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From animal cage to aircraft cabin: An overview of evidence translation in jet lag research --Manuscript Draft--

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| Abstract: | <p>Recent laboratory experiments on rodents have increased our understanding of circadian rhythm mechanisms. Typically, circadian biologists attempt to translate their laboratory-based findings to treatment of jet lag symptoms in humans. We aimed to scrutinise the strength of the various links in the translational pathway from animal model to human traveller. First, we argue that the translation of findings from pre-clinical studies to effective jet lag treatments and knowledge regarding longer-term population health is not robust, e.g., the association between circadian disruption and cancer found in animal models does not translate well to cabin crew and pilots, who have a lower risk of most cancers. Jet lag symptoms are heterogeneous. Therefore, the true prevalence and the effects of any intervention are difficult to quantify precisely. The mechanistic chain between in vitro and in vivo treatment effects has weak links, especially between circadian rhythm disruption in animals and the improvement of jet lag symptoms in humans. While the number of animal studies has increased exponentially between 1990 and present, only 1-2 randomised controlled trials on jet lag treatments are published every year. There is one relevant Cochrane review, in which only 2-4 studies on melatonin, without baseline measures, were meta-analysed. Study effect sizes reduced substantially between 1987, when the first paper on melatonin was published, and 2001. We suggest that knowledge derived from a greater number of human randomised controlled trials would provide a firmer platform for circadian biologists to cite jet lag treatment as an important application of their findings.</p> |
| Response to Reviewers: | Please see attachment |

Response to Reviewers

Editors comments

One reviewer has noted some points that I did not pick up when I looked through your submission: coloured Figures. Do you intend to use colour? I do not get access to this information. If you do not plan to have colour, then they will need to be modified for B/W clarity.

Many thanks. We intend to use colour for the online version as these Figures are free of charge. We have checked all figures for clarity in B/W and only Figure 2 needed to be amended – We think this was a good thing for generally improving the labelling of the various lines in the Figure anyway, so many thanks.

In addition, I agree that Figure 3 should be presented as Table.

Figure 3 is now a table (Table 1).

Reviewers' comments:

(1) Figures:

Coloured Figures: It is the responsibility of the authors to cover the costs of coloured Figures. Is this acceptable to you? If not, then the Figures need to be modified for black and white publication.

See above

Figure 1: I will not argue the point, but Figure 1 adds no further information, and is therefore redundant. It would seem to be in the best interests of the authors to avoid redundancies in their work. There is still an undefined abbreviation within that Figure.

As mentioned, Figure 1 is adapted from one presented only recently by Doug Seals. His publication was the first to show these translational steps to a mainstream physiological audience. We think our Figure not only presents these steps to jet lag researchers, but is also useful for all physiologists. We think the Figure guides the reader through the salient issues in our paper, especially the weak link between animal circadian disruption and jet lag symptoms in humans.

Figure 2: It will be impossible to differentiate among these curve in black and white print.

Please see above.

Figure 3: This is a Table and not a Figure. Accordingly, it needs to be presented as a Table.

Figure 3 is now a Table (Table 1). Thanks

Figure 4: The "effect size" has not been included on the Figure. Of course knowledgeable readers will know this, but that approach is not acceptable. Figure and Tables must stand alone.

Figure 4 (now Figure 3) has an improved legend for clarity. Thanks.

(2) This reviewer is aware of the often over-stated significance of randomised controlled studies. However, there is significant inappropriate use of these design, as there is with blinding. Accordingly, the default position cannot be that such designs are always superior, as this is simply not the case. The authors' response is troubling, for it is consistent with inflexibility and bias that can arise within the less experienced. There is no need to respond to this comment, but please consider the point that is being made.

We thank the reviewer sincerely for emphasising this issue, which we think is important enough to add some information in a new Table (Table 2). We now go through each proposed criticism of randomised controlled trials in the context of jet lag treatment and we conclude that every one of these criticisms is not upheld in jet lag research. There are no ethical reasons to withhold a jet lag treatment from the control participants for example. We have also emphasised the fact that a poorly designed and executed RCT is inferior to a well- designed observational study. We thank the reviewer for helping us to include this, because a previous version of our paper was submitted to Chronobiology International. The editor returned the manuscript with the message that randomised controlled trials are too difficult to implement in jet lag research.

From animal cage to aircraft cabin: An overview of evidence translation in jet lag research

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Summary

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4 circadian rhythm mechanisms. Typically, circadian biologists attempt to translate
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6 their laboratory-based findings to treatment of jet lag symptoms in humans. We
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8 aimed to scrutinise the strength of the various links in the translational pathway from
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10 animal model to human traveller. First, we argue that the translation of findings from
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12 pre-clinical studies to effective jet lag treatments and knowledge regarding longer-
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14 term population health is not robust, e.g., the association between circadian
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16 disruption and cancer found in animal models does not translate well to cabin crew
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18 and pilots, who have a lower risk of most cancers. Jet lag symptoms are
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20 heterogeneous. Therefore, the true prevalence and the effects of any intervention
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22 are difficult to quantify precisely. The mechanistic chain between *in vitro* and *in vivo*
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24 treatment effects has weak links, especially between circadian rhythm disruption in
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26 animals and the improvement of jet lag symptoms in humans. While the number of
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38 suggest that knowledge derived from a greater number of human randomised
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40 controlled trials would provide a firmer platform for circadian biologists to cite jet lag
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42 treatment as an important application of their findings.
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56 **Key words:** Evidence translation; External validity; Mechanistic research;

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Introduction

Recent laboratory-based experiments have furthered our understanding of circadian biology. For example, in a recent study entitled “*Vasopressin V1a and V1b receptors are resistant to jet lag*”, it was reported that pharmacological blockade of vasopressin receptors in the suprachiasmatic nuclei of wild-type mice accelerates the adjustment of circadian timing following shifts of the light dark cycle (Yamaguchi et al. 2013).

Therefore, [Yamaguchi et al. \(2013\)](#) postulated that vasopressin signalling could be a target for treating jet lag. In an [accompanying](#) commentary, it was stated that “*Jet lag is a blessing to circadian biologists because the disruption of mental and physical well-being immediately highlights the importance of our internal body clock*” (Hastings 2013). Nevertheless, it was also noted by Hastings (2013) that, at present, there is no cure for jet lag.

