Stress and the hypothalamic-pituitary-adrenal axis: how can the COVID-19 pandemic inform our understanding and treatment of acute insomnia?

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Abstract

Stress and sleep are very closely linked, and stressful life events can trigger acute insomnia. The ongoing COVID-19 pandemic is highly likely to represent one such stressful life event. Indeed, a wide range of cross-sectional studies demonstrate that the pandemic is associated with poor sleep and sleep disturbances. Given the high economic and health burden of insomnia disorder, strategies which can prevent and treat acute insomnia, and also prevent the transition from acute insomnia to insomnia disorder, are necessary. This narrative review outlines why the COVID-19 pandemic is a stressful life event, and why activation of the hypothalamic-pituitary-adrenal (HPA) axis, as a biological marker of psychological stress, is likely to result in acute insomnia. Further, this review outlines how sleep disturbances might arise as a result of the COVID-19 pandemic, and why simultaneous HPA axis measurement can inform the pathogenesis of acute insomnia. In particular, we focus on the cortisol awakening response (CAR) as a marker of HPA axis function, as cortisol is the end product of the HPA axis. From a research perspective, future opportunities include identifying individuals, or particular occupational or societal groups (e.g. frontline health staff), who are at high risk of developing acute insomnia, and intervening. From an acute insomnia treatment perspective, priorities include testing large-scale online behavioural interventions; examining if reducing the impact of stress is effective, and finally, assessing whether "sleep vaccination" can maintain good sleep health by preventing the occurrence of acute insomnia, by preventing the transition from acute insomnia to insomnia disorder.

Keywords: stress, acute insomnia, HPA axis, cortisol awakening response, sleep, COVID-19

Introduction

Insomnia disorder is highly prevalent: it is estimated that within industrialised societies, approximately 6-10% of the population have insomnia, and approximately 50% of the population report having symptoms of insomnia (Ohayon, 2002; Pallesen, Sivertsen, Nordhus, & Bjorvatn, 2014). Insomnia disorder has a significant economic burden (Daley, Morin, LeBlanc, Gregoire, & Savard, 2009) and is associated with an increased risk of multiple deleterious physical and psychological health conditions (Baglioni et al., 2011; Li, Zhang, Hou, & Tang, 2014; Riemann & Voderholzer, 2003).

Theoretical models of insomnia, such as Spielman's "*3P*" model, suggest that stressful life events can potentially result in clinically-significant short-term insomnia, which is known as acute insomnia (Ellis, Gehrman, Espie, Riemann, & Perlis, 2012; Spielman, Caruso, & Glovinsky, 1987; Spielman, Nunes, & Glovinsky, 1996). Acute insomnia refers to a self-reported disruption in sleep continuity which occurs for a duration of between two weeks and three months (Ellis, 2019; Ellis, Gehrman, et al., 2012). Indeed, a range of previous studies have demonstrated that stress is associated with various subjective and objective sleep disturbances (Bastien, Vallieres, & Morin, 2004; Reynolds 3rd et al., 1992; Reynolds 3rd et al., 1993). Acute insomnia is also highly-prevalent: annually, it has been estimated that the incidence of acute insomnia may be as high as 40% (Ellis, Perlis, Neale, Espie, & Bastien, 2012; Perlis et al., 2020). A further problem is that acute insomnia can also trigger (longer-term) insomnia disorder, or cause variable disturbances to subjective sleep continuity (i.e. disturbances to sleep initiation and/or sleep maintenance which are not of a sufficient severity to be considered acute insomnia) which can subsequently lead to insomnia disorder at a later date (Perlis et al., 2020). In order to inform the aetiology and treatment of acute insomnia, it is important to understand how, and why, stressful life events may result in acute insomnia.

This is important as preventing, and treating, acute insomnia may prevent the later development of insomnia disorder.

The aim of the present narrative review is to outline why the ongoing COVID-19 pandemic should be considered a stressful life event and potential cause of acute insomnia, and mechanistically, why psychological stress caused by COVID-19 is likely to result in acute insomnia through activation of the hypothalamic-pituitary-adrenal (HPA) axis. The implications of this review are twofold: firstly, this review will directly inform future mechanistic studies which will further the understanding of the pathogenesis of acute insomnia. Secondly, this review will inform the design of future treatment studies, focussed on addressing, and preventing, acute insomnia, through targeted interventions which are likely to reduce HPA axis activity.

