Sleep, circadian rhythms and mental health: advances, gaps, challenges and opportunities

A Wellcome Commissioned Report

Authors

Dr Nicholas Meyer

Insomnia and Behavioural Sleep Medicine Clinic, University College London NHS Foundation Trust
Institute of Psychiatry, Psychology and Neuroscience, King's College London

ORCID: https://orcid.org/0000-0002-7640-0284

Professor Matthew Jones

School of Physiology, Pharmacology and Neuroscience, University of Bristol

ORCID: https://orcid.org/0000-0001-5396-3108

Introduction

Sleep is central to life[1], playing critical roles in brain development and ageing, cognition, emotion, immunity and metabolism[2]. The timing of sleep is regulated through its interaction with the circadian system, which aligns sleep and wake physiology with the day-night cycle. Circadian oscillators operate throughout the body and influence every aspect of our biology, including physical activity, feeding and fasting, alertness, mood, cognition, body temperature and cardiovascular function[3]. Sleep patterns shift over the life course, from new-borns sleeping most of the day to infants sleeping 12h per night, adolescents becoming “night owls”, and some older adults struggling to sleep more than 5h per night. The reciprocal interrelationships between sleep, wake and circadian rhythms are therefore ‘moving targets’: changes in the timing, quantity or quality of sleep can only be fully interpreted in the context of neurodevelopmental stage and behaviour across the 24h cycle.

Disturbances in sleep and circadian rhythms are bidirectionally intertwined with almost every category of mental disorder[4,5]. Sleep and circadian rhythm disturbances (SCRD) predict the onset of mental disorder[6], and are one of the earliest signs of relapse[7]. They occur during and between episodes of mental illness, and the intensity of sleep and psychiatric disturbances typically co-vary[8]. Pharmacological and psychological treatment of sleep disturbance can alleviate psychopathology, and vice versa. The hypothesis that SCRD play causal roles across a range of mental disorders, and represent modifiable risk factors for their development, is therefore compelling.

Despite remarkable progress in our understanding of sleep and circadian biology, the mechanisms linking SCRD to causes and symptoms of mental illness remain poorly understood. Many studies, particularly those based on sleep-lab polysomnography, are underpowered and inconsistent [9–11]. Studies examining circadian disturbance lag behind those of sleep. Although progress has been made in understanding the effects of experimental sleep disruption on cognitive and emotional functions in non-clinical populations[12], these findings have yet to be extended to the context of disease mechanisms in psychiatric disorder and often do not account for inter-individual vulnerability and neurodevelopmental trajectory. Employing standardised sleep-circadian measures, and technologies which allow longitudinal multimodal measurement in the field, stands poised to accelerate discovery.

The translation of psychological and pharmacological interventions which target sleep-circadian dysfunction into innovative treatments for psychiatric disorder is a promising avenue of investigation. For example, emerging data suggest that CBT for insomnia alleviates psychopathology[13], and might even prevent its development[14], and circadian interventions such as light therapy are effective in mood disorder[15]. However, our understanding of the mechanisms through which promising interventions work remain incomplete.

This scoping report offers a broad overview of the current landscape of our understanding in sleep-circadian aspects of mental disorder, with a focus on depression, anxiety disorders, affective and non-affective psychosis, to identify important gaps and opportunities for further research. The peak age of onset of most psychiatric disorders is in adolescence and the third decade of life [16,17], so we emphasise data from youth and adolescent populations, in whom early detection and intervention promise the greatest benefit.

Search strategy and selection criteria

We searched PubMed for the exploded MeSH headings “sleep", “circadian rhythm", “CBT-I”, “chronotherap*”, “melatonin”, “light”; and combined these with the terms: “depression”, “anxiety disorder”, “bipolar disorder”, “mood disorder”, “schizophrenia”, “psychosis”, “suicide”, “mental health”; between January 2017 – April 2022, in the English language.

Due to the broad scope of the review, we initially restricted results to narrative reviews, systematic reviews and meta-analyses, and then consulted reference lists for further studies, including older publications, where necessary.

We also interviewed key opinion-leaders in the field, where discussion was guided around the following themes:

1. *Key questions at the intersection between sleep, circadian rhythms and mental disorder*
2. *Candidate mechanisms linking sleep and mental health*
3. *Barriers to progress in understanding and treating sleep and circadian disruption in mental health disorders*
4. *Possible approaches to addressing these questions and challenges*
5. *Important measurements and analytic approaches*

Opinion-leaders are listed in Appendix 1.

Sleep and circadian disturbance as a risk factor for the development of mental disorder

Poor sleep has commonly been viewed as a by-product of mental disorder and is often overlooked by clinicians. This conceptualisation has been challenged by evidence that supports a converse direction of effect, where sleep problems precede the onset of mental disorder, and contribute to its development. For example, the distinction between primary and secondary insomnia has been abandoned in DSM-5, and the category *insomnia disorder* introduced. This recognises insomnia as a treatable disorder in its own right, regardless of whether it occurs in the context of a co-morbid mental disorder. However, the tendency to overlook patients' sleep problems persist, perpetuated by lack of sleep education and awareness in healthcare providers[18–20].

The majority of longitudinal studies have focused on symptoms of insomnia as the primary indicator of sleep disturbance, and used a range of subjective, observer or self-rated, and single-item measures[21]. Insomnia has been established as a risk factor for the development of a range of new-onset mental disorders: meta-analyses of longitudinal studies have shown that insomnia predicts the subsequent emergence of depression with odds ratios of 2.27 - 2.83[22–24], and bipolar disorder[25], anxiety disorder and alcohol misuse, with similar effect sizes[24]. In epidemiological studies of psychotic disorders, insomnia was associated with 2-3 times greater odds of developing delusions and hallucinations[26–28].

Although insomnia undoubtedly presents as a core sleep phenotype in mental disorder, focusing solely on insomnia also risks overlooking the wider range of co-existing sleep profiles, including hypersomnia, nightmare disorder, and disorders of sleep timing. Certain other sleep-circadian disorders may be particularly relevant in children, who more commonly report nightmares which in turn associate with psychopathology, including suicidality[29]. Further, different mechanisms may underlie clinically comparable sleep phenotypes. For example, delayed sleep phase (arising from circadian misalignment) and sleep onset insomnia (reflecting psychophysiological hyperarousal) may appear similar, yet have distinct mechanisms and require different interventions[30].

Disturbances in circadian rhythms and sleep timing are attracting growing interest as risk factors for the development of mental disorder. Studies in both adolescents and adults have reported that a preference for later bedtimes and rise times (*evening chronotype*), and an associated polygenic risk for this chronotype, low-amplitude rest-activity profiles, measured with actigraphy and characterised by low levels of daytime activity, and greater day to day variability in bed and rise times, are transdiagnostic risk factors for depression, bipolar disorder, and schizophrenia[31–35]. To date, however, studies have mainly examined proxies of circadian rhythmicity, such as chronotype or behavioural rhythms, which are influenced by a range of intrinsic and environmental factors, and do not necessarily reflect endogenous circadian rhythms. Incorporating biomarkers of circadian rhythm into longitudinal studies is therefore essential, to allow a better understanding of the contribution and magnitude of circadian misalignment.

Are adolescents particularly vulnerable to the effects of SCRD?

To date, most studies have focused primarily on adults, often in those with established mental disorder. Given that depression, bipolar and psychotic disorders are three of the four most burdensome disorders in youth and adolescence[36], these groups warrant greater focus. How sleep and circadian disruption at different neurodevelopmental stages map to specific long-term outcomes remains poorly understood, with few studies illuminating

temporal interrelationships between sleep and first-onset psychiatric illness in children or adolescents[37]. Work in animal models, which allow for precise control of the timing of experimental sleep-circadian disruption, could be used to inform this gap. Some features of sleep EEG (e.g. slow-wave activity) hold promise as markers of cortical network maturity[38], and recent imaging work in an adolescent cohort suggests that sleep mediates development of functional networks and associated mental well-being[39].

The proportion of adolescents sleeping for more than 7 h per night has fallen to less than 40% over the past 20 years[40], even though adolescents left undisturbed sleep on average for over 9 h per night[41]. This curtailed sleep reflects complex and interacting factors including a biological shift to later sleep timing and evening chronotype, light at night, use of caffeine and other stimulants, the pressures of 24/7 online communication[42], and socioeconomic disparities. While the reduction in adolescent sleep is paralleled by a steady increase in the prevalence of mental disorders in this group, relatively few studies have specifically examined sleep disturbances in adolescents and young adults and the subsequent, lifelong impact on development of mental disorders[43].

Perinatal maternal insomnia has been associated with adverse childhood social-emotional development[44], and childhood sleep problems with the onset of later depression, bipolar disorder, self-harm and suicidality[45,46]. Any type of sleep disturbance has been reported to confer an increased likelihood (OR 1.62-1.88) for developing a mood or psychotic disorder in adolescence or adulthood[21]. Shorter or poorer quality sleep during early adolescence predicts instances of depression later in life[47,48], while longer and better quality sleep appears to be protective, and associated with lower rates of anxiety and depression[49]. Conversely, evidence for depressive symptoms predicting the onset of sleep problems is more limited[50]. Adolescents with insomnia show strong correlations between sleep quality measures and ADHD, conduct disorder, anxiety and affective problems[51], with sleep disruption also associating with risk-taking, alcohol and drug use[52]. Recurring sleep disturbance in adolescents with affective disorders predicts relapse and poorer treatment response[53]. In the extreme, sleep loss and concomitant effects on mood increase suicide risk[54–56], with adolescents who report less than 6 h of sleep per night three times more likely to consider suicide than those achieving 8 h of sleep[56]. In adolescents at ultra-high risk of psychosis, several sleep metrics predict the longitudinal course of psychotic symptoms[57]. Nightmares can prelude psychotic experiences[58] or future suicidal ideation, underscoring the predictive potential of sleep disturbances in the context of adolescent mental health[59,60].

In summary, convergent evidence indicates that adolescent sleep impairment contributes to detrimental patterns of behaviour, preludes the emergence of mental health disorders and correlates with symptom severity and duration. However, the range of sleep disturbances associated with poor adolescent mental health is wide and often derived from subjective, non-standardized evaluation of sleep quality, duration, and behavioural rhythm. Further studies of objective sleep measures encompassing the period before and after onset of neuropsychiatric disorder are required, and the development of an international consensus on a standardised set of measures and instruments for capturing a wider range of age-relevant sleep disturbances is an important goal.

Key messages:

- Convergent evidence from epidemiological and clinical studies points to SCRD as important predictors for the development of anxiety, depression and psychotic disorders.
- SCRD are of transdiagnostic significance across the lifespan, though adolescence may be a period of particular vulnerability.
- SCRD are modifiable, and interventions that target them therefore hold promise as pragmatic, accessible and non-stigmatising primary and secondary prevention strategies for alleviating the burden of mental disorder.

Key limitations:

- The majority of existing studies have focused on:
    - Cross-sectional measures, rather than longitudinal and dynamic interactions between sleep/circadian activity and mental status
    - Adults as opposed to younger populations
    - Insomnia as opposed to other sleep disorders and dimensions of sleep health
    - Affective disorders, more commonly than psychotic disorders
- The pathophysiological mechanisms interlinking SCRD with the symptoms of anxiety, depression and psychosis are not well understood.
- Dimensions of poor sleep health including inactivity during day, greater variability in sleep timing, and poor sleep hygiene, are inconsistently measured.
- Most studies rely on proxy measures of circadian rhythm, and fail to capture both sleep and circadian variables together, in the same individuals.