Basic mechanistic experiments like the one undertaken by Yamaguchi et al. (2013) constitute the first step in the physiological translational pathway (Seals 2013). This pathway can be made specific to jet lag research (Figure 1). The first translational step moves from the results of animal experiments on basic circadian biology to human circadian physiology. There are two other translational steps. Findings from experiments on human circadian physiology need to translate adequately to clinical practice, which, in the present context, includes jet lag treatments for populations that are viewed to benefit from clinical intervention, e.g., airline pilots. These findings then need to translate to longer-term population health, e.g., whether transmeridian flights are associated with an increased risk of cancer. The pathway is a bidirectional closed loop where information can translate through translational steps one to three, or from steps three to one. This latter type of translational research where population

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level studies might inform how basic research is undertaken has been termed, “reverse translation” (Seals 2013).

Typically, circadian biologists, who examine the adjustment of animal circadian rhythms in response to changes in laboratory conditions, suggest that their findings will translate to proposed treatments for jet lag and/or shift work disorder, i.e. from translation steps one to two/three. Because millions of people fly across time zones every year, new studies that are relevant to jet lag can generate considerable interest. Sometimes, the translation of pre-clinical findings from laboratory-based experiments on rodents can be somewhat overhyped in the media, e.g., <http://www.bbc.co.uk/news/health-23880152>. Furthermore, recent developments in technology have meant that people can now easily access advice about jet lag. For example, predominantly theoretical models of the human circadian pacemaker (Forger et al. 1999) have been translated by mathematicians to a Smartphone-based App called *Entrain*. This software is designed to improve jet lag symptoms by supplying advice regarding timing of light exposure on each day after the flight, <http://entrain.math.lsa.umich.edu/>.

It is clear that jet lag is of interest to both basic circadian biologists and applied researchers who want to use mechanistic information to develop effective treatments for jet lag. In the present review, we discuss several fundamental questions that arise in this causal pathway between animal and human traveller. These questions are informed by the checklist for using mechanistic research to justify extrapolation of study results to target human populations (Howick et al. 2013);

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1. What is jet lag and how is it measured?

2. In which population is jet lag clinically important enough to treat, and does this population differ from those studied by researchers?

3. What is the evidence that the proposed treatments are effective in reducing jet lag symptoms following transmeridian travel?

3-4. _____ Does the evidence from animal experiments on circadian rhythm disruption translate to population health research?

1. What is jet lag and how is it measured?

The conceptualisation and, consequently, the published definitions of jet lag can vary in terms of the relative focus on jet lag symptoms and/or the misalignment of circadian rhythms. For example, Samuels (2012) defined jet lag as “*a syndrome of symptoms manifested by physiologic adaptations that occur when the body is shifted into a new time zone*”. Nevertheless, it is clear from some of the study titles in the literature that measurement of the adjustment of circadian rhythms of animals *per se* is also referred to as jet lag. For example, Yamaguchi et al. (2013) modelled jet lag on the basis of a nocturnal animal delaying their initiation of activity in response to a change in the timing of lights-off. This interchangeable use of the term jet lag is not particularly helpful, since it relies on the assumption of a robust correlation between measured changes in circadian rhythm timing in either animals or humans and overt jet lag symptoms, which cannot be measured directly in animal models.

1 The strength of the correlation between changes in circadian timing and jet lag
2 symptoms is rather unclear at present. Sack (2010) suggested that the circadian
3 timing of the melatonin rhythm adjusts approximately 1 hour per day following an
4 eastwards flight. Nevertheless, people travelling over 1-3 time zones tend to
5 experience negligible symptoms of jet lag (Waterhouse et al. 2007), suggesting non-
6 linearity in the correlation between rhythm adjustment and symptoms. Moreover, this
7 estimate of daily circadian adjustment would mean that it takes approximately 10
8 days for circadian rhythms to adjust completely following an easterly flight across 10
9 time zones, e.g., from the UK to eastern Australia. In contrast, data from Edwards et
10 al (2000) indicated that the various symptoms of jet lag are negligible (<0.5 on a 0-10
11 simple analogue scale) six days after such a flight.

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29 Jet lag symptoms are clearly caused by circadian rhythm disruption following a flight
30 across time zones. But the study of the causal pathway between circadian rhythm
31 disruption and jet lag symptoms is confounded by a myriad of other human and
32 environmental factors, which impinge on post-flight feelings. Although these overt
33 feelings are influenced by circadian rhythm disruption, there is no strong evidence to
34 indicate that the rate of circadian rhythm adjustment *per se* can be used as a reliable
35 proxy for jet lag symptoms in humans. This is notwithstanding the fact that jet lag
36 symptoms are the fundamental outcomes to be treated and may be easier to
37 measure and monitor than some circadian rhythms (e.g. salivary melatonin) during a
38 post-flight period.

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56 As highlighted in previous reviews (Waterhouse et al. 1997; Waterhouse et al. 2007;
57 Sack 2010), the measurement of jet lag symptoms is extremely complicated. Not

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surprisingly, there is marked variation in the types and severity of jet lag symptoms both between- and within-individuals over the course of the post-flight period (Waterhouse et al. 1997; Waterhouse et al. 2007; Sack 2010). For global jet lag ratings on a 0-100 scale, the between-subjects standard deviation often exceeds 90% of the sample mean (Herxheimer and Petrie, 2002). This between-subjects coefficient of variation reflects an extraordinarily large inter-individual heterogeneity in overall jet lag perception. Heterogeneity is also apparent in the types of symptoms experienced. These symptoms of sleepiness, insomnia, clumsiness, headache, gastro-intestinal disturbances are not specific to jet lag and can vary in their degree of association with the overall construct of jet lag (Waterhouse et al. 2002).

Despite the availability of measurement tools which focus on multiple symptoms (Waterhouse et al. 2002; Spitzer et al. 1999), there is currently no uniform approach to the measurement of jet lag symptoms. Researchers tend to select different primary outcomes for indicating jet lag severity. Herzheimer and Petrie (2002) were able to meta-analyse only 2-4 of the 10 studies on melatonin that met the inclusion criteria for a systematic review. This was after the data from two of these studies (Claustrat et al. 1992; Nicholson et al. 1991) needed to be converted to the selected common outcome of the overall perception of jet lag on a 0-100 scale. The systematic review by Herxheimer and Petrie (2002) is discussed in more detail in section 3.