Stressful events and the impact of the COVID-19 pandemic upon sleep

Stress can affect sleep (Altena et al., 2016; Lo Martire, Caruso, Palagini, Zoccoli, & Bastianini, 2020) and it is well-established from a range of naturalistic studies, that stressful events, including earthquakes, hurricanes and war, are shown to have a deleterious effect upon sleep (Askenasy & Lewin, 1996; Kato, Asukai, Miyake, Minakawa, & Nishiyama, 1996; Mellman, David, Kulick-Bell, Hebding, & Nolan, 1995). The COVID-19 pandemic, which has been ongoing since March 2020, represents one such stressful event, and potentially represents a stressor of unknown duration, accompanied by a wide range of societal and lifestyle changes (Altena et al., 2020).

Cross-sectional evidence certainly indicates that the COVID-19 pandemic disrupts sleep. This includes sleep problems related to national or local ‘lockdown’ occurrences, sleep problems that are caused by or related to pandemic-related anxiety and stress, and sleep

problems which have occurred as a direct consequence of the disease itself. For instance, the results of an online study of 842 adults, which was conducted during lockdown periods in May/June 2020, where social interaction and movement were limited, reported a significant negative impact on sleep (Perez-Carbonell et al., 2020). Specifically, this study found that a range of sleep disturbances were apparent: approximately 70% of respondents reported a change in their sleep pattern, 46% of people were sleepier in comparison with before the lockdown period, 43% reported "disrupted sleep", 35% reported falling asleep unintentionally, and approximately 30% of respondents had difficulties falling asleep or staying asleep, and reported later bedtimes (Perez-Carbonell et al., 2020). Additionally, the majority (65%) of participants stated that the pandemic/lockdown period had an impact upon their mental health, and only 45% of respondents reported having refreshing sleep (Perez-Carbonell et al., 2020). Two further cross-sectional studies, from China and Italy respectively, also appear to confirm the negative impact of the pandemic upon sleep (Casagrande, Favieri, Tambelli, & Forte, 2020; Wang et al., 2020). Evidence from Italy, in an online survey of approximately 2,300 adults in March/April 2020, showed that approximately 58% of participants reported poor sleep quality, 42% reported distress, 32% reported high levels of anxiety, and 8% reported symptoms of post-traumatic stress disorder (PTSD) (Casagrande et al., 2020).

In addition to cross-sectional evidence, a recent meta-analytic study has provided further evidence in support of the negative impact of the pandemic upon sleep (Jahrami et al., 2022). In this review of 250 studies (n = 493,475), the estimated global prevalence of sleep disturbances was estimated to be approximately 41%, with higher rates observed in healthcare workers (42%) and in patients who had reported having COVID-19 (52%). Another systematic review observed a similar pattern, whereby sleep problems were more frequently observed in COVID-19 patients, and that sleep problems were also positively

associated with depression and anxiety (Alimoradi et al., 2021). It is particularly important to prevent the transition from acute to chronic insomnia in this context, since it is known that insomnia symptoms can continue even after the emotional consequences of the initial cause (e.g. a trauma or upsetting life event) have been effectively treated (López et al., 2019) This is also important as, for example, insomnia treatment can effectively prevent the occurrence of comorbid depression (Irwin et al., 2022; Leerssen et al., 2022)

Further recent studies have shown that the COVID-19 pandemic is considered to be a traumatic stressful event (Bridgland et al., 2021; Saalwirth & Leipold, 2021), with meta-analytic work estimating that 20-30% of the general population may have experienced elevated stress levels (Cooke, Eirich, Racine, & Madigan, 2020; Salari et al., 2020). This point is backed up by the results of recent population survey studies, which have indicated that subjective stress levels have increased during the pandemic (Hsing et al., 2020; Robillard et al., 2020).

Stress, the hypothalamic-pituitary-adrenal (HPA) axis, and insomnia

The term ‘stress’ refers to experiences which are considered to be emotionally or physiologically demanding, and to the adaptative response involving multiple physiological systems (Lo Martire et al., 2020; McEwen, 2007). The HPA axis is an endocrine system which has an important role in ensuring that the body adapts to bodily and environmental challenges (Fries, Dettenborn, & Kirschbaum, 2009; Hucklebridge, Hussain, Evans, & Clow, 2005). As part of the primary stress response, both the sympathetic nervous system and HPA axis are activated, and this leads to a “fight-or-flight” response, whereby catecholamines and glucocorticoids are released into the bloodstream (Lee & Harley, 2012; McEwen, 2007), and redirect energy resources, in order to restore homeostasis (Herman et al., 2003).

