronic*) AND (#04 = insomnia*)
(#04 = ADHD) or (#04 = obese) or (#04 = obesity) or (#04 = pregnan*) or (#04 = cancer*) or (#04 = tumour*) or (#04 = tumor*) or (#04 = narcolep*) or (#04 = anesthesi*) or (#04 = anaesthesi*) or (#04 = asthma*) or (#04 = antidepress*) or (#04 = Parkinson*) or (#04 = alcohol*) or (#04 = HIV*) or (#04 = stroke*) or (#04 = cesarean*) or (#04 = caesarean*)
(#04 = chemotherapy) or (#04 = aphasia) or (#04 = appetite) or (#04 = migraine*) or (#04 = smoking) or (#04 = infection*) or (#04 = seizure*) or (#04 = rhinitis) or (#04 = headache*) or (#04 = diabet*) or (#04 = urinary) or (#04 = pain) or (#04 = analges*) or (#04 = schizophreni*) or (#04 = infarction*) or (#04 = preterm*) or (#04 = epilep*) or (#04 = melanoma*) or (#04 = dementia) or (#04 = tetrapleg*) or (#04 = thrombo*)

or (#04 rats) or (#04 = bruxism) or (#04 = eczema) or (#04 = fetal*) or (#04 = osteo*) or (#04 = arthriti*) or (#04 = fibromyalgia) or (#04 = sclerosis) or (#04 = Alzheimer*) or (#04 = COPD) or (#04 = ulcer*) or (#04 = dystrophy) or (#04 = autis*) or (#04 = anaemi*) or (#04 = anemi*) or (#04 = ischaemi*) or (#04 = ischemi*) or (#04 = carcinoma*) or (#04 = tourette*) or (#04 = psycia*) or (#04 = dependen*) or (#04 = tobacco) or (#04 = athlet*)

CONTRIBUTIONS OF AUTHORS

KK undertook all aspects of the review process including data collection, data analysis and writing the review.

PJE advised on all aspects of the review process with particular input into the data analysis.

LF helped screen the records, contact authors and checked KK's data extraction.

IR advised on all aspects of the review process.

KB helped to devise the search strategy and locate papers.

PJE, LF, IR and KB all commented on the draft review.

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None known

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The protocol for this review was published as 'Interventions for preventing injuries caused by impaired alertness in individuals with jet lag and shift work disorder' (Ker 2009). Due to the large number of studies identified in this area, we opted to divide the review by intervention type. This systematic review of caffeine constitutes one review within this wider topic area. Further reviews of the effects of the other interventions types are in progress and will be published in due course.

INDEX TERMS

Medical Subject Headings (MeSH)

Accidents, Occupational [*prevention & control]; Caffeine [*therapeutic use]; Central Nervous System Stimulants [*therapeutic use]; Cognition Disorders [*prevention & control]; Neuropsychological Tests; Psychomotor Performance [drug effects] [physiology]; Randomized Controlled Trials as Topic; Sleep Disorders, Circadian Rhythm [drug therapy]; Work Schedule Tolerance [*physiology]

MeSH check words

Humans