2. Is jet lag clinically important for everyone?

The extent to which any jet lag symptoms are considered to be debilitating differs greatly between individuals, ranging from the mild inconvenience experienced by

1 tourists, to the potential compromising effects of frequent flying across time zones on
2 vigilance and functioning outcomes in military and non-military flight crews. This
3 latter population has to cope with both advance/delay and delay/advance events,
4 usually with only 1-2 days at destination, which is all very difficult to simulate in the
5 laboratory. A popular protocol for modelling jet lag symptoms in animal experiments
6 is an 8-h advance of the light-dark cycle every two days over a 10-day period
7 (Filipski et al., 2004). When translated to human pilots and cabin crew, this protocol
8 would equate to the undertaking of five westerly flights, each being approximately 9-
9 13 hours in duration, and all being undertaken within a 10 day period. This degree of
10 circadian disruption would be extremely unusual for non-military pilots and crew.
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27 Another target population for jet lag treatments is athletes (Reilly et al., 2001), but
28 the clinical relevance of jet lag can depend on the athlete's competitive standard.
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31 Although world-class athletes clearly report symptoms of jet lag following
32 transmeridian travel (Edwards et al. 2000), the re may be sufficient finances for the
33 athlete to travel well in advance of any competition or tournament so that jet lag
34 symptoms subside prior to competition. It is not known whether jet lag interferes with
35 training during this post-flight period to the extent that subsequent competitive
36 performances are impaired. It is also not known at present whether jet lag increases
37 the risk of injury in athletes preparing for competition.
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51 It is plausible that jet lag could affect the performances of world-class athletes who
52 compete soon after travelling from another important competition, as part of an
53 international tour. There is evidence from simulation studies and field studies that jet
54 lag detrimentally affects subjective and simple performance measures, e.g. grip
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1 strength, (Reilly et al. 2001). Nevertheless, the authors of a recent review on the
2 effects of airline travel on sports performance were unable to locate a single study
3 from which quantitative data could be extracted for externally-valid performance
4 outcomes (Leatherwood and Dragoo, 2013). Therefore, despite the number of good
5 quality laboratory simulation studies in which performance-relevant outcomes are
6 measured in a repeated measures fashion (Leatherwood and Dragoo, 2013), the
7 translation of evidence through steps one/two (Figure 1) is not particularly robust for
8 world class athletes.
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12 For the occasional traveller, a clinical knowledge summary on jet lag has been
13 published by the UK National Institute for Health and Care Medicine (NICE 2009). In
14 this summary, the prevalence of clinically important jet lag symptoms is stated to be
15 “*unknown*”. Therefore, while more knowledge is being derived about the
16 mechanisms of circadian timing and these findings are attempted to be translated to
17 jet lag treatments, the prevalence, symptomology and minimal clinically importance
18 difference of jet lag symptoms seem unclear at present.
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22 **3. Are the treatments suggested by animal and human simulations effective in** 23 **reducing jet lag symptoms?** 24

25 In this section, published systematic reviews and evidence summaries on each
26 proposed jet lag treatment will be summarised. However, before the evidence for the
27 effectiveness of each treatment is discussed, there are some salient issues to
28 consider regarding the translational value of animal models as well as which part of
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1 the translational pathway (animal experiments, human experiments, real-world trials)
2 tends to be emphasised in jet lag treatment research.
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7 **3.1. Animal models and evidence translation in science**

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9 It appears that the general translation of evidence from mechanistic animal
10 experiments to the implementation of useful medical treatments is low. It has been
11 reported that only about a third of highly-cited animal research is tested later in
12 human trials. Only 8% of these clinical trials have been reported to successfully pass
13 Phase I, which is when an intervention is examined for its safe use in human healthy
14 volunteers (Mak et al 2014). Van der Worp et al. (2010) produced recommendations
15 for the reporting of study quality when treatment strategies are being compared in
16 animal models of disease ([Table 1](#)). These guidelines included the presence of
17 sample size estimations, animal eligibility criteria, animal allocation concealment
18 from main researchers, blinding and [transparency regarding](#) the flow of animals
19 throughout the study, e.g., whether some animals had been excluded from the
20 eventual data analysis. To date, the quality of animal experiments relevant to
21 potential jet lag treatments has not been scrutinised against such standards.
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44 It is important to note that there are examples of health interventions arising from
45 serendipitous discoveries through the course of basic research, e.g. Penicillin,
46 although how reliant some chance discoveries have been on any preceding animal
47 model research is often not clear (van der Worp et al., 2010). While such future
48 discoveries are possible in the field of circadian biology, it is clear that many
49 circadian biologists, who undertake laboratory-based experiments on animals,
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currently cite the treatment of jet lag as an application of their findings. Therefore, this proposed application is open to scrutiny.

3.2. Which translational step is emphasised in jet lag research?

Once a proposed clinical treatment has successfully passed phases I-II, including studies on animals, the treatment should, be appraised for effectiveness, ideally using the gold-standard randomised controlled trial approach (Torgerson and Torgerson, 2008). A good quality randomised controlled trial that has robust components of participant allocation (both randomised and concealed), placebo control if the treatment is a drug, and reports the findings in accordance with the Consolidated Standards of Reporting Trials, is the ideal [approach to quantifying effect sizes](#) (Shulz et al. 2010).

Other study designs, such as observational comparisons or non-comparator trials might provide useful information regarding jet lag. But it is difficult to accept any philosophical or practical drawbacks to undertaking a randomised controlled trial in the context of jet lag treatment. In Table 2, a list of perceived drawbacks of adopting a randomised controlled trial approach is presented alongside the appraisal of how relevant each perceived drawback is in the context of jet lag research. It is also relevant to question how many externally-valid and robust human randomised controlled trials on jet lag treatments have been undertaken and published compared with the number of laboratory-based simulations on animals and humans.