A stress marker which of particular interest with regards to the development of acute insomnia is cortisol, which is the end product of the HPA axis. In the context of stress, a perceived threat causes the hypothalamus to release corticotropin-releasing hormone (CRH), which then triggers the anterior pituitary gland release of adrenocorticotropin hormone (ACTH), and finally the release of cortisol from the adrenal cortex (Clow, Thorn, Evans, & Hucklebridge, 2004). Cortisol is highly responsive to physical and psychological stress, and it is well-established that acute psychological stress can increase cortisol levels (Dickerson & Kemeny, 2004). (Lo Martire et al., 2020)

The HPA axis and insomnia

Alterations to HPA axis activity are relevant to the pathogenesis of both acute insomnia and insomnia disorder. The hyperarousal theoretical model of insomnia suggests that elevated cognitive, emotional and physiological activity (expressed as, for example, heightened autonomic or central nervous system activity) are important in the pathophysiology of insomnia disorder (Dressle et al., 2022; Riemann et al., 2015; Riemann et al., 2010). Acute insomnia, and insomnia disorder, can both be considered to be a stress-related condition, whereby an initial stressful event can result in physiological hyperarousal, and over time, insomnia disorder becomes stressful in its own right (Dressle et al., 2022).

Activation of the HPA axis is a feature of acute insomnia, where the initial stress response is observed as a consequence of the response to the initial stressor (Dressle et al., 2022). However, alterations to HPA axis activity are also a feature of the transition from acute insomnia to insomnia disorder, where following the initial stressor, heightened HPA axis activity can negatively affect sleep (Dressle et al., 2022). The initial sleep disturbance which accompanies the acute stressor can potentially cause sleep fragmentation or

deprivation. This can, in itself, negatively affect the HPA axis and maintain the sleep disturbance, potentially due to chronic HPA axis hyperarousal affecting sleep and circadian rhythmicity (Buckley & Schatzberg, 2005; Dressle et al., 2022; Lo Martire et al., 2020). Additionally, stress reactivity, and sleep, could potentially moderate the relationship between acute and chronic stress, and HPA axis activity (Dressle et al., 2022; van Dalfsen & Markus, 2018). Taken together, altered HPA axis activity is relevant to acute insomnia in terms of the initial stress response, and is also relevant to the maintenance of acute insomnia, and subsequent progression towards insomnia disorder.

Certainly, several studies show that there are specific alterations to cortisol, and the CAR, which could potentially indicate that elevated HPA axis activity is a feature of insomnia disorder (Riemann et al., 2015). Specifically, studies have observed that relative to people without insomnia disorder, those with insomnia display elevated levels of morning cortisol, increased cortisol awakening responses, and higher 24-hour cortisol levels (Grimaldi et al., 2021; Xia, Chen, Li, Jiang, & Shen, 2013; Zhang et al., 2014). Despite the relevance of the HPA axis to insomnia disorder, currently, very little is known about HPA axis activity during the acute phase of insomnia; to the best of our knowledge, no studies have specifically sought to examine this, or have been able to do so, to date.

The cortisol awakening response (CAR)

Cortisol is a particularly suitable biological marker of stress in the context of acute insomnia, since it can be easily, reliably, and non-invasively measured, in order to quantify stress. Cortisol secretion fluctuates in a circadian pattern: cortisol levels sharply increase in the hour after awakening; decline three hours after awakening, then gradually decline until the nadir which occurs during the first half of the sleep period, and finally, gradually rise until

awakening (Elder, Wetherell, Barclay, & Ellis, 2014; Fries et al., 2009). Connections between the suprachiasmatic nucleus (SCN) and paraventricular nucleus (PVN) of the hypothalamus are responsible for synchronising the time of day to cortisol output (Buijs, van Eden, Goncharuk, & Kalsbeek, 2003).

In contrast to other indices of HPA axis function, cortisol can be easily and reliably measured in a non-invasive manner using saliva sampling, with salivary cortisol levels showing a high level of agreement with plasma cortisol levels (Hellhammer, Wust, & Kudielka, 2009). Additionally, compared to other methods of assessing HPA axis function, saliva sampling is advantageous as firstly, blood sampling is considered to be a stressor in its own right (Prinz, Bailey, Moe, Wilkinson, & Scanlan, 2001) and secondly, since blood collection is not required, this means that participants can self-collect saliva samples outside of a sleep laboratory environment (Elder, Ellis, Barclay, & Wetherell, 2016; Elder et al., 2014). In contrast, other measures of HPA axis function, such as ACTH or CRH, are difficult to measure due to their instability, or the fact that only low levels of these measure circulate within blood (Dressle et al., 2022; Spencer & Deak, 2017).