Sleep and circadian disturbances co-morbid with mental disorder

Sleep disturbances

The development of sleep medicine and polysomnography in the 1960s and 70s raised the possibility that diagnostically specific signatures of sleep dysfunction could be discovered[61]. The well-mapped neural circuitry underpinning arousal state transitions and sleep-dependent EEG oscillations also enables mechanistic insight into disorder-associated abnormalities. In depression, the observation that rapid eye movement (REM) sleep occurred earlier in the sleep episode than in healthy controls, with increased duration and density of REM sleep and reduced slow-wave sleep (SWS), fuelled this line of investigation[62]. Although these findings have been replicated, initial enthusiasm has been tempered by subsequent studies which found them not to be disorder-specific, with meta-analyses reporting comparable disturbances across mood, anxiety and psychotic disorders[10,11,63].

The links between disrupted NREM neurophysiology and psychiatric symptoms are perhaps best characterized in schizophrenia, which has been associated in several studies with reductions in spindle measures[64,65]. Psychotic symptoms and deficits in sleep-dependent memory consolidation correlate with aberrant NREM EEG signatures, even in the absence of overt disruption of sleep quantity or architecture[66–68]. There is debate however regarding the reproducibility[69] and specificity of sleep spindle phenotypes in schizophrenia, with some evidence that spindle activity is also disrupted in young people diagnosed with depression[70]. Most studies have been undertaken in adults in the chronic phase of illness, or first-degree relatives.

The majority of sleep studies have been performed in sleep laboratories, which are unfamiliar environments where bedtimes may be misaligned with an individual's habitual sleep times. Other factors complicating interpretation of polysomnographic findings include heterogeneity in age, stage of illness, sex and medication status, all of which influence sleep architecture. Further, few studies have concurrently examined circadian phase, which also influences sleep architecture, including the timing of REM sleep[71]. Abnormalities in the timing and density of REM sleep in depression, for example, may arise from circadian disturbances, rather than a primary disturbance of sleep architecture. Many psychiatric disorders follow a relapsing-remitting course, and studying within-person sleep parameters, across different stages of illness, will be necessary. Few studies have focused on early-course disease in adolescents[72].

Polysomnographic investigation of mental disorders therefore remains incomplete, and our understanding of this complex area will be strengthened by studies which better account for these factors, across the developmental and disease trajectory. Harnessing emerging technologies, including wearable EEG to allow recording at scale, high-density EEG to study sleep with greater fidelity, and measuring circadian biomarkers in concert with brain activity, will strengthen this effort. Higher-order analyses of sleep microarchitecture (for example EEG coherence, inter-hemispheric asymmetry[73]) may prove more sensitive or specific, but such studies remain uncommon. Some studies have also begun to compare sleep and wake EEG suggesting, for example, that elevated 'beta' power is evident during both sleep and wake in insomnia, potentially reflecting hyperarousal[74,75].

In parallel to studies of the sleep EEG, a large body of evidence has accumulated from epidemiological, self-report and actigraphy studies, which characterise the prevalence, associations and nature of sleep problems across mental disorders. Similar to findings investigating physical health outcomes, sleep duration and prevalence of mental disorder follow a U-shaped relationship. A cross-sectional analysis from a national survey, for

example, found a prevalence of mental disorder of 55% in individuals who sleep <5h/night, 48% for those sleeping ≥9h/night, versus 28% for 7h/night[76]. Although these associations are robust, underlying sleep phenotypes, causal directions and mechanisms remain uncertain.

Insomnia has been estimated to be comorbid in up to 60% of individuals with depression, increasing to 90% during a mood episode[77], 70% of those with anxiety disorder[78] and in inter-episode bipolar disorder[79] and up to 44% of those with schizophrenia[80]. Greater severity of insomnia is associated with higher levels of psychopathology, increased risk of relapse, and poorer treatment outcomes[5]. Meta-analyses of actigraphy studies in mood[84,85] and psychosis-spectrum disorders[86] have provided greater detail around the nature of these processes, and demonstrate that regardless of diagnosis, individuals with mental disorder take longer to fall asleep, have more fragmented sleep, have longer overall sleep duration, and are less active during the hours of wakefulness. These variables have been shown to worsen prior to and during episodes of deterioration in mental status[87,88], further supporting the hypothesis that deterioration in sleep plays a causal role in relapse. Finally, interest is growing in sleep regularity as an important variable[89], with greater intra-individual variability in sleep being associated with greater negative mood and poorer subjective sleep quality[90].

In interpreting these findings, it is important to remain aware of the current limitations in our understanding of insomnia. Insomnia prevalence estimates vary depending on diagnostic definition, and the term insomnia can be employed as a broad-brush proxy for describing a range of disturbances in sleep-wake physiology. Insomnia is not necessarily synonymous with reduced quantity of sleep – in fact, the majority of insomnia patients have relatively normal *objective* sleep duration, but a markedly shortened *subjective* sleep duration[81]. The basis for the discrepancy between subjective and objective sleep remains unclear, and may only be resolved with more sensitive and comprehensive methods of measuring sleep[82]. It has been hypothesised that the poorer health outcomes in individuals with insomnia occur only in the subgroup with shorter objective sleep duration, of less than 6 h[83].

Key messages:

- Common features of sleep disturbances across psychiatric disorders include poorer subjective sleep quality, difficulty falling and staying asleep, and greater intra-individual variability in sleep timing.
- Greater severity of subjective and objective sleep problems is associated with greater severity and poorer prognosis of mental disorder, and sleep disruption increasingly recognised as a risk factor for suicide.
- Sleep EEG abnormalities also associate with mental disorders, albeit with some conflicting findings regarding consistency and specificity.
- Sleep may constitute a *transdiagnostic process* with shared cognitive, neurobiological, and treatment mechanisms contributing to both sleep dysfunction and psychiatric disorder. By extension, interventions that target a transdiagnostic sleep process may demonstrate benefit across a range of psychiatric disorders.

Key limitations:

- A diverse range of subjective and objective measures have been employed, limiting systematic comparisons and pooling of data.
- Polysomnographic studies are typically limited to sleep labs and underpowered to deal with effects of age, sex, medications status and circadian phase.
- Studies investigating the role of homeostatic sleep process in mental disorders have been limited.

- Understanding of how these disturbances relate to phases of illness (premorbid, prodromal, acute, remission) is currently reliant on syntheses of disparate studies, each with varying methodologies.
- A better understanding of the subtypes of insomnia, and their relevance to the development of mental disorder, is necessary.

Circadian disturbances

Through its interaction with the homeostatic sleep process, the circadian timekeeping system plays a crucial role in regulating the timing of sleep and wakefulness, as well as vigilance, mood and energy levels, within the 24-hour day. In health, sleep homeostasis and circadian systems are delicately counter-balanced[91], with misalignment between these systems leading to disorders of sleep, alertness and mood[92].

Self-report, genome-wide association and behavioural rhythm measures commonly reveal disturbances in the timing of sleep and wakefulness across most categories and phases of mental disorder, suggesting dysfunction at some level of the circadian system. Note, however, that the terms circadian disruption and dysfunction are widely used, but often poorly defined. The multitude of definitions of circadian dysfunction can lead to false-positive associations between circadian and psychopathological variables[35].

Evening chronotype, delayed sleep phase and reduced amplitude of the rest-activity rhythm are seen in both adolescents and adults with depression, bipolar disorder and psychosis[30,35,93,94]. Genetic liability for chronotype also intersects with genetic risk for these psychiatric disorders[95]. Mood disorder is sensitive to seasonal changes, with approximately 8% of patients experiencing episodes of depression in autumn or winter months[96], correlating with shortening of the photoperiod[97,98]. In young people with depression, a 'circadian depression' subgroup has been proposed, with a specific clinical phenotype underpinned by circadian dysregulation, for whom targeted circadian interventions may be indicated[30,34]. Overall, genetic association, chronotype and actigraphy findings suggest the existence of transdiagnostic associations between sleep-circadian parameters and mental disorders, rather than disorder-specific associations[35,99].

Chronotype reflects both trait and state aspects of the circadian system, can be sampled at scale, and demonstrates moderate correlations with the phase and period of the biological rhythm[100]. Despite these strengths, chronotype is also influenced by a range of other factors, including sleep homeostasis and developmental age, and is not necessarily a precise reflection of the phase of the internal clock. Similarly, actigraphy is a measure of behavioural rhythmicity, and is particularly suited to examining the amplitude and variability in rest-activity patterns over several days. Amplitude of the rest-activity rhythm, however, is a composite of daytime activity, which can be influenced by mood, as well as sleep, and does not directly reflect amplitude of the endogenous circadian rhythm. Though valuable for investigating questions such as the diurnal balance of rest and activity over 24-hour day, actigraphy is at best a proxy of the internal circadian rhythm. Interpretation of actigraphy studies has also been complicated by inconsistent methods of analysis (e.g. cosinor vs non-parametric approaches), leading to difficulties in pooling and comparison of data. Approaches that examine parameters of the biological rhythm are therefore required to disentangle circadian from sleep systems, elucidate the mechanisms by which circadian dysfunction is implicated in mental disorder, and guide the timing of interventions that target circadian dysfunction.

Of the studies that have included such biomarkers, mood disorder, in particular bipolar disorder, have received the most attention. Studies in depression have pointed towards dampened amplitude of endocrine and temperature rhythms[101], attenuated and shifted peak timing of gene expression[102], and delayed circadian phase relative to sleep[103,104]. Though results from studies in bipolar disorder have been mixed[35], there is tentative support for circadian phase delay in depression, and advances in mania[105]. In the schizophrenia-spectrum disorders, clock genes have been implicated in animal models of the disorder, and blunted and phase-shifted endocrine rhythms and arrhythmic gene expression have been reported[94,106]. However, studies in schizophrenia have not yet reached a level of maturity that allow clear conclusions to be drawn.

Drugs that are commonly used in mood disorders, including lithium, sodium valproate, and the serotonin reuptake inhibitor antidepressants, may exert their effects through interactions with circadian machinery, through mechanisms that are not fully elucidated[35,107]. A subgroup of patients with bipolar disorder have been identified who are lithium-responsive, characterised by greater morningness and a shorter circadian period[108]. Further studies that enhance our understanding how psychotropic medications influence clock-processes are required. More broadly, the effects of medications as a co-variate in clinical studies are needed.

In order to maintain stable timing with the environment, the phase of the central pacemaker in the superchiasmatic nucleus (SCN), which has an average period of 24.15h, is synchronised or *entrained* to the day-night cycle primarily by light, the strongest zeitgeber in humans[109]. Photic inputs project not only to the SCN, but also to a range of regions involved in mood regulation[110]. Despite this critical role of light in circadian function, its role in the pathogenesis mental disorder has received relatively little attention. Given the evidence for considerable inter-individual variability in sensitivity to light[111], and the possibility that populations with mental illness experience marked differences in light exposure to non-clinical populations, studies examining this key variable are necessary. Multi-sensor studies which sample light exposure during the course of daily life may be invaluable.

Key messages:

- Late chronotype, low amplitude and irregular rest-activity rhythms have been associated with mood and psychotic disorders.
- There is tentative support for delay in circadian phase in depression, and phase advance in mania; a circadian depression subtype, and lithium-responsive bipolar disorder subgroup, has been proposed.
- Psychotropic medications, including lithium and sodium valproate, may exert some therapeutic effects through interactions with the circadian system.