In the Scopus database (1960-2014), a search for the term *jet lag*, and its variants, was completed in August 2014, and this resulted in a total of 1368 research outputs

1 (Figure 2). Three hundred and seventy-five of these outputs were labelled in Scopus
2 as reviews. Seven hundred and twenty-two outputs were labelled as original articles
3 or book chapters. One hundred and eighty of these articles involved an animal
4 model. Importantly, only 1-2 publications per year appeared to be randomised
5 controlled trials of jet lag treatments following real flights. Not all these studies might
6 be robust randomised controlled trials. A formal systematic review of these studies
7 (currently underway by the present authors) would also rate each of these trials for
8 quality and adherence to the Consolidated Standards of Reporting Trials (Schulz et
9 al. 2010), so the number of good quality trials could be extremely low. It is clear that
10 the number of randomised controlled trials of treatment effectiveness is not mirroring
11 the number of animal and human simulation studies on the efficacy of jet lag
12 treatments (Figure 2). However, evidence syntheses of some of these trials have
13 been undertaken, and these syntheses can now be discussed below categorised by
14 each type of proposed treatment.
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33 34 35 36 37 **3.3. Evidence that melatonin is a useful jet lag treatment**

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39 In the sole Cochrane review dedicated to a potential treatment (melatonin) for jet lag
40 following actual air travel, ten studies met the inclusion criteria of randomised trials
41 with placebo or other medication and a primary outcome of subjective jet lag rating
42 (Herxheimer and Petrie 2002). Eight of these studies were deemed by Herxheimer
43 and Petrie (2002) to report positive effects of ingesting melatonin pills. Nevertheless,
44 it can be seen in the subsequent meta-analysis undertaken by Herxheimer and
45 Petrie (2002) that at least two of these eight studies did not report statistically
46 significant effect sizes (see also Figure 4). For the 2-4 studies from which a common
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1 outcome of overall jet lag rating (on a 0-100 scale) could be extracted by Herxheimer
2 and Petrie (2002), melatonin mediated a pooled reduction of 19.5 (95%CI: 10.9-
3 28.1) and 17.3 (95%CI: 7.3-27.3) units for eastwards and westwards flights,
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5 respectively. These effect sizes are large when considered against the between-
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7 subjects standard deviations reported by Herxheimer and Petrie (2002).
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11 Nevertheless, there are some important caveats to these data.
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16 First, it is relevant to question why two relatively large studies, which did not report
17 any useful effects of melatonin on jet lag symptoms, were excluded by Herxheimer
18 and Petrie (2002). In the first of these studies (Spitzer et al. 1999), the baseline
19 measurements prior to an eastwards flight home across 6 time zones were obtained
20 five days after the outward flight. This study was eventually excluded from the meta-
21 analyses even though it was one of the few studies to measure symptoms at
22 baseline and adjust for them in the analyses. It is interesting that melatonin was
23 reported by Spitzer et al. (1999) to have had negligible effects on the jet lag
24 symptoms incurred by this short-stay (5 d at destination) travel schedule, which is
25 typically followed by business travellers and tourists. Airline pilots may have even
26 less than five days recovery between long-haul trans-meridian flights. The
27 measurement tool employed by Spitzer et al. (1999) allowed many different types of
28 subjective jet lag symptoms like tiredness and clumsiness to be recorded.
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32 Undoubtedly, if such subjective feelings are collected from any person, whether they
33 have undertaken a flight or not, the summed values of these symptoms would not be
34 zero. Unfortunately, only follow-up measures could be meta-analysed in the
35 systematic review by Herxheimer and Petrie (2002) rather than the change in
36 symptoms between follow-up and a pre-flight baseline measure.
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3 Edwards et al. (2000) also recorded multiple symptoms of jet lag in their randomised
4 controlled trial on melatonin. The questions were phrased in order to measure
5 symptoms relative to how people might feel normally prior to the flight. Data were
6 analysed in several ways, including approaches similar to those adopted by the other
7 study authors whose study was included in the meta-analysis. Herxheimer and
8 Petrie (2002) cited reporting problems for non-inclusion of this study. Nevertheless,
9 Edwards et al. (2000) did attempt to analyse their data in accordance with previous
10 studies which involved a global measure of jet lag. First, average ratings of jet lag
11 were calculated over six post-flight days. No statistically significant differences
12 between melatonin and placebo groups were found ($P=0.741$). Second, when the
13 participant's ratings of jet-lag recorded on day 6 solely were compared, no
14 statistically significant group differences in jet lag ratings were found ($P=0.833$).
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36 In 2008, the systematic review on melatonin and jet lag by Herxheimer and Petrie
37 (2002) was checked for any further studies using a database search, but none were
38 located. Three studies have been published since 2001 In a recent clinical evidence
39 review, Herxheimer (2014) concluded that melatonin reduces subjective ratings of jet
40 lag on eastward and on westward flights compared with placebo. It was noted by
41 Herxheimer (2014) that (i) the adverse effects of melatonin (drug eruption, allergic
42 reaction) are uncertain and that epileptics and/or people taking an oral anticoagulant
43 should not use melatonin without medical supervision, and (ii) that the quality control
44 of melatonin products, particularly those purchased online, is suspect.
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3 Using the statistical information reported in Spitzer et al. (1999) and Edwards et al.
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5 (2000), standardised effect sizes can be calculated for overall jet lag symptoms.
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7 These standardised effect sizes can also be calculated for the four studies meta-
8
9 analysed by Herxheimer and Petrie (2002) so that all six studies on eastwards flights
10
11 can be considered together (Figure 3). It can be seen that reported effect sizes for
12
13 melatonin have decreased since the first study was published in 1987. This particular
14
15 study (Arendt et al. 1987) resulted in a remarkably large effect size of 1.5 standard
16
17 deviations, which influences greatly the magnitude of the overall pooled effect size.
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19 The effect sizes for four of these six studies are not statistically significant.
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21 Therefore, this fresh analysis of the studies on melatonin questions its usefulness for
22
23 reducing jet lag symptoms. It is clear that the effects reported in early studies from
24
25 the same research group have not been replicated in subsequent studies.
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36 **3.4. Evidence for other proposed treatments**