Of particular relevance is the "cortisol awakening response" (CAR). The CAR refers to a distinct phase of the circadian cortisol profile, whereby there is a sharp increase in cortisol levels observed upon awakening: during the CAR, cortisol levels increase by 38-75% and peak approximately 30 minutes after awakening (Elder et al., 2014). The CAR is a robust marker of HPA axis function, and although other physiological stress measures can be obtained (e.g. heart rate variability, electrodermal activity), a particular advantage of focussing upon the CAR, is that the link between sleep and HPA axis activity is generally well-understood (van Dalfsen & Markus, 2018). Unlike other biological markers of stress activity, there are specific CAR measurement protocols which have been designed for use in sleep medicine and sleep research environments, and which were developed with insomnia

research in mind (Elder et al., 2016; Elder et al., 2014). Multiple different measurement indices of the CAR can be examined, including cortisol levels at each sampling time point, awakening cortisol levels, or total cortisol secretion, or the magnitude of change between awakening levels and peak levels, or finally, the mean increase in cortisol levels (Elder et al., 2016; Elder et al., 2014). As is the case with cortisol, the CAR is sensitive to periods of stress: the CAR is associated with periods of increased demand and/or anticipation of forthcoming demand (Brant, Wetherell, Lightman, Crown, & Vedhara, 2010; Elder, Barclay, Wetherell, & Ellis, 2018). Finally, the CAR should also be considered an appropriate marker of HPA axis activity because our understanding of HPA axis activity is also informed by a large body of work focussing on depression, which is itself very closely linked to insomnia (Riemann et al., 2010). Taken together, the CAR is likely to be useful in understanding HPA axis function in stress-related acute insomnia.

Stress and HPA axis activation as a result of pandemic-related stress

There are numerous stressors, which have occurred in the context of the pandemic, that are relevant and could trigger acute insomnia, as they have been shown to also result in HPA axis activation. These stressors include being forced to remain at home (during lockdown periods), working from home, working more hours in stressful circumstances, and managing health risks (Altena et al., 2020). Other associated changes, such as potential or actual unemployment, are relevant: one study found that factors such as financial worry, self-rated health, perceived control, and concern in relation to catching COVID-19 were predictors of subjective stress (Newby, O'Moore, Tang, Christensen, & Faasse, 2020).

These events have also been associated with altered HPA axis functioning. For example, unemployment can result in alterations to the CAR (Gallagher, Sumner, Muldoon,

Creaven, & Hannigan, 2016). Altered HPA axis function may also be useful for examining the impact of stress within particular groups of individuals, or for example, specific occupational groups. For instance, it has been shown that cortisol levels in healthcare workers were higher during the peak of the first wave of the pandemic relative to immediately before, and that those individuals who worked in higher-risk environments demonstrated increased cortisol levels compared to low-risk workers (Rajcani, Vytykacova, Solarikova, & Brezina, 2021). Separate studies, conducted during the pandemic, have shown that the relative change in cortisol levels can predict subsequent burnout in healthcare workers, and that the CAR is associated with the emotional response to the pandemic (Baliyan et al., 2021; Marcil et al., 2022); importantly, one demonstrated that hair cortisol levels *increased* from pre-pandemic to post-pandemic onset (Marcil et al., 2022). Overall, this provides further support to demonstrate that the simultaneous measurement of stress and HPA axis activity is relevant to the pathogenesis of acute insomnia.

Research opportunities: predispositional and situational risk factors for acute insomnia

One potential area for research is to examine predispositional and situational factors which may increase the individual risk of developing acute insomnia from the initial pandemic-related trigger of poor sleep.

According to the Spielman 3P model of insomnia, predisposing factors are trait-like characteristics such as worry, or specific personality traits (Spielman et al., 1996). Indeed, recent work has demonstrated that factors including anxiety, insomnia severity, and personality aspects including conscientiousness and openness to experience, are predictive of the development of acute insomnia following the initial sleep disturbance (Ellis et al., 2021).

More recently, the concept of "sleep reactivity" has been investigated in relation to the hyperarousal model of insomnia disorder, whereby the response to stress might be an important risk factor for future insomnia development (Drake, Richardson, Roehrs, Scofield, & Roth, 2004; Kalmbach et al., 2018; Walker et al., 2022). Sleep reactivity is the extent to which stress can disrupt sleep, and this can be influenced by environmental stress, or other factors such as genetics, a family history of insomnia, or rumination/worry (Kalmbach et al., 2018). Indeed, it is the experienced stress, and not the number of stressful events experienced, that is predictive of the development of insomnia (Morin, Rodrigue, & Ivers, 2003).

It is evident that there is a great deal of heterogeneity in the way in which sleep has changed in response to the pandemic. In one Canadian study, conducted in Spring 2020, three distinct profiles of sleep-related changes to behaviour were observed: those who demonstrated a reduction in their subjective time in bed, those who delayed their sleep time, and those who extended their duration of time in bed (Robillard et al., 2020). Importantly, this study examined clinically-significant changes in subjective stress and found that both the group with reduced time in bed, and the delayed sleep group, each had a greater proportion of individuals with a clinically-significant worsening in stress, relative to the extended time in bed group.