Key limitations:

- The majority of studies have investigated sleep and circadian function in isolation, rather than examining these concurrently, in the same individuals.
- Most inferences are drawn from a constellation of small studies, using a variety of self-report, actigraphy, gene association and endocrine measures; synthesis into coherent conclusions remains challenging and fails to integrate fundamental knowledge of circadian biology.
- Understanding of circadian disturbances is better developed in unipolar depression and bipolar disorder than in psychosis and anxiety disorder.

- Circadian variables have been conceptualised primarily as stable trait markers. Acute, state dependent changes in circadian function, e.g. misalignment between sleep and circadian phase prior to relapse, have received less attention.
- The majority of studies have examined proxies of circadian function, estimated through chronotype measures, sleep diaries or actigraphy; fewer studies have measured true circadian biomarkers.
- Measures of endogenous circadian rhythm focus on phase of the biological clock. Current methods are less suited to measuring circadian amplitude.
- The role of light in sleep circadian disturbance in mental disorder warrants greater attention.

Mechanisms linking sleep and circadian disturbances to psychiatric disorder

Our understanding of the pathways through which sleep disruption gives rise to symptoms of mental illness remains in its early stages, a situation exacerbated by challenges of back-translating mental symptoms to animal models. At the macroscopic level, brain imaging is beginning to reveal convergent network signatures of sleep disruption, but links between brain-wide signatures with circuit, cellular and molecular-level mechanisms remain speculative. Studies of this type are typically underpowered to navigate heterogeneity and illuminate inter-individual differences in response to sleep disruption, and theoretical frameworks binding putative mechanisms are scarce[112].

The genetic architecture of sleep-circadian variation and psychiatric risk

Genome-wide association studies have begun to identify common gene variants associated with sleep duration, quality, timing and the sleep EEG[113–115], though the majority of data are not derived from ethnically diverse populations, employing heterogenous sleep metrics of limited resolution[116]. Approaches including gene association[117,118] and Mendelian randomization[119] have begun to generate evidence that sleep and circadian (or diurnal) phenotypes are causally related to risk of psychopathology and share genetic signatures. For example, genetic liability for morningness is associated with reduced odds of developing depressive symptoms[119].

In support of SCRD preceding the onset of mental disorders, small individual studies show associations between genetic liability for schizophrenia and sleep EEG features in healthy populations[120,121]. Mechanistic insights are also emerging from animal studies, in which the manipulation of rare coding variants associated with risk of psychosis – for example in voltage-gated calcium channels or glutamate receptors – generates abnormal sleep and circadian phenotypes[122,123].

Impact of sleep loss on emotional regulation, reward and cognition

Experimental studies suggest that the mechanisms underpinning sleep reduction and fragmentation overlap with the mechanisms underlying emotional and cognitive regulation, driving the development of psychopathology through a mix of “top-down” (driven by cortical hyperarousal) and/or “bottom-up” (driven by brainstem arousal circuitry) routes. Recent mouse work continues to dissect the neural circuitry of arousal and sleep state control[124–126], informing an integrated view of the forebrain, midbrain and hindbrain circuits associated with REM and non-REM states. This high-resolution approach reveals how top-down and bottom-up circuitries are interlinked, potentially overlapping with motor and reward pathways that may drive symptoms including sleepiness, blunted motivation and anhedonia. This framework affords important opportunities for measurement and interpretation of neural circuit studies in humans.

Poor sleep is consistently associated with compromised emotional regulation, spawning greater reactivity to negative events and blunted reactivity to positive events[127]. In both rodents and humans, sleep deprivation impairs the mesolimbic reward system, disrupting dopaminergic signalling and reward coding across ventral tegmentum, striatum, limbic system and frontal cortices[128]. Potentially critical mechanisms relate to REM sleep, which is normally associated with activation of (e.g.) amygdala and reduced activity of noradrenergic

and serotonergic neuromodulator systems. REM sleep is often cited as making preferential contributions to emotional memory consolidation[129]. However, the relative contributions of REM and non-REM sleep in this context remain far from clear-cut. For example, rodent work shows that amygdala and hippocampus are co-activated (reactivated) during non-REM sleep following aversive conditioning, a presumed mechanism of sleep-dependent memory consolidation; this reactivation was not evident during REM sleep[130].

In rats, reward signalling pathways in the ventral striatum following appetitive learning are also co-activated with the hippocampus during sleep, with the most salient information of recent experience (e.g. neurons signalling location of reward) more likely to be reactivated[131]. This affords a potential mechanism for tuning of memory consolidation, prioritising the "most important" information for integration into knowledge and long-term storage. Recent work has begun to translate monitoring of neural reactivation/replay into humans using MEG/EEG-based pattern recognition[132], but whether aberrant biassing of sleep-dependent information processing contributes to symptoms in depression or psychosis remains to be systematically explored. For example, might the failure of patients with psychosis to adaptively update perceptual beliefs reflect aberrant sleep-dependent memory consolidation?

The age-dependent contributions of sleep to the development of healthy emotional regulation also remain underexplored, though emerging evidence suggests that adolescence is a critical period, when sleep disruption may be particularly damaging. For example, preventing REM sleep for even a few hours can increase noradrenergic tone, causing hyperactivity of the affective salience network innervated by the locus coeruleus[129,133]. Chronic REM sleep restriction in adolescent rodents is associated with increased anxiety behaviours and higher noradrenaline levels in the amygdala and hippocampus[134]. Reduced sleep duration also decreased PFC inhibitory control of amygdala activity[135,136] and PFC excitatory drive to the striatum, potentially confounding the developmental rebalancing that occurs within cortico-limbic circuits during normal adolescence. Recent mouse work has shown that experimental sleep disruption during an adolescent "critical period" – but not during adulthood – impairs the development of dopamine circuits in the ventral tegmental area (VTA) and disrupts reward signally during social interaction[137].

The impact of sleep disruption on the limbic system, which contributes to affect regulation[129] and undergoes synaptic refinement during adolescence, may be one mechanism. However, the roles of sleep stage-specific disturbances in REM or non-REM sleep remain unclear. One hypothesis suggests that adolescent sleep is trapped between a late-shifted chronotype and societal pressure to wake early, therefore reducing the opportunity for REM sleep, which would normally occur during later sleep cycles.

The synaptic homeostasis hypothesis

An influential hypothesis which seeks to explain a fundamental function of sleep relates to the sleep-dependent downscaling of net synaptic strength during slow-wave sleep, thereby maintaining neocortical connectivity and signal-to-noise within a dynamic working range[138]. The slow-waves of NREM sleep reflect homeostasis-associated plasticity and connectivity, with slow-wave activity accumulating during extended wakefulness and dissipating during initial sleep cycles. In related, preliminary analyses, slow-wave gradients (a metric of neocortical synaptic strength) have been shown to change over the course of neurodevelopmental pruning of synapses during adolescence[139,140]. Whether or not these neurodevelopmental synaptic dynamics are implicated in mental disorders has not yet been extensively tested, though pilot work indicated potential disruption of synaptic homeostasis in adult patients with depression[141–143].

Inflammation and neuroimmune dysfunction

In adults, curtailed or extended sleep and experimental sleep disruption are associated with increases in circulating markers of inflammation, including C-reactive protein (CRP), interleukin-6 (IL-6), and tumour necrosis factor α (TNFα)[144,145]. Meanwhile, a recent UK Biobank Mendelian Randomization study corroborates substantial evidence that aberrant IL-6 signalling is likely to have a causal influence on depression[146] though whether different inflammatory markers and mechanisms mediate sleep-depression links in different age ranges and populations remains unclear[147].

Other evidence interlinking inflammation, depression and sleep includes:

- Interferon alpha potentiates the immune response, induces depressive symptoms in almost 50% of recipients, and disrupts sleep in a manner potentially related to that seen in depression (including increased REM onset latency[148]).
- Cancer patients show positive associations between sleep disturbance and inflammatory markers (IL6, CRP).
- Maternal immune activation during pregnancy, for instance as a consequence of OSA, is associated with disrupted neurodevelopment in offspring in humans[149] and animal models[150].
- Menopause is associated with low-grade inflammation, sleep disruption and anxiety/depression[151] – though the causal relationships between these symptoms remain to be established.

In many cases, these interrelationships are bidirectional, with circadian rhythm disruption and misalignment in both animals (e.g. via clock gene knockdown or SCN lesion) and human (e.g. shift work) amplifying inflammation and associated pathologies including cancer, obesity, insulin resistance and cardiometabolic impairment[152,153]. Sex differences also need investigated further[154,155]. Nevertheless, convergent evidence supports a model in which insomnia and inflammation constitute “two hits” that identify vulnerable individuals at risk of mental health disorders[156].

This model is also supported by evidence from young people. The EDEN French longitudinal cohort recruited ~2000 mothers and followed their offspring from early pregnancy until the age of five years[157]. Based on a sample of 687 EDEN children and adjusting for covariates, shorter sleep duration (<10h/night) and variable sleep duration (≥11h30/night then 10h30/night) were associated with higher serum levels of IL-6 and TNF-α at age five. Mental health outcomes were not examined in this study, though other longitudinal work does suggest that sleep disruption during the first year of life predisposes to mental health problems aged 10 years[158].

In an actigraphy and questionnaire-based analysis relating CRP levels to sleep duration and quality in ~300 healthy 14-18 year olds, shorter or more variable sleep duration was weakly correlated with higher blood CRP[159]. A subsequent PSG-based study showed that more severe adolescent insomnia symptoms were accompanied by significantly elevated CRP[160]. These individual studies are corroborated in the US National Longitudinal Study of Adolescent to Adult Health (Add Health, n ~10,000), which shows shorter sleep correlating with higher CRP levels, albeit only in males[161]. Note that systemic inflammation is also associated with OSA in boys, and BMI / cardiorespiratory fitness need to be considered carefully in this context.

Most evidence points to an elevated inflammatory state in young people with a range of psychiatric diagnosis[162]. Positive correlations between sleep disruption and inflammatory markers also appear to hold in young people diagnosed with mental disorders, though evidence is emergent and the directionality of effects equivocal. For example, adolescents diagnosed with MDD harbour both disrupted sleep and elevated TNFα, but TNFα levels may not mediate a large proportion of the sleep-depression association[163]. Schizophrenia is also associated with pro-inflammatory status in adults and adolescents[164] and, in adult in-patients, inflammatory markers positively correlate with actigraphy-derived severity of sleep disruption[165], an effect that may be more pronounced in females[166]. In symptomatic adolescents with bipolar disorder, more balanced pro- to anti-inflammatory ratios were associated with better neurocognitive flexibility, but whether such correlations relate to sleep remains to be established.

Microglial and astrocyte-mediate synaptic pruning presents one mechanistic process plausibly perturbed by inflammation. For example, the final maturational stages of frontal cortical development rely, in part, on glial contributions to synaptic pruning and myelination during adolescence. In mice, adolescent sleep disruption leads to elevated microglial activation, synaptic phagocytosis and astrocytic transcriptome changes; a similar process might underlie the reductions of grey matter volume and synaptic density observed in human studies of insomnia and schizophrenia[140].

The sleep-dependent glymphatic system, which removes harmful interstitial metabolic waste products from the brain by convective fluid transport[167], can be disrupted by inflammation, which may compromise CSF transport and associated clearance mechanisms[168]. Nascent work in mice suggests that glymphatic dysfunction may modulate vulnerability to sleep loss[169], and recent hypotheses posit links between glymphatic dysfunction and mood disorders[170].