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38 Light exposure schedules have been formulated from the results of laboratory-based
39
40 studies (Waterhouse et al. 1997; Waterhouse et al. 2007; Sack 2010). Nevertheless,
41
42 the first pilot randomised controlled trial of supplementary light treatment for
43
44 alleviating real jet lag symptoms was published only last year (Thompson et al.
45
46 2013). Prior to this study, only non-randomised and/or non-controlled investigations
47
48 were available (Boulos et al. 2002; Lahti et al. 2007). Thompson et al. (2013) could
49
50 not detect any clinically relevant effects of the supplementary light treatment on jet
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52 lag symptoms in a sample of elite female soccer players who flew, easterly, from
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54 North America to Portugal. The soccer players undertook their normal training habits
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1 in the post-flight period prior to competing in an international tournament. The
2 intervention participants sat approximately 50 cm from 2500 lux of supplementary
3 bright light in their bedrooms for 45-60 min at a time-of-day predicted to accelerate
4 circadian adjustment. Jet lag ratings were higher, not lower, in the supplementary
5 light group on the first two post-flight days, but overall there were no clinically-
6 relevant differences between groups in all jet lag symptoms. In agreement with the
7 data presented by Herxheimer and Petrie (2002), the inter-individual differences in
8 the perception of jet lag symptoms were large with the between-subjects SD for
9 overall jet lag rating being > 60% of the sample mean values (on a 1-10 scale).
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24 Herxheimer (2014) could not locate any externally-valid randomised controlled trials
25 on lifestyle/environmental interventions such as exercise, diet, avoiding alcohol,
26 caffeine and sleep schedules. There is evidence from animal and human simulation
27 experiments that these treatments may be useful in accelerating adjustment of
28 circadian rhythms (Atkinson et al., 2007), but randomised controlled trials of these
29 interventions following transmeridian travel appear, again, rare. Van Dongen et al.
30 (2014) recently completed the first randomised controlled trial of a complex
31 intervention based on chronobiological theory and evidence from simulation studies.
32 The intervention was designed to improve longer-term outcomes of fatigue and sleep
33 quality in aircraft personnel undertaking frequent flying. Five hundred and two airline
34 pilots were randomised to either an intervention or comparator group. Intervention
35 participants could access a mobile device application, which provided tailored advice
36 on various circadian zeitgebers (light, activity, meal times, etc). The control group
37 was directed to a website with standard information about fatigue. Outcomes were
38 measured through online questionnaires at baseline and at three and six months
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1 after baseline. At the six month follow-up time-point, the intervention reduced self-
2 reported fatigue compared to the comparator group and improved some aspects of
3 health-related behaviour such as physical activity, snacking behaviour as well as
4 sleep quality, but not other measures of sleep (latency, duration, use of sleep-related
5 medication). It would be interesting to examine similar interventions applied to
6
7 reducing the shorter-term jet lag symptoms in the post-flight period following a one-
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9 off flight. A freely available mobile device application together with online reporting of
10 symptoms could be relatively easy to research.
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22 A recent clinical evidence statement included an appraisal of hypnotics
23 (benzodiazepines; zopiclone; zolpidem; zaleplon) for reducing jet lag symptoms
24 (Herxheimer, 2014). It was concluded that zopiclone or zolpidem, taken before
25 bedtime on the first few nights after flying, may reduce the effects of jet lag by
26 improving sleep quality and duration, although a formal meta-analysis of effect sizes
27 was not undertaken. Herxheimer (2014) noted that hypnotics are associated with
28 adverse effects including headache, dizziness, nausea, confusion, and amnesia.
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43 **4. Does evidence from jet lag studies translate to population health?**

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46 The effects of jet lag on longer-term health outcomes have also been studied in
47 animal experiments. There are again difficulties in translating evidence from these
48 studies to human health, i.e. through translational steps 1-3 (Figure 1). For example,
49 a higher risk of cancer has been inferred from the results of experiments in which the
50 light dark cycle in animal cages is advanced or delayed (e.g. Filipowski et al. 2004). The
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1 most recent and largest epidemiological study on humans has just been published
2 (Hammer et al. 2014). Mortality was analysed in a pooled cohort of 93,771 aircraft
3 cabin and cockpit crew members from 10 countries, with a mean follow-up period of
4 21.7 years (20 million person-years). Overall mortality and cardiovascular-related
5 mortality was substantially lower in both men and women, with standardised
6 mortality rates of 0.46 to 0.73 being reported. Mortality from radiation-related cancers
7 was also lower in men (standardised mortality rate: 0.73), but not different from the
8 general population in women. Breast cancer mortality was unaffected in women, as
9 was leukaemia and brain cancer in both men and women. Besides the obvious
10 increased risk of death in an aircraft accident (which are obviously extremely rare
11 events), the only substantial increase in risk in non-communicable disease was for
12 malignant melanoma in men (standardised mortality rate: 1.57). The risk of AIDS of
13 highly elevated in male cabin crew (standardised mortality rate of 14).

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36 There is a plausible mechanistic pathway between circadian disruption of the
37 melatonin rhythm and cancer development (Leonardi et al., 2012). Nevertheless,
38 there are alternative explanations for an increased risk of skin cancer in cabin and
39 cockpit crew. Hammer et al. (2014) thought that aircraft windows provide adequate
40 shielding of ultra-violet radiation exposure during the flight itself, and postulated that
41 non-occupational factors, such as the opportunity for sunbathing, are more
42 important. Hammer et al. (2014) cited the study by Dos Santos et al. (2013) who
43 compared skin melanoma rates between British flight crew and air traffic controllers.
44 The risks were similar between these samples, the strongest predictors of melanoma
45 being light skin and sunbathing in both groups. Although these two occupational
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1 group are not substantially different in social status and employment-related health
2 requirements, Hammer et al. (2014) thought these factors could still play a role in
3 explaining their own findings of decreased mortality from most causes in cabin and
4 cockpit crew.
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10 11 12 13 14 15 **5. Conclusions**