Perhaps counterintuitively, it should be noted that various studies have also demonstrated that sleep has actually *improved* in certain groups of individuals (Kocevska, Blanken, Van Someren, & Rosler, 2020; Partinen et al., 2021). These findings may be due to changes in sleep *timing*, where relative to before the pandemic, people may have had an increased opportunity to obtain sleep, particularly in the context of work days (Korman et al., 2020). One potential reason for this is potentially due to the marked shift towards remote, or flexible, working during the pandemic, which has also potentially led to greater levels of flexibility in the sleep schedule of some individuals (Staller & Randler, 2021; Yuan, Zitting,

Maskati, & Huang, 2022). Work is an important determinant of sleep quality and timing, and additionally, other employment-related factors such as work stress, work demands, and the time spent commuting to work, can also affect sleep (Linton et al., 2015; Myllyntausta et al., 2022; Petrov et al., 2018). One potential reason as to why this increased flexibility could have affected sleep is that at a biological level, this societal shift might have negated the impact of 'social jetlag'. Specifically, for some individuals, and particularly those with a later diurnal preference, the increased flexibility offered by this societal change is likely to have negated or removed the mismatch between their actual, and desired, timing of sleep (Blume, Schmidt, & Cajochen, 2020; Wittmann, Dinich, Merrow, & Roenneberg, 2006).

As the effect of the pandemic upon sleep has not been consistently negative across individuals, this certainly warrants the further investigation of subgroups who may have had different experiences of the stress-sleep link during the pandemic. For example, it is known from PTSD literature that not everyone develops PTSD following a major traumatic event; figures demonstrate that on average, approximately 10% of military personnel develop PTSD (Kilpatrick et al., 2013; Miao, Chen, Wei, Tao, & Lu, 2018). It would undoubtedly be of value to understand why some groups of people do not experience negative effects upon sleep.

In addition to pertinent trait characteristics which may heighten the risk of sleep disturbances resulting in acute insomnia, there may be a range of situational factors which are relevant in the context of the pandemic, such as occupational, or environmental factors. For instance, individuals who work in certain employment sectors, which may put them at a greater actual or perceived risk of COVID-19 infection, or stress, may be at a greater risk of developing stress-related sleep disturbances, and there are even likely to be variations within employment sectors. For example, one study found that healthcare workers had greater levels of subjective work-related stress, relative to non-healthcare staff, and within healthcare staff,

paramedic staff reported higher levels of stress than non-paramedic medical doctor staff (Couarraze et al., 2021). In terms of environmental factors, these might include periods of forced or voluntary home confinement, either as a consequence of illness, or, for example, due to the lockdown restrictions generally observed earlier in the pandemic; increase in home-working activity, or an increase in co-sleeping with children during stressful periods, which itself can negatively impact parental sleep (Altena et al., 2020; Teti, Shimizu, Crosby, & Kim, 2016). All of these factors have the potential to negatively impact sleep, potentially through the sleep/stress pathway (Altena et al., 2020). This may mean that a more precise approach will need to be adopted in order to identify who may be at a high risk of developing acute insomnia. In other words, given that the potential impact of the pandemic is not equitable in terms of stress, specific groups should be targeted for sleep interventions.

There may also be a temporal effect of relative infection severity, driven by the timing of COVID infection 'waves'. For instance, an international online survey which had the aim of documenting the prevalence and incidence of sleep disturbances during the pandemic, found that the pandemic severity influenced both sleep disturbances and related daytime symptoms (Partinen et al., 2021). Specifically, this study examined cumulative COVID-19-confirmed deaths as a marker of pandemic severity, and found that the prevalence of sleep disturbances, fatigue, and daytime sleepiness, increased in countries including the UK and USA, during a period where the pandemic severity was increasing (Partinen et al., 2021). Whilst future work could also examine the impact of case numbers, as this may be related to perceived infection risk, it may be difficult to disentangle the specific impact of this risk from other political, social and psychological factors (Partinen et al., 2021). That said, the severity of the pandemic does appear to be relevant: one large global survey showed that perceived stress was positively associated with the severity of COVID-19 in a given country (Kowal et al., 2020) and longitudinal work from Hong Kong seems to confirm that specific COVID-19

waves can negatively influence sleep disturbances (Lam et al., 2021). Wang and colleagues observed that sleep disturbances were more likely to be present in individuals who believed that COVID-19 had caused a high number of deaths, and those who considered that COVID-19 was not easy to cure (Wang et al., 2020). Taken together, this suggests that particular groups may be a greater risk of pandemic-related sleep disturbances, and that the fear of infection may play an important role in this relationship.