In summary, concurrent longitudinal measurement of immune function, inflammation, sleep and mental health in ages spanning perinatal to adolescent promises to illuminate causal mechanisms interlinking these factors. This work also paves the way for rational design of interventions, from pharmacological modulation of immune function to the use of anti-inflammatory diets to improve sleep quality[171,172].

Key messages:

- A range of largely indirect evidence implicates neuroinflammation, aberrant limbic-dependent emotional processing and compromised synaptic homeostasis as primary candidate mechanisms contributing to the impact of SCRD on mental health.
- Recent, high-resolution detailing of sleep and circadian neurobiology in animals affords vital opportunities for translational insights.

Key limitations:

- The molecular, cellular and circuit mechanisms through which SCRD culminates in the aberrant neural activity underpinning affective, cognitive and perceptual symptoms remain unmapped, impeding rational design of interventions.
- Whether or how mechanisms implicated by studies in adults impact the immature brains of infants, children and adolescents remains underexplored, however tracing mechanisms across timescales spanning several years is challenging.

Interventions targeting sleep and circadian rhythmicity in mental disorders

Cognitive behavioural therapy for insomnia

Given that insomnia affects over 60% of individuals with mood disorders[77–79], with which a bidirectional relationship is hypothesised[173], treatments that target insomnia represent an important therapeutic opportunity.

Cognitive behavioural therapy for insomnia (CBT-I) is a multicomponent therapy recommended in international consensus guidelines, including those from NICE[174], the British Association of Psychopharmacology[175] and the European Sleep Society[176], as the first-line treatment for chronic insomnia. CBT-I includes educational (e.g. sleep hygiene), cognitive (cognitive reappraisal and control of worry) and behavioural strategies (sleep restriction, stimulus control, relaxation) components. A robust evidence base has accumulated for its effectiveness in improving self-reported sleep outcomes[177] and associated daytime symptoms[178], though effects on the latter were small-moderate.

Recent meta-analyses suggest that CBT-I is also effective in treating insomnia in youth and adults with co-morbid mental disorder, with moderate to large effect sizes. Moreover, CBT-I also improves psychiatric symptoms themselves, with small to moderate effect sizes [13,179–181]. These studies have found, however, that although effects of CBT-I on insomnia are generally sustained over time, effects on psychiatric symptoms diminished and were no longer significant at follow up[13,181]. Adequately powered studies that test adaptations to CBT-I that maximise durability of effect on both sleep and psychopathology, with longer-term follow up, are necessary. Identifying components of CBT-I that are particularly relevant for treating psychopathology, and maximising acceptability in (a) populations with mental disorder and (b) different age ranges (particularly children and young people), are key aims.

Second, the majority of studies have examined insomnia with co-morbid depression and anxiety, with a limited number of studies investigating bipolar disorder[182] and psychosis[183], as well as alcohol use disorders, eating disorders, PTSD and ADHD. The effectiveness of CBT-I on improving psychopathology in these disorders has yet to be demonstrated. Third, although the interventional RCTs discussed above provide evidence for a causal role of sleep disturbance, examination of underlying mechanisms, such as the effects of insomnia on emotional regulation, has not been incorporated into these studies.

In the first study of its kind, CBT-I in older adults with insomnia without psychiatric co-morbidity has also been shown to prevent the development of major depression at 3-year follow-up[14]. These promising findings warrant further studies, over a broader range of mental disorders, demographic backgrounds and income settings.

Despite proven effectiveness and widespread recommendation for CBT-I, a major barrier remains access to CBT-I, which has not been established in routine clinical practice in most countries[82]. One factor underlying this treatment gap is the limited education and training in sleep medicine and the assessment and treatment of insomnia, for clinicians working in both primary and secondary care settings[18,20]. Another reason relates to the limitations in scalability of psychological interventions. Digital CBT-I interventions such as Sleepio[184] and SHUTi[185] are now widely available in the UK and US, and go some way to closing this gap. Comparable effects to in-person CBT-I, including treatment and prevention of anxiety and depression symptoms[185,186], have been reported. Delivering CBT-I in digital format will be particularly valuable as the first level of a stepped care approach for insomnia, with

graduation to increasingly tailored in-person input as complexity and co-morbidity increases[82].

Though CBT-I is clearly effective, research in other areas including pharmacological treatments, which are currently only recommended for the short-term treatment of insomnia, have stagnated. Further trials which integrate pharmacological and cognitive-behavioural approaches[187] to support personalised therapies are warranted. Recently, CBT-I has been adapted to populations with serious mental illness (SMI). TranS-C, a transdiagnostic sleep intervention which targets circadian rhythm disruption as well as insomnia, improved sleep and functional outcomes in people with SMI living in the community[188]. Adaptations such as SLEEPexpert[189] and OWLS[190], which focus on treating sleep in inpatient psychiatric settings have also shown early promise.

Key messages:

- CBT for insomnia is the guideline treatment for insomnia, both for individuals with and without psychiatric co-morbidity.
- In those with co-morbid mental disorder, CBT-I has been shown to treat both insomnia, and depression and anxiety symptoms. However, current evidence suggests that effects on psychiatric symptoms are not sustained at long-term follow up.
- There is emerging evidence that CBT-I can prevent the development of new-onset depression.
- Digital CBT-I has been shown to be effective for treatment of insomnia and psychiatric symptoms, and facilitates delivery of insomnia treatment at scale.
- CBT-I has been a useful tool for demonstrating causal relationships between insomnia and mental disorder.

Key limitations:

- There is strong evidence that CBT-I is effective in treating insomnia across a range of populations and settings. There however remains a large treatment gap between clinical demand and availability of this guideline treatment.
- CBT-I and related treatments are yet to be integrated into the standard treatment of mental disorder.
- The effects of CBT-I in mental disorder have predominantly focused on anxiety and depression, with fewer studies in bipolar disorder and psychosis.
- CBT-I is not helpful for everyone with insomnia, and substantial motivation and engagement are required in order to benefit. The ‘minimal characteristics’ of effective CBT-I are not yet clear.
- The extent to which improvements in sleep mediate the association with improvements in psychopathology is unclear.
- CBT-I primarily addresses dimensions related to sleep, with only brief discussion of circadian factors, which are more likely to be disturbed in those with psychiatric co-morbidity.
- While the evidence-base for CBT-I have burgeoned, research into other treatments, including pharmacological and circadian interventions, has been slow.

Chronotherapeutic interventions

Circadian disturbances have been implicated across a wide range of disorders, and interventions which influence the circadian system – light and dark therapy, sleep deprivation ('wake therapy'), melatonin agonists, and psychological and behavioural therapies that target diurnal behaviours – have been a longstanding focus of interest. Despite a strong theoretical basis for these treatments, the evidence base for chronotherapy remains limited, with studies in small samples over short durations, and translation into clinical practice remains slow[92].

Particular interest has focused on the affective disorders, with the strongest evidence supporting the use of light therapy in unipolar and bipolar depression, where exposure to bright light in the morning or daytime has been shown to lead to clinically significant improvement in mood[15,191,192]. Equivalent studies in psychosis have not been undertaken. Though recommended as a first-line treatment of moderate to severe depression, the optimal parameters including the timing, duration and intensity of dose, light spectra, and duration of exposure remain unclear, and larger and longer trials are needed to determine these. Appropriately timed light therapy also results in modest improvements in sleep timing and continuity in neuropsychiatric disorders[193]; the extent to which improvements in sleep-circadian parameters mediate the effects on psychopathology is an important and as yet unexplored avenue of investigation.

The role of dark therapy has been limited to three published studies in mania[191], using either a dark environment or using blue-light blocking glasses, which provide preliminary support for its use as an adjunctive treatment for mania.

Total (36 hours) and partial (first or second half of the night) sleep deprivation paradigms have shown comparable efficacy in the treatment of unipolar and bipolar depression, with 50 – 60% of patients demonstrating a significant response[191,194]. Although response to sleep deprivation is rapid, benefits are not sustained, with deterioration of mood following recovery sleep[195]. Attempts have been made to augment the effects of wake therapy through the addition of light therapy and strategies to advance the sleep phase, with so-called 'triple chronotherapy'[196]. Several protocols have been used, however, limiting the ability to synthesise evidence in meta-analyses and therefore inform consensus guidelines. Prolonging the therapeutic effects of sleep deprivation on mood therefore remains an important challenge, and wake therapy has yet to be widely adopted in clinical practice.

Exogenous melatonin acts primarily as a chronobiotic, inducing advances or delay in circadian phase depending on the time at which it is taken[197]. Melatonin also has a mild hypnotic effect, which is more pronounced when levels of endogenous melatonin are low. Studies have been small, with considerable variation in phase of illness, timing of administration, dose, and melatonin formulation. Of the few trials investigating melatonin in psychiatric populations, prolonged release melatonin may be helpful in improving sleep outcomes in those with insomnia and circadian rhythm disorders. There is currently however insufficient evidence to support treatment of psychiatric symptoms with melatonin in acute unipolar and bipolar depression, mania, anxiety disorder or psychosis[15,191,198].

Developed from the observation that psychosocial stressors and disrupted social and behavioural rhythms correlate with mood episodes, interpersonal and social rhythm therapy (IPSRT[199]) identifies and stabilises these processes over 16-24 weeks of treatment. Efficacy in acute depression, and prevention of relapse of mood disorders, has been demonstrated[15,191]. Similarly, CBT-I has been adapted to extend the scope of the intervention beyond insomnia, to address the broader range of sleep and circadian problems observed across psychiatric diagnoses, including misalignment and instability in biological rhythms. For example, TranS-C[200] – a multicomponent intervention, has shown promise in

improving functional impairment, psychiatric symptoms, sleep disturbance and sleep-related daytime impairment, in adolescents and adults. A key challenge is ensuring that these interventions are translated into clinical practice, appropriate for age, race, ethnicity and culture of both the patients and clinicians.

Despite secure theoretical underpinnings, implementation of chronotherapeutics into clinical practice has been slow. For interventions such as light therapy or sleep deprivation, finding appropriate control conditions can be challenging, making a standard RCT design difficult to implement. Many chronotherapies are not patentable, reducing financial incentives for research and leading to an under-representation of these potentially highly effective interventions in research studies and clinical practice.

Key messages:

- Chronotherapies including light therapy, sleep restriction and deprivation, and chronobiotics have a clear theoretical basis.
- Evidence is strongest for treating acute unipolar or bipolar depression with light therapy and sleep deprivation.
- Melatonin and melatonin agonists may be useful in treating insomnia and circadian rhythm disorders in neuropsychiatric disorder.
- Psychological and behavioural interventions that also target the circadian dimension, such as IPSRT and TranS-C, show promise in treating and preventing relapse in mood disorder.

Key limitations:

- The timing and dosing of chronotherapies are rarely guided by knowledge of underlying circadian physiology, and therefore rely on empirical estimates.
- Few studies have investigated chronotherapy in psychotic disorders.
- In comparison to pharmacological treatments for mental disorder, chronotherapeutic approaches are under-researched. One reason is that these treatments are less likely to be patentable, and do not offer the same financial returns as drug treatments.
- Due to diverse treatment protocols, the effects of chronotherapy on mood and sleep parameters have been challenging to synthesise in meta-analyses, which are commonly used to guide clinical guidelines.
- Mechanisms of chronotherapeutic interventions are incompletely understood, and further mechanistic research is likely to enlighten our understanding of pathophysiology of mental illness, and permit stratification of patients and targeted treatment.
- The effects of sleep-circadian manipulations such as phase shifting and sleep deprivation have not been adequately characterised in both non-patient and clinical populations.