16
17 Despite the wealth of laboratory simulations of jet lag, and a penchant for some
18 circadian biologists to mention jet lag treatment as a potential application of their
19 findings, there is still a lack of well-controlled randomised controlled trials on jet lag
20 treatments involving human participants travelling rapidly across world time zones.
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27 This lack of randomised controlled trials clouds the causal pathway between the
28 intervention effects in animal and human simulations studies, and the intervention
29 effects on real-world outcomes. In Figure 4, we present a simple model of this causal
30 pathway in order to apply the probabilistic nature of reasoning to jet lag research
31 (Howick et al. 2010). Each of the four basic components in the causal pathway are
32 linked in a probabilistic chain. The intervention effects in one component depend on
33 the correlation (r) with the intervention effects upstream in the mechanistic chain.
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44 The various correlations in the causal pathway can dilute the overall correlation
45 between intervention effects in animal simulations and intervention effects on
46 outcomes relevant to humans. For example, if each of the four correlations in Figure
47 4 was a large $r=0.7$, the overall correlation between intervention effects in
48 simulations and effects in real-world outcomes could be as low as $0.7^4 = 0.24$.
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In view of the above evidence that has been presented, and in conclusion, there is clearly not only a lack of good quality randomised controlled trials on jet lag treatments, but also a lack of reliable knowledge regarding the nature and clinical importance of jet lag in human travellers. As highlighted in section 3, more studies in the future could examine the post-flight effectiveness of all the potential chronobiological treatments identified from basic research, e.g., supplementary light, melatonin, etc., amalgamated into a complex intervention delivered through mobile devices. Importantly, there may be an aggregation of marginal gains from these treatments and interactions between treatments may be able to be explored (Durrand et al. 2014). Although challenging, such studies are needed to translate information adequately from the chronobiological bench to the real world. This would also help circadian biologists justify the clinical importance of their hard work and informative studies.

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Table 1. A list of reporting requirements for appropriate quality of animal studies on health-related interventions. (van der Worp et al., 2010).

| Quality Aspect | Explanation |
|-------------------------------------|--|
| Sample size calculation: | How the sample size was determined, and which assumptions were made <u>regarding minimal important effect size and selected variance statistic.</u> |
| Eligibility criteria: | Inclusion and exclusion criteria for <u>eligibility</u> |
| Treatment allocation: | The method by which animals were allocated to experimental groups. If this allocation was by randomisation, the method of randomisation <u>and who undertook it.</u> |
| Allocation concealment | The method <u>used</u> to implement the allocation sequence, and if this sequence was concealed until <u>actual</u> assignment. |
| Blinding: | <u>Which</u> investigators <u>were</u> blinded to the treatment allocation, and at which points in time during the study. |
| Flow of animals: | Flow of animals through each stage of the study, with <u>particular reference to any animals excluded from the data analyses, with reasons.</u> |
| Control of physiological variables: | <u>Full details on which</u> physiological <u>variables</u> were monitored and controlled. |
| Control of study conduct: | Whether a third party <u>oversaw</u> the conduct of the study. |
| Statistical methods: | Which statistical methods were used for which analysis |

Table 2. Six typical arguments against the adoption of a randomised controlled trial approach for quantifying the effects of an intervention (Rosen et al. 2006).

Each argument is considered in the context of research on treatments for jet lag following transmeridian travel.

| Critical argument | Relevance to jet lag research | Comments |
|--|--------------------------------------|--|
| Withholding a treatment from the control group | Not upheld | The ethical concerns about some participants not receiving the jet lag treatment are low, given the low seriousness of jet lag symptoms compared with life-threatening illnesses such as cancer. |
| Jet lag is too complex an issue | Not upheld | Randomised controlled trials can be undertaken on both complex interventions and complex outcomes (Rosen et al. 2006). These factors do not preclude the undertaking of a randomised controlled trial for jet lag treatment. |
| Randomised controlled trials are relevant only in the short-term | Not upheld | Jet lag is by its very nature transient and can be studied during the short post-flight follow-up period. Randomised controlled trials have also been undertaken on multiple periods of jet lag over several months (van Drongelen et al. 2014). |
| Randomised controlled trials reduce study generalizability | Not upheld | A study on jet lag following transmeridian travel is naturally real-world research outside the laboratory. Participants can, in theory, be drawn from any population who travel across time zones. |
| Randomised controlled trials have no relevance to community health | Not upheld | Jet lag is not a community health issue, but can be experienced by any traveller who lives in any geographical community in the world. |
| Randomised controlled trials are too | Not upheld | The costs of incorporating robust randomisation, blinding and allocation concealment are minimal. The main costs of a jet lag study are due to the travel itself, but it is possible for approaches like internet- |

expensive

based research to keep costs down while optimising sample size and helping participants report their symptoms remotely. Studies in the past have also involved participants who travelled to an event or meeting. It might be expensive to measure circadian rhythms, such as those in melatonin and body temperature, during a trial, but refer to section 1 of this review where the potential disparity between these rhythms and overt jet lag symptoms is highlighted.

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List of Figures

Figure 1. The basic steps in translational physiology with respect to treatments for jet lag and the impact of jet lag on population health. Drawn from information presented by Seals (2013) and made specific to jet lag research. The translational pathway has three main steps. Findings from animal laboratory-based experiments first need to be reliably translated to inform human laboratory-based experiments (T1 in the Figure). Then findings from human experiments need to be reliably translated to good quality randomised controlled trials on humans after transmeridian flights so that clinical guidelines regarding jet lag treatment can be formulated (T2 in the Figure). Then this evidence needs to be reliably translated to public health policy on longer-term health problems and mortality (T3 in the Figure). Finally, findings from the latter epidemiological type studies can be translated to inform mechanistic experiments on animals (reverse translation).

Figure 2. Results of a literature search using the SCOPUS database. The total number of studies that refer to jet lag and associated terms is plotted on a yearly basis. Also shown are the yearly records for those studies in which an animal model was referred to, and those studies that referred to a randomised controlled trial.