Additionally, the temporal changes in relation to the pandemic also raise the possibility that as the pandemic progresses, it is possible that for some individuals, the ongoing pandemic could be considered to be a *perpetuating* factor in the context of the 3P model, whereby this may maintain drive the transition to insomnia disorder, rather than the *precipitating* acute stressor. Within the 3P model, perpetuating factors typically refer to behavioural and cognitive factors in relation to insomnia symptoms and their consequences (Spielman et al., 1987; Spielman et al., 1996). Speculatively, perpetuating factors could encompass pandemic-related behaviours such reacting to a heightened fear of infection, or the perception of infection severity and/or likelihood during subsequent pandemic 'waves', since this has been demonstrated to negatively affect sleep (Lam et al., 2021; Partinen et al., 2021). Other related perpetuating factors might include the mismatch between the ability and opportunity of individuals to sleep, which could also be influenced by pandemic-related factors such as poor mental and/or physical health (Perlis et al., 2021).

The impact of anticipated stress may also be relevant, even in healthy individuals without sleep disturbances, as anticipation can affect both sleep and the HPA axis; observational studies have shown that even the anticipation of future work-related tasks can disrupt objective sleep (Torsvall & Akerstedt, 1988; Torsvall, Castenfors, Åkerstedt, & Fröberg, 1987). The anticipation of demand can also affect the magnitude (increase) of the CAR, although in this particular study, neither subjective or objective sleep were affected,

most likely as a result of the stressor not being personally-salient, or of a sufficient duration, to disrupt sleep (Elder et al., 2018). The COVID-19 pandemic is highly likely to be considered personally-salient and disruptive.

Work should also examine if the HPA axis stress response can make a quantifiable contribution to the risk of acute insomnia: it is possible that individuals who may be 'at risk' of acute insomnia during the pandemic may be more sensitive to stress-related sleep disturbances, and this is likely to be accompanied by increased HPA axis activity. Although stress can be quantified using subjective self-report measures, such as the Perceived Stress Scale (Cohen, Kamarck, & Mermelstein, 1983), work could simultaneously examine the CAR, since this would allow for both subjective stress and objective HPA axis activity to be measured.

Although, as stated, sleep medicine and sleep research-focussed CAR measurement protocols exist (Elder et al., 2016; Elder et al., 2014), these were originally designed with a sleep laboratory environment in mind and may need to be modified or updated to allow for potential COVID-19 restrictions (e.g. social distancing or fear of infection), or other pandemic-related events, which may limit the ability to undertake laboratory research. This may also present a research opportunity: this might facilitate the further development of a bespoke sleep research and sleep medicine CAR protocol which can be utilised within an ambulatory environment. An advantage of this approach is that such a measurement protocol would appropriately balance cost, technical requirements and the required levels of control for the measurement of the CAR in sleep research. This could be done by using the electronic monitoring of saliva sampling, which relies upon time-stamping the opening of saliva collection bottles (Kudielka, Hawkley, Adam, & Cacioppo, 2007), and by using actigraphy to verify awakening times and light exposure. Additionally, blackout blinds and/or ultraviolet light bulbs may also be used to minimise the influence of light upon the HPA axis, since light

levels can affect the CAR and lead to incorrect measurements (Elder et al., 2014). Participant screening and training to ensure high levels of adherence may also increase measurement accuracy, although the target participant group may need to be considered; for example, individuals with cognitive impairment may find this difficult. Whilst the level of agreement with sleep laboratory protocols should be tested, this may facilitate the measurement of the HPA axis in a home environment, with better levels of control than most ambulatory studies. Moreover, this could be combined with the simultaneous measurement of other relevant physiological stress variables; e.g. one recent study has combined ambulatory cardiac monitoring with actigraphy to derive measures including heart rate variability (Rosler et al., 2022).

Concurrent measurement of the HPA axis would also allow for the examination of whether behavioural and/or societal changes which have occurred alongside, or as a result of COVID-19, might have increased stress and concurrent HPA axis activity. This could provide a useful insight into particular groups of people, or occupations, who may be at increased risk of developing acute insomnia through this pathway. Finally, studies should focus on examining if the anticipation of highly stressful situations may trigger increased HPA axis activation and result in acute insomnia; experimental work in healthy sleepers has demonstrated that the anticipation of a short period of demand can still activate the CAR, irrespective of whether or not the demand is actually experienced (Elder et al., 2018; Elder, Wetherell, Pollet, Barclay, & Ellis, 2020).