The emerging landscape

Sleep health

The sleep health framework[201] aims to look beyond conceptualising sleep solely in terms of the presence or absence of sleep disorder, and adopt a positive frame of reference where healthy sleep is viewed across multiple measurable dimensions, each of which are associated with physical and mental wellbeing.

Six dimensions are articulated in the framework: *regularity* of sleep and rise times; *satisfaction* with sleep and sleep quality; *alertness* during wakefulness; the appropriate *timing* of sleep within the 24 h day; *sleep efficiency*, calculated time asleep as a proportion of time in bed; and *duration* of sleep across 24 h.

In addition to providing measurable targets for optimising sleep, these dimensions of sleep health provide a framework within which researchers can characterise sleep across multiple levels of analysis (e.g. genetic, cellular, network, and behavioural), and gain insight into which dimensions are associated with health, wellbeing or disease. In addition, the framework has underpinned the development of sleep-circadian interventions, such as TranS-C[200].

Sleep and physical health comorbidities

The cumulative burden of several common, chronic physical health conditions is amplified by their consistent association with elevated risk of mental health problems, particularly anxiety and depression. For example, the 2007 WHO World Health Survey (~250,000 participants from 60 countries) found significantly higher prevalence of depression in adults with one or more chronic conditions than in those without (3.2% depression in healthy respondents, *versus* 9% given diabetes, 11% arthritis, 15% angina and 18% asthma)[202]. Similar positive associations with depression apply to eczema[203], chronic pain conditions such as fibromyalgia[204], and obstructive sleep apnoea[205].

Given that all these physical conditions are also associated with some degree of SCRD, does SCRD mediate a proportion of their effects on mental health? Few studies attempt to address this hypothesis directly, but convergent evidence of associations and mechanistic links does suggest that these associations warrant further scrutiny. Other illuminating case studies include: type 1 diabetes, with diabetic children having shorter sleep than controls, an effect potentially exacerbated by poor blood glucose control[206]; psoriasis, in which targeted treatment also alleviates fatigue and depression[207]. One possibility is that shared inflammatory vulnerabilities link peripheral inflammation to brain dysfunction and mental disorder[208].

Sleep and circadian health in low and middle-income countries

Almost all the evidence cited in this report stems from research conducted in high income countries (HICs), and often fails to account for societal, familial, cultural, economic and geographical diversity.

Studies of sleep health in low- and middle-income countries (LMICs) are emerging, but remain sparse and unevenly distributed, with most conducted in the Americas or Western

Pacific. A 2018 systematic review and meta-analysis of sleep health epidemiology in LMICs uncovered limited high-quality data, though did indicate similar levels of disturbed/poor quality sleep (~30%) to those seen in the general population of HICs [209]. Smaller analyses based in individual African and Asian countries report similar prevalence of sleep problems, though estimates and causes, particularly in urban vs. rural settings, vary widely[210,211]. For example, associations between accelerometer-assessed sleep patterns and exercise, sedentary behaviours and screen time tend to be stronger in HICs, where these lifestyle behaviours have been more prevalent[212]. Other factors – for instance perceived neighbourhood safety and social media use – may prove globally important determinants of sleep quality[213,214].

Regarding mental health, the epidemiology of childhood and young people's mental health disorders in LMICs remains under-investigated and challenging to compare directly with HIC data given methodological and cultural nuances[215,216]. LMIC populations are large, young, and vulnerable to mental health problems; rates of recognition, belief in and treatment of mental health disorders are low, and differences between conditions in rural vs. rapidly expanding urban centres are substantial.

Where examined, general associations between sleep disturbance and poor mental health in adults hold in LMICs, though can be moderated by age and economic factors. For example, analyses of the cross-national Global School-based Health Survey (2003–2017, covering 11-18 year olds from 88 countries) suggest that associations between sleep problems and suicidal thoughts and behaviours are stronger in adolescent males and in countries that are either wealthier, or have bigger income inequality[217]. Suicidal ideation itself is estimated to affect 14% of global young people (21% in African countries).

Environmental disruptors of sleep and circadian rhythms

Many facets of the natural and built environment bear on both mental health and sleep/circadian rhythms. However, most individual facets lack categorical evidence showing that their effects on mental health are mediated via sleep or circadian disruption, in part because so many are interdependent and coincident. In most contexts, the cumulative burden of several environmental factors should be systematically related to SCRD and mental health. This is supported by a cross-sectional study of >300k adults in the Netherlands, which showed joint odds ratios based on combined exposure to air pollution, traffic noise and decreased surrounding green space were higher than the odds ratios of single exposure models. Urbanicity is often blamed, and associates with noise, light and air pollution alongside manifold societal pressures, and is also associated with increased risk of mental disorder in both European and Asian populations. However, the causal pathways underlying these correlations remain unmapped. Such mapping is vital given that most humans live in urban settings.

Potential mechanisms, which range from direct effects of pollutants on gene expression or synaptic transmission to psychological effects, also remain largely unexplored. This is particularly challenging given that mechanisms and consequences vary according to neurodevelopmental stage of exposure, from in utero to adulthood[218]. This report includes brief consideration of environmental factors that are common, known to associate with both poor mental health and sleep/circadian disruption, can be monitored alongside SCRD in large and diverse populations and are likely to impact children and young people.

Light and health

It is estimated that >80% of the global population is impacted by nocturnal electric light. A 2020 cross-sectional study of Artificial light at night (ALAN, assessed via satellite images) in the US showed that ALAN is positively associated with adolescent mood and anxiety disorders, bipolar disorder and depression, after adjusting for demographics, population density and socio-economic status[219]. Light at night delays circadian phase, and is associated with eveningness in adolescents[220]. ALAN is also associated with sleep disorders in Chinese city-dwellers, and may be particularly disruptive in children under 12 years[221]. These effects may be exacerbated by concomitant decreased exposure to UV-B during daytime, and additional blue light from computer and phone screens[222,223]. Importantly, some studies have begun to examine the life course effects of early-life light exposure, for example indicating that early exposure may moderate vulnerability to future circadian disruption.

The potential neurobiological mechanisms through which light pollution can shift circadian rhythms and disrupt sleep and emotional regulation are relatively well understood[224–226]. Adopting recommendations on light exposure during the daytime, evening, and night[227], and reaching consensus on protocols in light research [228,229], will be essential for elaborating the mechanistic links between light and mental health. To date, however, integrated analyses of dynamic interactions between light, SCRD and mental health remain sparse.

The impact of noise

The 2020 WHO/EEA briefing on health risks caused by environmental noise concluded that >100 million people in Europe are exposed to harmful levels of environmental noise pollution, particularly road traffic noise in urban areas[230]. Of these, 22 million suffer chronic 'high annoyance' and 6.5 million suffer chronic sleep disturbance, accounting for the bulk of the burden of disease linked to noise (1 million healthy years of life lost per annum due to the effects of noise on health).

However, while recent studies and systematic reviews / meta-analyses indicate associations between some noise sources (e.g. transport noise) and depression in adults or cognition, emotion, conduct and mental health in children and adolescents, power is limited by available data[231–233]. As such, potential mediating effects of sleep/circadian disruption remain equivocal, and must be carefully disentangled from confounders and covariates such as air pollution and socioeconomic status.

Air pollution

In common with light and noise pollution, air pollution is a growing problem fuelled by industrialisation and urbanisation. Exposure to particulate and/or gas pollutants increases risk for a multitude of health complaints via respiratory, CNS and other mechanisms[234]. Consequences include sleep disruption[235] and – again – associations with mental health disorders are intuitive, somewhat evident, mechanistically ill-defined and equivocal. However, a recent London-based study reported robust evidence that sustained exposure to nitrogen oxides, ozone and particulates increased odds of common mental disorders and psychotic experiences by approximately 20-30% in adults.

What leads to sleep disruption in the first place? Sleep reactivity and hyperarousal

Major life stress, particularly during early life, is a critical risk factor for mental disorders. Individual responses to adversity and stress vary widely and depend critically upon age,

experience, gender, and a wide range of psychosocial and neurobiological factors. 'Sleep reactivity' refers to the susceptibility of an individual's sleep and circadian processes to disturbance by stress and, though adaptive in the healthy population and harmless over acute timescales, may reflect aspects of premorbid vulnerability to insomnia[236]. Sleep reactivity can be described as "trait-like", but is nevertheless plastic, potentially becoming sensitized following major stress and/or insomnia development[237]. As such, sleep reactivity is a useful construct to consider in the context of early, premorbid development of mental health disorders, with important implications for deciphering interactions between the peripheral nervous system, CNS excitability and the hypothalamic-pituitary-adrenal (HPA) axis. However, at present, few studies examine sleep reactivity in children or young people.

'Hyperarousal' is a related construct framing psychological and neurobiological routes through which maladaptive responses to acute stress may ultimately lead to neuromodulatory dysfunction and insomnia[238,239]. Hyperarousal manifests during both wake and sleep, and implicates a mix of peripheral and central dysregulation[240]; thus waking and peripheral neurophysiology should be considered when refining metrics of sleep and circadian disruption.

Is "good sleep" protective? Sleep and mental health resilience

Resilience reflects a capacity to accommodate and overcome adversity, and derives from both psychological and physiological plasticity. Precisely when and how these adaptations arise varies widely according to the genetics and experience of individuals, though neural correlates of resilience – and opportunities to enhance resilience – are increasingly well understood[241]. There is some evidence that 'resilience interventions' (e.g. building stronger social and community networks) can improve quality of life in adults, and school-based interventions show promise in reducing adolescent depression and internalizing problems. Meanwhile, it is clear that inter-individual responses (for example fatigue, attentional effects, emotional regulation) to experimental sleep restriction vary widely in adults, displaying trait-like, intra-individual stability and potentially reflecting varied epigenetic responses. Resilience may also mediate the impacts of poor sleep on child behaviour. Triangulation across the neural circuitry of resilience, the neural consequences of sleep deprivation and the aetiology of mental disorders should illuminate mechanisms of vulnerability and potential interventions.

Sleep and circadian factors have been overlooked in most resilience studies to date. However, a recent systematic review and meta-analysis pooling across 63 international studies and a wide age range (11-60+ years) reports weak positive correlations between sleep duration/quality and resilience (r=0.11, 95% CI: 0.04e0.17 / r=0.27, 95% CI: 0.20e0.34) in the healthy general population[242].

Systematic studies assessing the contributions of sleep/circadian factors to innate and acquired resilience in young people should therefore be encouraged. Longitudinal studies able to delineate relationships between early-life SCRD and later vulnerability to subsequent disruption would also be valuable.

Key messages:

- The sleep health framework allows the dimensional quantification of sleep and its association with positive, as well as negative, health outcomes.
- It is imperative that studies of SCRD and mental health are extended, adapted and made relevant to LMICs.

- Sleep and circadian rhythms are sensitive to a wide array of physical health, social and environmental factors, many of which are increasing in prevalence and intensity across the modern world.
- Establishing mechanisms of inter- and intra-individual resilience should facilitate stratification of risk and treatments.
- Establishing the extent to which SCRD mediate the effects of social and environmental factors, and chronic physical health conditions, on mental health remains complex and challenging.
- The field remains biased towards ethnically homogenous populations in high income settings. Understanding and accommodating different cultural attitudes to sleep and mental health must be approached sensitively.