Figure 3. A random-effects meta-analysis of standardised effect sizes from six studies on melatonin ingestion after westerly flights. The standardised effect sizes relate to an overall rating of jet lag relative to the standard deviation of the ratings. The standardised effect sizes from two studies (Spitzer et al. 1999; Edwards et al. 2000) were calculated from reported test statistics and P-values relating to an overall

1 | rating of jet lag. These effect sizes were then analysed together with those
2 | standardised effect sizes calculated from four studies that were meta-analysed in a
3 |
4 | previous systematic review (Herxheimer and Petrie, 2002). Note how the effect sizes
5 |
6 | tend to decrease over the decades since the first and smallest study was published
7 |
8 | (Arendt et al., 1987).
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12 | **Figure 4.** The probabilistic mechanistic chain between the effects of an intervention
13 | (I) on circadian rhythms of animals and humans studied in the laboratory and the
14 | effects of an intervention on externally valid outcomes (O) such as pilot- or athlete-
15 | relevant performance measures. The robustness of this chain depends on how
16 | strong are the correlations (r) between the various links in the chain (Howick et al.
17 | 2010). These correlations are difficult to quantify precisely but they serve to
18 | demonstrate how the overall link between basic and applied research is reliant on
19 | the strength of these correlations. The various correlations in the causal pathway can
20 | dilute the overall correlation between intervention effects in animal simulations and
21 | intervention effects on outcomes relevant to humans. For example, if each of the four
22 | correlations in Figure 5 was a large $r=0.7$, the overall correlation between
23 | intervention effects in simulations and effects in real-world outcomes could be as low
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Figure 1
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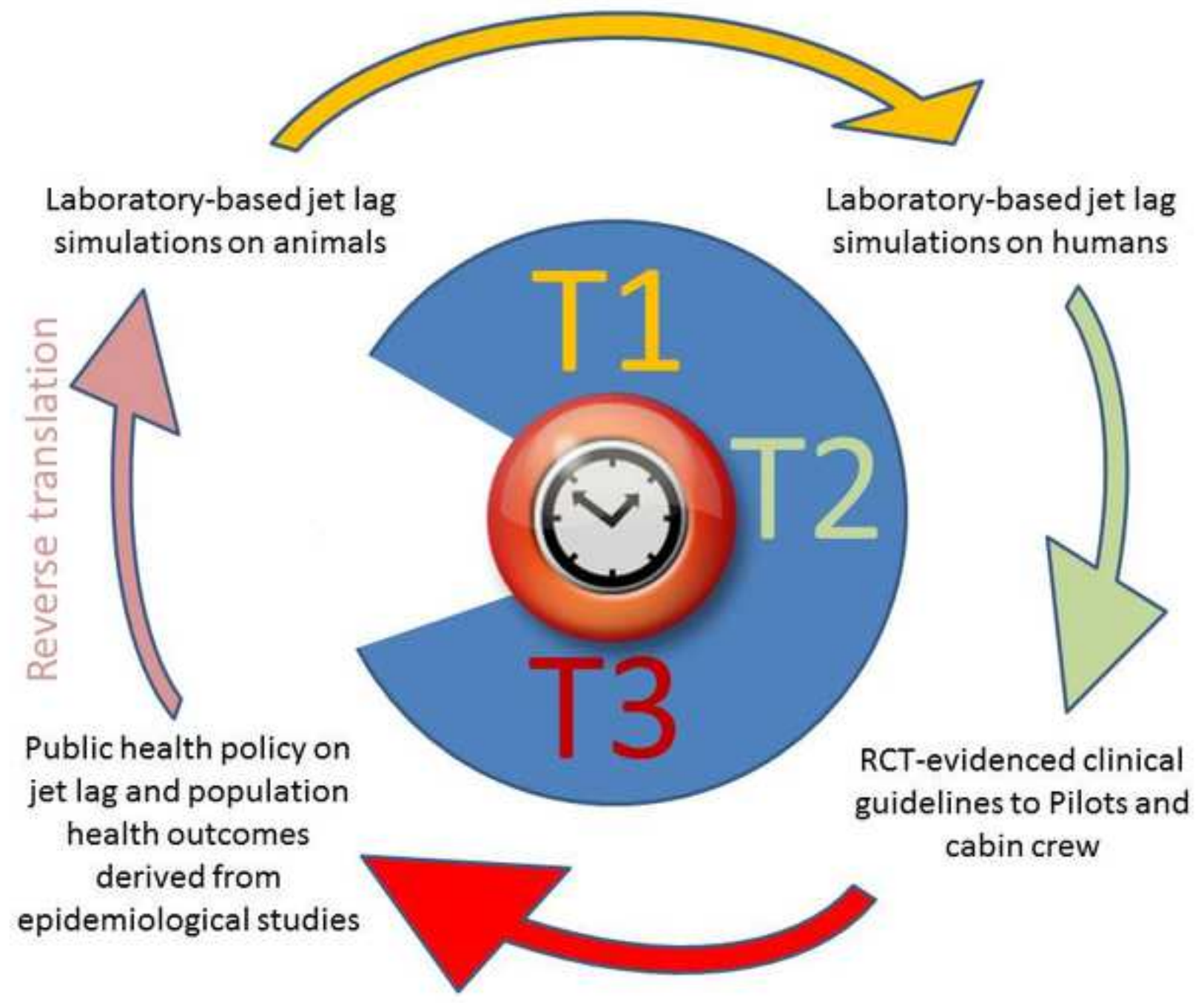