Therapeutic opportunities for acute insomnia

It is beyond the scope of the present review to provide a comprehensive guide for the clinical treatment of acute insomnia during the pandemic, as other reviews provide practical

recommendations (Altena et al., 2020). However, there are a number of intervention studies which could be trialled in order to maximise the effectiveness of existing treatments in the context of sleep disturbances caused by COVID-19, and these may also be effective post-pandemic. For instance, these include adapting treatments for use during the pandemic, or targeting particular groups who might be at high risk of developing acute insomnia.

Cognitive behavioural therapy for insomnia (CBT-I) is recommended as a first-line treatment for insomnia disorder (Riemann et al., 2017). However, a major barrier to the widespread delivery and uptake of CBT-I is in the high attrition levels, and lack of qualified providers; subsequently, CBT-I may be too time-intensive and resource-intensive to be able to be rolled out at the scale required during the pandemic (Ellis, Cushing, & Germain, 2015; Sawdon, Elder, Santhi, Alfonso-Miller, & Ellis, 2021). Although pharmacological approaches, such as benzodiazepines and hypnotic benzodiazepine receptor agonists, can be used in the treatment of insomnia in the short-term (Riemann et al., 2017), these can have a number of side effects, including drowsiness, tolerance, and negative impacts upon cognition, (Kripke, Langer, & Kline, 2012; Siriwardena, Qureshi, Dyas, Middleton, & Orner, 2008; Stranks & Crowe, 2014). Additionally, pharmacological approaches to the treatment of acute insomnia may be particularly unsuitable for particular groups, such as older adults, who are at risk of adverse side effects and for whom polypharmacy is especially problematic (Elder & Flo-Groeneboom, 2022; Glass, Lanctot, Herrmann, Sproule, & Busto, 2005).

Given the highly effective nature of CBT-I, and advantages over the pharmacological treatment of insomnia (e.g. the lack of interaction with other medications, good treatment durability and concomitant reductions in anxiety and depressive symptoms), work should focus on whether the CBT-I treatment regimen can be modified to facilitate the widespread deployment. Indeed, previous work has demonstrated that “one-shot” CBT-I is effective for acute insomnia, where a single 60-70 minute session of face-to-face CBT-I is provided

alongside a behavioural intervention consisting of a self-help leaflet based on stimulus control, cognitive control and imagery distraction techniques (Ellis et al., 2015). Follow-up work has demonstrated that a one-shot approach is feasible and effective in a group format, and in a male prison environment (Boullin, Ellwood, & Ellis, 2016; Randall, Nowakowski, & Ellis, 2019), therefore, modifications to the traditional CBT-I programme may be effective.

Aside from the advantages over a traditional CBT-I programme in terms of scale and cost, an online or remote behavioural intervention may also have other practical benefits. For instance, online and remote interventions can be delivered without it being necessary to accommodate social distancing measures, and from a feasibility point of view, can mitigate against the fear of contagion which may be present in face-to-face scenarios (Weiner et al., 2020); this is important as the fear of infection may in itself disrupt sleep and the use of remote interventions may be advantageous (Wang et al., 2020). In developing such programmes, consideration should be given as to how adherence can be improved in a remote scenario. It is known from using behavioural interventions for depressive symptoms that online interventions can sometimes result in higher drop-out rates when compared to face-to-face therapy (Webb, Rosso, & Rauch, 2017); this may be an issue for insomnia research, as attrition rates as high as 50% have been observed in some instances (Luik, van der Zweerde, van Straten, & Lancee, 2019). Although online CBT-I appears to be promising, work should investigate whether this is effective in the short-term and long-term, since it is a cost-effective method of delivering CBT-I (van der Zweerde, Lancee, Ida Luik, & van Straten, 2019). For instance, it may be the case that even if behavioural interventions are shown to be effective, then sleep “booster” interventions may be required to maintain these effects (Ellis et al., 2015). Similarly, the use of videoconferencing software in the delivery of insomnia treatment (i.e. telemedicine) appears to result in good levels of efficacy (Arnedt et al., 2020).

Studies have already shown that CBT-I may help to prevent insomnia in the context of COVID-19. For instance, Cheng et al. have shown that insomnia patients that had received CBT-I before the outbreak of COVID-19 had less insomnia and depression symptoms, less stress and less COVID-related cognitive intrusions compared to a group that had received sleep education only before the outbreak (Cheng, Casement, Kalmbach, Castelan, & Drake, 2020). Others have provided COVID-19 related insomnia treatment to small samples of schoolchildren and university staff (Schlarb, Fründ, Kovacevic, & Faber, 2021; Schlarb, Schulte, Selbmann, & Och, 2020), while other CBT-I trials are ongoing (Becker, 2022; Sawdon et al., 2021).