Technologies and standards for measuring sleep and circadian physiology

Since its introduction in the 1960s, polysomnography (PSG) has formed the cornerstone of sleep measurement in clinical and research settings. By combining information from the sleep EEG with a range of sensors measuring cardiorespiratory function, eye movements and muscle activity, PSG allows staging into wake, NREM and REM sleep, and remains a valuable tool for the identification of sleep disorders such as sleep disordered breathing, leg movements or parasomnias.

Traditional PSG, however, requires overnight stays in a sleep laboratory, supervised by trained sleep technologists. This renders PSG expensive, and an impractical tool for monitoring sleep for any longer than a few nights, making it challenging to examine longitudinal changes in sleep over time. Some other limitations to PSG are noteworthy. In most settings, although several machine learning-based automated scoring algorithms have been developed, scoring of the polysomnogram is still performed manually, and disagreement between two experienced scorers is not uncommon[243]. Therefore, although commonly used as the gold-standard reference against which other sleep technologies have been validated, PSG can itself be subject to measurement uncertainty. This raises the question of how 'gold' the 'gold-standard' measure actually is[244]. The PSG is also subject to the 'first night effect', where, due to the individual attempting to sleep in an unfamiliar environment whilst connected to sensors, sleep duration, continuity and efficiency are lower than in the home setting.

The second widely employed approach for sleep measurement in both clinical and research settings is actigraphy, which uses a wrist-worn device to capture the continuous rest-activity profile around the 24 h period. Sleep is inferred through the absence of movement, using published algorithms[245]. Actigraphy is relatively inexpensive, and has the advantage of sampling physical activity during wakefulness, in addition to sleep variables, in the home environment. Actigraphy can estimate certain sleep metrics (duration of sleep, awakenings from sleep, sleep latency when used in conjunction with a sleep diary) but is unable to stage sleep. Overall, when compared to PSG, actigraphy has high sensitivity (i.e. it correctly identifies sleep over 90% of the time) but at best moderate specificity (i.e. it only correctly identifies wake approximately 50% of the time)[246]. In other words, although actigraphy is able to correctly classify most instances of sleep, it suffers from a tendency to misidentify restful wake as sleep, and overestimate total sleep time.

With the exception of home sleep apnoea testing, the fundamental approaches to studying sleep have evolved relatively little since their introduction. The paucity of readily accessible and objective tools for quantifying sleep physiology outside of the laboratory setting represents a significant barrier to translating the enormous progress that has been made in sleep and circadian science, into improved human health.

Emerging methods in sleep-circadian research: consumer sleep technologies.

Advances in the miniaturisation, energy-efficiency, and inter-connectedness of micro-electronic technologies, together with their falling cost, has driven a rapid proliferation of devices for tracking sleep. Much of the innovation has been driven by the consumer wellbeing market, where myriad multi-sensor wearable, 'nearable' and wireless measurement systems, as well as novel analytic approaches, have found global reach.

The transformative potential for adopting these technologies as low-cost, low-burden yet powerful tools for the longitudinal characterisation of sleep-wake parameters over days, weeks, and even years, in the real world is increasingly being recognised by the research community[247,248]. Smartphones and consumer-grade wearable technologies have been leveraged to study sleep-wake variables in depression[249,250], bipolar disorder[251,252], and psychosis[253,254].

Modern wearable devices use signals from a range of sensors, including accelerometer and photoplethysmography (PPG), to evaluate a range of sleep variables including sleep duration and fragmentation. Many devices claim to stage sleep, reporting either 'light' or 'deep' sleep, or REM/NREM status, inferred from heart rate and heart rate variability estimates[255]. Other categories of device include apps that track sleep using smartphone sensors, in-bed sensors, and non-contact bedside devices. A key advantage of these devices is their usability and wireless capability, which allows for remote and real-time sampling and transfer of data to the clinical or research team, and provides the opportunity for rapid feedback of insights and recommendations to the patient.

A critical question, therefore, is the performance of these devices for identifying sleep and wakefulness, and whether they are appropriate tools for research. Several groups have begun to investigate this issue, through comparison of consumer devices against clinical-grade actigraphy and PSG. In general, the accuracy of consumer wearable devices for detecting sleep and wake is equal to, if not slightly higher than, validated actigraphy, with high sensitivity for sleep but low to moderate specificity for wake[256,257]. Currently available devices may therefore play a useful role in types of studies where actigraphy has previously been utilised.

Although many devices use the PPG signal to report more detailed metrics such as sleep stage, their agreement for these variables when compared to PSG is moderate at best[246]. Therefore, presently available wrist-worn devices with multimodal sensors do not yet offer an acceptable alternative to polysomnography, where sleep stage is part of the research question. Wearable in-ear or headband EEG devices have been developed, and show moderate to good agreement with PSG[246,258,259]. These devices therefore demonstrate potential as alternatives to PSG in the home setting.

Further important issues to consider in relation to consumer wearable devices include their scoring algorithms, which are based on sleep-wake characteristics from normative populations. Performance may therefore vary, in unexpected ways, in groups where sleep is disturbed, including those with mental disorder or insomnia. Their ability to detect episodes of daytime sleep including naps may also be limited, as many devices are 'tuned' to detect only longer sleep episodes. Consumer devices use proprietary algorithms, and access to raw data is not facilitated. Finally, device algorithms are periodically updated through firm-ware updates, which may introduce unforeseen bias if this occurs in the middle of a research study.

The potential for these technologies to reveal key relevant sleep-mental health associations, at scale and in the natural environment, across age and geographical boundaries, is substantial. Their successful adoption as tools for research will necessitate that researchers become comfortable with the increasingly blurred line between research and consumer devices, including unique legal and ethical considerations, and embrace rigorous new frameworks for their evaluation. A key proposal is a shift from a focus on a single 'validation study' of a consumer device against a gold-standard devices such as PSG, towards an iterative process of 'performance evaluating' new devices using a standardised framework[260–262]. Under this model, the performance criteria for each device against a reference such as PSG are evaluated in different populations and contexts (e.g. different mental diagnoses, stage of illness, age), allowing researchers to select the most appropriate

tool for their specific research question. This framework acknowledges that a device that is appropriate and 'validated' in one population or setting, may not be the most appropriate choice in another context[244], and recognises that every device carries a payoff between usability and accuracy.

Consumer sleep technologies may play a further, largely unexplored therapeutic role in informing behavioural change interventions. In their current form, insights from these devices can be fed-back to the user. By itself, feedback is not enough[244], and a key challenge is translating objective data from sleep tracking devices into personalised, graded recommendations which promote improvement in sleep behaviours, and better mental health.

Finally, the adoption of new business models which promote collaboration between academia and consumer sleep technology manufacturers, and allow researchers access to algorithms through which output variables are derived, would represent a significant breakthrough.

Emerging methods in sleep-circadian research: circadian biomarkers

Circadian rhythmicity is a manifestation of the oscillation of the central pacemaker – a cluster of neurons located in the suprachiasmatic nucleus (SCN), and its interaction with peripheral oscillators distributed throughout the tissues and organs of the body[263]. The phase and amplitude of the central pacemaker are reflected in the rhythms of melatonin concentration[264], and that of core body temperature.

Accepted measures of circadian rhythm in the field are the salivary dim light melatonin onset (DLMO) and urinary 6-sulfatoxymelatonin (a-MT6s). Although these markers of circadian rhythm are cost-effective and available, and have successfully been used to investigate circadian phase in patients with mood disorder[265,266] and schizophrenia[267,268], they remain under-utilised in studies of psychiatric disorder. One factor limiting their wider implementation is that the endogenous rhythm can be obscured, or *masked*, by environmental and behavioural rhythms. For example, light suppresses melatonin secretion, and light exposure must therefore be minimised during sampling, to avoid masking effects. Clear guidance to study participants around the conditions of sample collection are therefore required, with samples ideally being obtained under supervision.

In view of the perceived complexity of obtaining these biomarkers, novel techniques for estimating circadian parameters are under development[269]. One approach uses multivariate, -omics based biomarkers from two or more serial blood samples. These approaches have shown good performance, estimating melatonin phase within 1h, in individuals living under entrained conditions. Accuracy falls considerably, however, in cases where sleep is displaced, as is the case in shift-work[270,271], limiting their current real-world usability. Another approach predicts circadian phase based on rest-activity profiles from wearable accelerometers, using mathematical models. Again, these have reported high precision in predicting melatonin phase in those with fixed sleep schedules[272], with decreasing prediction accuracy as the sleep-wake schedule became more unpredictable[272,273]. Mathematical modelling approaches have also shown comparable accuracy when using data from consumer wearable devices[274], and have also been used to simulate interventions that normalise sleep-wake timing in schizophrenia[275].

These approaches are promising, and further evaluation studies in varied populations and contexts, including groups with mental disorder, are urgently needed. In the meantime, the

use of markers with accepted performance such as salivary and urinary melatonin, is encouraged.

Key messages:

- Emerging research-grade and consumer digital and wearable technologies are extending the reach, affordability, and practicability of measuring longitudinal sleep and rest-activity variables in real-world settings.
- Studies of some consumer wearable devices demonstrate comparable performance to traditional actigraphy and accelerometery in estimating sleep measures. An inability to access algorithms, and uncertainty over their accuracy in populations with disturbed sleep, however, remain significant limitations.
- Wearable home EEG devices show potential for measuring sleep in the field.
- Novel circadian assays and physiologically-informed mathematical models promise to deliver less invasive, point-of-care tests for measuring endogenous circadian rhythm.

Conclusions, and summary of key gaps and opportunities

1. Research into mental health is poised to take advantage of the extraordinary advances that have been made in sleep and circadian science, and translate this into improved understanding of the pathophysiology and treatment of mental disorder.

2. There is growing evidence that sleep disruption and mental disorder, particularly mood and anxiety disorders, are bidirectionally linked. Although we are beginning to elucidate some of the mechanisms underlying this relationship, substantial gaps remain, including whether mechanisms are specific to, or generalisable across, different disorders.

3. In comparison to the study of sleep variables, there have been fewer studies investigating the relationships and mechanisms linking circadian variables with mental disorder, particularly in the psychotic disorders. To date, research into sleep and circadian rhythms have also remained largely separate, with limited theoretical or practical integration. Sleep and circadian processes are however highly interlinked, and both are implicated in mental disorder. A key opportunity therefore exists for the concurrent investigation of these two domains, to accelerate discovery of mechanisms and interventions.

4. The field has been limited by studies of small, heterogenous and sometimes poorly defined samples, using a wide range of outcome measures that limit the ability to make comparisons. Employing standardised parameters and constructs across studies and research groups is likely to aid synthesis of findings.

5. Sleep is a '24 hour phenomenon': psychiatric symptoms, behaviours and environmental factors during wakefulness (such as mood, energy, physical activity, light exposure and medication) strongly influence sleep quality and quantity. Incorporating measures of these variables with investigation of sleep-circadian function, where possible in the home environment, is an important objective.

6. Research into the effects of manipulating sleep and circadian function on dimensions of psychopathology in non-clinical and clinical populations, and inter-individual variability in vulnerability to sleep and circadian disruption, has been limited.