Figure 2
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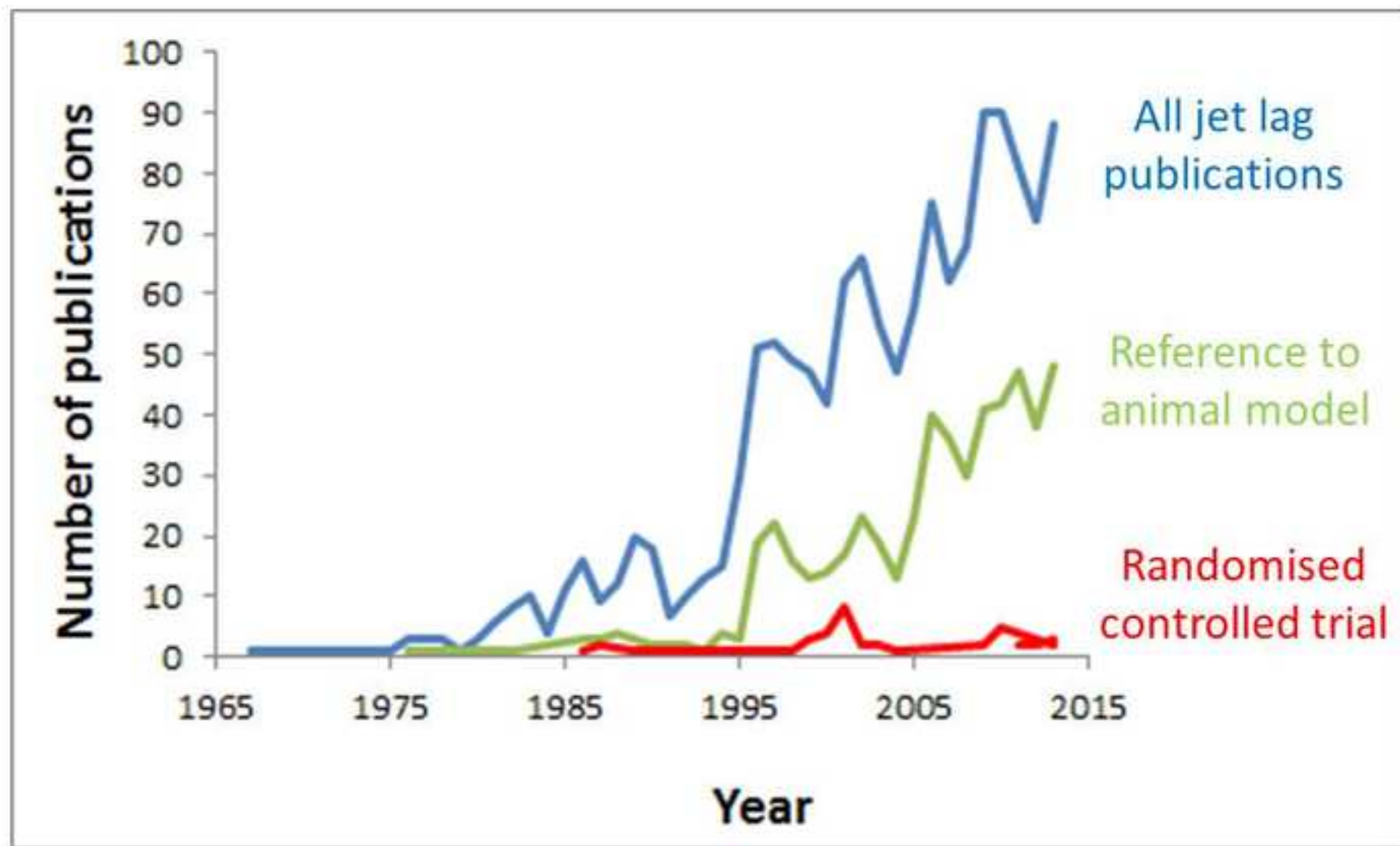


Figure 3

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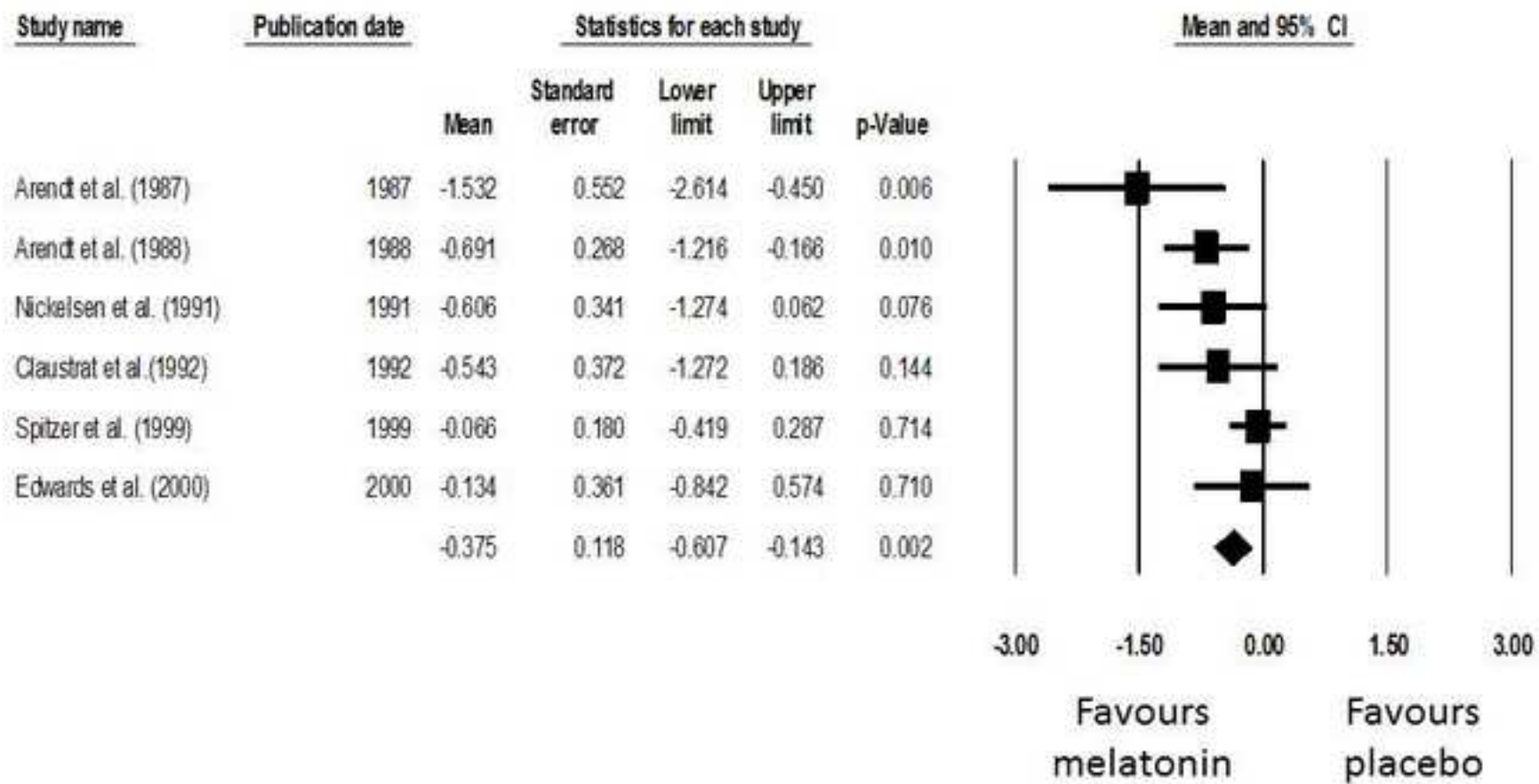


Figure 4
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