Focussing on the specific impact of stress may also inform the development of specific treatments for acute insomnia. Current approaches to the treatment of acute insomnia primarily rely upon "one-shot" CBT-I techniques which aim to prevent the development of subsequent insomnia disorder (Ellis, 2019). Given the close links between stress, the HPA axis and sleep, work should also examine if interventions, which specifically aim to modify and reduce stress, can be used to prevent the transition from the acute insomnia phase to insomnia disorder and also reduce HPA axis activity. These could be used in tandem with CBT-I approaches and may also improve the effectiveness of existing one-shot acute insomnia interventions. For instance, one recent study found that an eight-week mindfulness-based online intervention reduced perceived stress after the first Italian COVID-19 lockdown period (Bossi et al., 2022). Evidence from the PTSD literature indicates that imagery rehearsal, which has typically been used in the context of the treatment of post-traumatic nightmares and involves psychoeducation, imagery exercises and cognitive restructuring, is an effective treatment for post-traumatic insomnia when combined with CBT-I (Brownlow, Harb, & Ross, 2015; Nappi, Drummond, & Hall, 2012); this combination may be applicable and effective in the context of COVID-19.

Given that the economic cost of poor sleepers to society is approximately ten times greater than the impact of good sleepers (Daley et al., 2009), therapeutic studies should also specifically examine if the impact of an upcoming stressor upon poor sleep can be prevented. In this context, an intervention would function as a form of "*sleep vaccination"*: instead of using an intervention to treat the resulting sleep disturbance, the intervention would be used to maintain good sleep, potentially by mitigating the impact of upcoming stressors upon sleep, in healthy normal sleepers. The sleep vaccination concept is therefore focussed upon the prevention of acute insomnia, since theoretically, it is possible to protect sleep by encouraging individuals to 'bank' resources (Ellis, Gehrman, et al., 2012). As the COVID-19 pandemic should be considered an ecologically-valid and provocative stressor, the sleep vaccination approach is conceptually attractive and indeed, an ongoing trial is investigating if this approach might be effective in healthy normal sleepers (Sawdon et al., 2021).

As well as the potential economic advantages of a preventative sleep vaccination approach, there may also be clear individual and societal health benefits of this strategy; for example, sleep may affect the immune response to COVID-19 vaccination or may influence relevant disease outcomes. Sleep disturbances are likely to negatively affect antibody response and immune function (Besedovsky, Lange, & Born, 2012) and indeed, sleep duration has been shown to be positively associated with post-vaccination antibody response levels (Schmitz, van der Werf, & Lammers-van der Holst, 2022), and it has also been shown that poor sleep is associated with prolonged COVID-19 related hospitalisation (Zhang et al., 2020). Therefore, maintaining good sleep health, including potentially through a preventative sleep vaccination approach, is likely to be of significant clinical and research value, both during the pandemic, and beyond. For instance, if effective, one possibility is to target groups who are known to be at risk of developing sleep disturbances, including healthcare workers, or other key workers, who exhibit high levels of stress (Couarraze et al., 2021). Similarly, this

may also be useful from a sleep health-focussed policy perspective: it has been shown that demographic factors can have a disproportionate negative impact upon COVID-19 outcomes, and it is known that many of these factors can affect sleep in their own right (Brown, Wilkins, Craig-Neil, Upshaw, & Pinto, 2021; Grandner, 2020). It is possible that groups who may be more negatively affected by COVID-19 may be at a greater risk of sleep disturbances related to COVID-19. In the longer term, this may enable a "precision medicine" approach to the prevention and treatment of acute insomnia.

Conclusions

A range of cross-sectional studies demonstrate that poor sleep and sleep disturbances are associated with the COVID-19 pandemic. The pandemic should be considered a highly stressful life event, which is likely to trigger acute insomnia, potentially as a result of increased HPA axis function. Future work should identify those who are at high risk of acute insomnia (e.g., frontline or healthcare workers, or people with high levels of sleep reactivity) and aim to prevent the transition to insomnia disorder. From a treatment perspective, work should examine if large-scale online behavioural interventions are appropriate and effective, given the scalability and cost of these interventions, and modifying acute insomnia treatment to lessen the impact of stress in addition to improving sleep. Finally, the concept of "sleep vaccination", where interventions are used with the prevention of acute insomnia in mind, should be tested in order to maintain good sleep health.

Author contributions.

GJE drafted the initial manuscript. All authors contributed to the conceptualisation, writing, critical review and editing of the manuscript.

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