7. Emerging technologies, including wearable and smartphone sensors, bedside devices and novel circadian biomarkers are likely to facilitate longitudinal and naturalistic experimental designs, and will deliver a profusion of multimodal data. For example, it will be increasingly possible to sample sleep-circadian variables and psychopathology in a trait and state manner, during remission and around relapse. Ensuring such technologies are appropriately evaluated is a key challenge, as is gathering, cleaning and making sense of these data, using shared, open-source analysis pipelines.

8. With the exception of CBT-I, the field suffers from a marked scarcity of interventions. The development of further innovative, scalable and practical sleep-circadian interventions is a priority, and should include the input of people with lived experience of mental illness. Interventions that treat sleep-circadian disturbance have also been used to test causal mechanisms. Such study designs therefore present an opportunity for both developing interventions and elucidating mechanisms.

References

1. Grandner, M.A., and Fernandez, F.X. (2021). The translational neuroscience of sleep: A contextual framework. Science (1979) *374*, 568–573.
2. Siegel, J.M. (2005). Clues to the functions of mammalian sleep. Nature *437*, 1264–1271.
3. Allada, R., and Bass, J. (2021). Circadian Mechanisms in Medicine. New England Journal of Medicine *384*, 550–561.
4. Freeman, D., Sheaves, B., Waite, F., Harvey, A.G., and Harrison, P.J. (2020). Sleep disturbance and psychiatric disorders. The Lancet Psychiatry *7*, 628–637.
5. Dolsen, M.R., Asarnow, L.D., and Harvey, A.G. (2014). Insomnia as a Transdiagnostic Process in Psychiatric Disorders. Current Psychiatry Reports *16*.
6. Ford, D.E., and Kamerow, D.B. (1989). Epidemiologic Study of Sleep Disturbances and Psychiatric Disorders: An Opportunity for Prevention? JAMA: The Journal of the American Medical Association *262*, 1479–1484.
7. Wehr, T., Sack, D., and Rosenthal, N. (1987). Sleep reduction as a final common pathway in the genesis of mania. American Journal of Psychiatry *144*, 201–204.
8. Gruber, J., Miklowitz, D.J., Harvey, A.G., Frank, E., Kupfer, D., Thase, M.E., Sachs, G.S., and Ketter, T.A. (2011). Sleep matters: Sleep functioning and course of illness in bipolar disorder. Journal of Affective Disorders *134*, 416–420.
9. Cohrs, S. (2008). Sleep disturbances in patients with schizophrenia: Impact and effect of antipsychotics. CNS Drugs *22*, 939–962.
10. Baglioni, C., Nanovska, S., Regen, W., Spiegelhalder, K., Feige, B., Nissen, C., Reynolds, C.F., and Riemann, D. (2016). Sleep and mental disorders: A meta-analysis of polysomnographic research. Psychological Bulletin *142*, 969–990.
11. Zangani, C., Casetta, C., Saunders, A.S., Donati, F., Maggioni, E., and D'Agostino, A. (2020). Sleep abnormalities across different clinical stages of Bipolar Disorder: A review of EEG studies. Neuroscience and Biobehavioral Reviews *118*, 247–257.
12. Van Someren, E.J.W., Cirelli, C., Dijk, D.-J., Van Cauter, E., Schwartz, S., and Chee, M.W.L. (2015). Disrupted Sleep: From Molecules to Cognition. Journal of Neuroscience *35*, 13889–13895.
13. Hertenstein, E., Trinca, E., Wunderlin, M., Schneider, C.L., Züst, M.A., Fehér, K.D., Su, T., Straten, A. v., Berger, T., Baglioni, C., et al. (2022). Cognitive behavioral therapy for insomnia in patients with mental disorders and comorbid insomnia: A systematic review and meta-analysis. Sleep Medicine Reviews *62*, 101597.
14. Irwin, M.R., Carrillo, C., Sadeghi, N., Bjurstrom, M.F., Breen, E.C., and Olmstead, R. (2022). Prevention of Incident and Recurrent Major Depression in Older Adults with Insomnia: A Randomized Clinical Trial. JAMA Psychiatry *79*, 33–41.
15. Geoffroy, P.A., and Palagini, L. (2021). Biological rhythms and chronotherapeutics in depression. Progress in Neuro-Psychopharmacology and Biological Psychiatry *106*, 110158.
16. Kessler, R.C., Berglund, P., Demler, O., Jin, R., Merikangas, K.R., and Walters, E.E. (2005). Lifetime Prevalence and Age-of-Onset Distributions of. Arch Gen Psychiatry *62*, 593–602.
17. Solmi, M., Radua, J., Olivola, M., Croce, E., Soardo, L., Salazar de Pablo, G., Il Shin, J., Kirkbride, J.B., Jones, P., Kim, J.H., et al. (2022). Age at onset of mental disorders worldwide: large-scale meta-analysis of 192 epidemiological studies. Molecular Psychiatry *27*, 281–295.
18. Salas, R.M.E., Strowd, R.E., Ali, I., Soni, M., Schneider, L., Safdieh, J., Vaughn, B. V., Avidan, A.Y., Jeffery, J.B., and Gamaldo, C.E. (2018). Incorporating sleep medicine content into medical school through neuroscience core curricula. Neurology *91*, 597–610.

19. Meaklim, H., Rehm, I.C., Monfries, M., Junge, M., Meltzer, L.J., and Jackson, M.L. (2021). Wake up psychology! Postgraduate psychology students need more sleep and insomnia education. Australian Psychologist *56*, 485–498.
20. Zhou, E.S., Mazzenga, M., Gordillo, M.L., Meltzer, L.J., and Long, K.A. (2021). Sleep Education and Training among Practicing Clinical Psychologists in the United States and Canada. Behavioral Sleep Medicine *19*, 744–753.
21. Scott, J., Kallestad, H., Vedaa, O., Sivertsen, B., and Etain, B. (2021). Sleep disturbances and first onset of major mental disorders in adolescence and early adulthood: A systematic review and meta-analysis. Sleep Medicine Reviews *57*, 101429.
22. Baglioni, C., Battagliese, G., Feige, B., Spiegelhalder, K., Nissen, C., Voderholzer, U., Lombardo, C., and Riemann, D. (2011). Insomnia as a predictor of depression: A meta-analytic evaluation of longitudinal epidemiological studies. Journal of Affective Disorders *135*, 10–19.
23. Li, L., Wu, C., Gan, Y., Qu, X., and Lu, Z. (2016). Insomnia and the risk of depression: A meta-analysis of prospective cohort studies. BMC Psychiatry *16*.
24. Hertenstein, E., Feige, B., Gmeiner, T., Kienzler, C., Spiegelhalder, K., Johann, A., Jansson-Fröjmark, M., Palagini, L., Rücker, G., Riemann, D., et al. (2019). Insomnia as a predictor of mental disorders: A systematic review and meta-analysis. Sleep Medicine Reviews *43*, 96–105.
25. Ritter, P.S., Höfler, M., Wittchen, H.U., Lieb, R., Bauer, M., Pfennig, A., and Beesdo-Baum, K. (2015). Disturbed sleep as risk factor for the subsequent onset of bipolar disorder - Data from a 10-year prospective-longitudinal study among adolescents and young adults. Journal of Psychiatric Research *68*, 76–82.
26. Koyanagi, A., and Stickley, A. (2015). The Association between Sleep Problems and Psychotic Symptoms in the General Population: A Global Perspective. Sleep *38*, 1875–1885.
27. Sheaves, B., Porcheret, K., Goodwin, G.M., Tsanas, A., Espie, C.A., Bebbington, P., Harrison, P.J., Foster, R., Wulff, K., and Freeman, D. (2016). Sleep and circadian rhythm and the risk of severe mental disorder: Findings from large epidemiological datasets. Sleep *39*, A294.
28. Zaks, N., Velikonja, T., Parvaz, M.A., Zinberg, J., Done, M., Mathalon, D.H., Addington, J., Cadenhead, K., Cannon, T., Cornblatt, B., et al. (2021). Sleep Disturbance in Individuals at Clinical High Risk for Psychosis. Schizophrenia Bulletin.
29. Stanley, I.H., Hom, M.A., Luby, J.L., Joshi, P.T., Wagner, K.D., Emslie, G.J., Walkup, J.T., Axelson, D.A., and Joiner, T.E. (2017). Comorbid sleep disorders and suicide risk among children and adolescents with bipolar disorder. Journal of Psychiatric Research *95*, 54–59.
30. Crouse, J.J., Carpenter, J.S., Song, Y.J.C., Hockey, S.J., Naismith, S.L., Grunstein, R.R., Scott, E.M., Merikangas, K.R., Scott, J., and Hickie, I.B. (2021). Circadian rhythm sleep–wake disturbances and depression in young people: implications for prevention and early intervention. The Lancet Psychiatry *8*, 813–823.
31. Ong, S., Wickramaratne, P., Tang, M., and Weissman, M.M. (2006). Early childhood sleep and eating problems as predictors of adolescent and adult mood and anxiety disorders. Journal of Affective Disorders *96*, 1–8.
32. Merikanto, I., Lahti, T., Kronholm, E., Peltonen, M., Laatikainen, T., Vartiainen, E., Salomaa, V., and Partonen, T. (2013). Evening types are prone to depression. Chronobiology International *30*, 719–725.
33. Lyall, L.M., Wyse, C.A., Graham, N., Ferguson, A., Lyall, D.M., Cullen, B., Celis Morales, C.A., Biello, S.M., Mackay, D., Ward, J., et al. (2018). Association of disrupted circadian rhythmicity with mood disorders, subjective wellbeing, and cognitive function: a cross-sectional study of 91 105 participants from the UK Biobank. The Lancet Psychiatry *5*, 507–514.

34. Carpenter, J.S., Crouse, J.J., Scott, E.M., Naismith, S.L., Wilson, C., Scott, J., Merikangas, K.R., and Hickie, I.B. (2021). Circadian depression: A mood disorder phenotype. Neuroscience and Biobehavioral Reviews *126*, 79–101.
35. McCarthy, M.J., Gottlieb, J.F., Gonzalez, R., McClung, C.A., Alloy, L.B., Cain, S., Dulcis, D., Etain, B., Frey, B.N., Garbazza, C., et al. (2021). Neurobiological and behavioral mechanisms of circadian rhythm disruption in bipolar disorder: A critical multi-disciplinary literature review and agenda for future research from the ISBD task force on chronobiology. Bipolar Disorders, 1–32.
36. Gore, F.M., Bloem, P.J.N., Patton, G.C., Ferguson, J., Joseph, V., Coffey, C., Sawyer, S.M., and Mathers, C.D. (2011). Global burden of disease in young people aged 10-24 years: A systematic analysis. The Lancet *377*, 2093–2102.
37. Tesler, N., Gerstenberg, M., and Huber, R. (2013). Developmental changes in sleep and their relationships to psychiatric illnesses. Current Opinion in Psychiatry *26*, 572–579.
38. LeBourgeois, M.K., Dean, D.C., Deoni, S.C.L., Kohler, M., and Kurth, S. (2019). A simple sleep EEG marker in childhood predicts brain myelin 3.5 years later. Neuroimage *199*, 342–350.
39. Yang, F.N., Liu, T.T., and Wang, Z. (2022). Functional connectome mediates the association between sleep disturbance and mental health in preadolescence: A longitudinal mediation study. Human Brain Mapping *43*, 2041–2050.
40. Keyes, K.M., Maslowsky, J., Hamilton, A., and Schulenberg, J. (2015). The great sleep recession: Changes in sleep duration among US adolescents, 1991-2012. Pediatrics *135*, 460–468.
41. Carskadon, M.A. (2011). Sleep in Adolescents: The Perfect Storm. Pediatric Clinics of North America *58*, 637–647.
42. Crone, E.A., and Konijn, E.A. (2018). Media use and brain development during adolescence. Nature Communications *9*.
43. Tonon, A.C., Constantino, D.B., Amando, G.R., Abreu, A.C., Francisco, A.P., de Oliveira, M.A.B., Pilz, L.K., Xavier, N.B., Rohrsetzer, F., Souza, L., et al. (2022). Sleep Disturbances, Circadian Activity and Nocturnal Light Exposure Characterize High Risk for and Current Depression in Adolescence. Sleep, 1–10.
44. Adler, I., Weidner, K., Eberhard-Gran, M., and Garthus-Niegel, S. (2021). The Impact of Maternal Symptoms of Perinatal Insomnia on Social-emotional Child Development: A Population-based, 2-year Follow-up Study. Behavioral Sleep Medicine *19*, 303–317.
45. Palagini, L., Domschke, K., Benedetti, F., Foster, R.G., Wulff, K., and Riemann, D. (2019). Developmental pathways towards mood disorders in adult life: Is there a role for sleep disturbances? Journal of Affective Disorders *243*, 121–132.
46. Asarnow, L.D., and Mirchandaney, R. (2021). Sleep and Mood Disorders Among Youth. Child and Adolescent Psychiatric Clinics of North America *30*, 251–268.
47. Goldstone, A., Javitz, H.S., Claudatos, S.A., Buysse, D.J., Hasler, B.P., de Zambotti, M., Clark, D.B., Franzen, P.L., Prouty, D.E., Colrain, I.M., et al. (2020). Sleep Disturbance Predicts Depression Symptoms in Early Adolescence: Initial Findings From the Adolescent Brain Cognitive Development Study. Journal of Adolescent Health *66*, 567–574.
48. Alvaro, P.K., Roberts, R.M., and Harris, J.K. (2014). The independent relationships between insomnia, depression, subtypes of anxiety, and chronotype during adolescence. Sleep Medicine *15*, 934–941.
49. Ojio, Y., Nishida, A., Shimodera, S., Togo, F., and Sasaki, T. (2016). Sleep duration associated with the lowest risk of depression/anxiety in adolescents. Sleep *39*, 1555–1562.
50. Lovato, N., and Gradisar, M. (2014). A meta-analysis and model of the relationship between sleep and depression in adolescents: Recommendations for future research and clinical practice. Sleep Medicine Reviews *18*, 521–529.
51. van Dyk, T.R., Becker, S.P., and Byars, K.C. (2019). Rates of mental health symptoms and associations with self-reported sleep quality and sleep hygiene in

adolescents presenting for insomnia treatment. Journal of Clinical Sleep Medicine *15*, 1433–1442.
52. Logan, R.W., Hasler, B.P., Forbes, E.E., Franzen, P.L., Torregrossa, M.M., Huang, Y.H., Buysse, D.J., Clark, D.B., and McClung, C.A. (2018). Impact of Sleep and Circadian Rhythms on Addiction Vulnerability in Adolescents. Biological Psychiatry *83*, 987–996.
53. Clarke, G., and Harvey, A.G. (2012). The Complex Role of Sleep in Adolescent Depression. Child and Adolescent Psychiatric Clinics *21*, 385–400.
54. Lee, Y.J., Cho, S.J., Cho, I.H., and Kim, S.J. (2012). Insufficient sleep and suicidality in adolescents. Sleep *35*, 455–460.
55. Liu, X. (2004). Sleep and adolescent suicidal behavior. Sleep *27*, 1351–1358.
56. Weaver, M.D., Barger, L.K., Malone, S.K., Anderson, L.S., and Klerman, E.B. (2018). Dose-Dependent Associations between Sleep Duration and Unsafe Behaviors among US High School Students. JAMA Pediatrics *172*, 1187–1189.
57. Lunsford-Avery, J.R., LeBourgeois, M.K., Gupta, T., and Mittal, V.A. (2015). Actigraphic-measured sleep disturbance predicts increased positive symptoms in adolescents at ultra high-risk for psychosis: A longitudinal study. Schizophr Res *164*, 15–20.
58. Sheaves, B., Onwumere, J., Keen, N., Stahl, D., and Kuipers, E. (2015). Nightmares in patients with psychosis: The relation with sleep, psychotic, affective, and cognitive symptoms. Canadian Journal of Psychiatry *60*, 354–361.
59. Thompson, A., Lereya, S.T., Lewis, G., Zammit, S., Fisher, H.L., and Wolke, D. (2015). Childhood sleep disturbance and risk of psychotic experiences at 18: UK birth cohort. British Journal of Psychiatry *207*, 23–29.
60. Oshima, N., Nishida, A., Fukushima, M., Shimodera, S., Kasai, K., Okazaki, Y., and Sasaki, T. (2010). Psychotic-like experiences (PLEs) and mental health status in twin and singleton Japanese high school students. Early Intervention in Psychiatry *4*, 206–213.
61. Riemann, D., Krone, L.B., Wulff, K., and Nissen, C. (2020). Sleep, insomnia, and depression. Neuropsychopharmacology *45*, 74–89.
62. Kupfer, D.J., and Foster, F.G. (1972). Interval Between Onset of Sleep and Rapid-Eye-Movement Sleep As an Indicator of Depression. The Lancet *300*, 684–686.
63. Benca, R.M., Obermeyer, W.H., Thisted, R.A., and Gillin, J.C. (1992). Sleep and Psychiatric Disorders: A Meta-analysis. Archives of General Psychiatry *49*, 651–668.
64. Lai, M., Hegde, R., Kelly, S., Bannai, D., Lizano, P., Stickgold, R., Manoach, D.S., and Keshavan, M. (2022). Investigating sleep spindle density and schizophrenia: A meta-analysis. Psychiatry Research *307*, 114265.
65. Ferrarelli, F. (2021). Sleep Abnormalities in Schizophrenia: State of the Art and Next Steps. Am J Psychiatry *178*, 903–913.
66. Bartsch, U., Simpkin, A.J., Demanuele, C., Wamsley, E., Marston, H.M., and Jones, M.W. (2019). Distributed slow-wave dynamics during sleep predict memory consolidation and its impairment in schizophrenia. NPJ Schizophr *5*.
67. Wamsley, E.J., Tucker, M. a, Shinn, A.K., Ono, K.E., McKinley, S.K., Ely, A. V, Goff, D.C., Stickgold, R., and Manoach, D.S. (2012). Reduced sleep spindles and spindle coherence in schizophrenia: mechanisms of impaired memory consolidation? Biol Psychiatry *71*, 154–61.
68. Demanuele, C., Bartsch, U., Baran, B., Khan, S., Vangel, M.G., Cox, R., Hämäläinen, M., Jones, M.W., Stickgold, R., and Manoach, D.S. (2017). Coordination of Slow Waves With Sleep Spindles Predicts Sleep-Dependent Memory Consolidation in Schizophrenia. Sleep *40*.
69. Chan, M.S., Chung, K.F., Yung, K.P., and Yeung, W.F. (2017). Sleep in schizophrenia: A systematic review and meta-analysis of polysomnographic findings in case-control studies. Sleep Medicine Reviews *32*, 69–84.

70. Lopez, J., Hoffmann, R., and Armitage, R. (2010). Reduced sleep spindle activity in early-onset and elevated risk for depression. J Am Acad Child Adolesc Psychiatry *49*, 934–943.
71. Dijk, D.J., and Czeisler, C.A. (1995). Contribution of the circadian pacemaker and the sleep homeostat to sleep propensity, sleep structure, electroencephalographic slow waves, and sleep spindle activity in humans. Journal of Neuroscience *15*, 3526–3538.
72. Hamann, C., Rusterholz, T., Studer, M., Kaess, M., and Tarokh, L. (2019). Association between depressive symptoms and sleep neurophysiology in early adolescence. Journal of Child Psychology and Psychiatry and Allied Disciplines *60*, 1334–1342.
73. Tamaki, M., Bang, J.W., Watanabe, T., and Sasaki, Y. (2016). Night Watch in One Brain Hemisphere during Sleep Associated with the First-Night Effect in Humans. Current Biology *26*, 1190–1194.
74. Zhao, W., Van Someren, J.W., Li, C., Chen, X., Gui, W., Tian, Y., Liu, Y., and Lei, X. (2021). CLINICAL REVIEW EEG spectral analysis in insomnia disorder: A systematic review and meta-analysis.
75. Zhao, W., van Someren, E.J.W., Li, C., Chen, X., Gui, W., Tian, Y., Liu, Y., and Lei, X. (2021). EEG spectral analysis in insomnia disorder: A systematic review and meta-analysis. Sleep Medicine Reviews *59*.
76. Geoffroy, P.A., Tebeka, S., Blanco, C., Dubertret, C., and Le Strat, Y. (2020). Shorter and longer durations of sleep are associated with an increased twelve-month prevalence of psychiatric and substance use disorders: Findings from a nationally representative survey of US adults (NESARC-III). Journal of Psychiatric Research *124*, 34–41.
77. Geoffroy, P.A., Hoertel, N., Etain, B., Bellivier, F., Delorme, R., Limosin, F., and Peyre, H. (2018). Insomnia and hypersomnia in major depressive episode: Prevalence, sociodemographic characteristics and psychiatric comorbidity in a population-based study. Journal of Affective Disorders *226*, 132–141.
78. Chellappa, S.L., and Aeschbach, D. (2021). Sleep and Anxiety: from Mechanisms to Interventions. Sleep Medicine Reviews *61*, 101583.
79. Harvey, Schmidt, A., Scarnà, A., Semler, C.N., and Goodwin, G. (2005). Sleep-related functioning in euthymic patients with bipolar disorder, patients with insomnia, and subjects without sleep problems. American Journal of Psychiatry *162*, 50–57.
80. Xiang, Y.T., Weng, Y.Z., Leung, C.M., Tang, W.K., Lai, K.Y., and Ungvari, G.S. (2009). Prevalence and Correlates of Insomnia and its Impact on Quality of Life in Chinese Schizophrenia Patients. Sleep *32*, 105–109.
81. Baglioni, C., Regen, W., Teghen, A., Spiegelhalder, K., Feige, B., Nissen, C., and Riemann, D. (2014). Sleep changes in the disorder of insomnia: a meta-analysis of polysomnographic studies. Sleep Med Rev *18*, 195–213.
82. Riemann, D., Benz, F., Dressle, R.J., Espie, C.A., Johann, A.F., Blanken, T.F., Leerssen, J., Wassing, R., Henry, A.L., Kyle, S.D., et al. (2022). Insomnia disorder: State of the science and challenges for the future. Journal of Sleep Research, 1–18.
83. Vgontzas, A.N., Fernandez-Mendoza, J., Liao, D., and Bixler, E.O. (2013). Insomnia with objective short sleep duration: The most biologically severe phenotype of the disorder. Sleep Medicine Reviews *17*, 241–254.
84. Tazawa, Y., Wada, M., Mitsukura, Y., Takamiya, A., Kitazawa, M., Yoshimura, M., Mimura, M., and Kishimoto, T. (2019). Actigraphy for evaluation of mood disorders: A systematic review and meta-analysis. Journal of Affective Disorders *253*, 257–269.
85. Geoffroy, P.A., Scott, J., Boudebesse, C., Lajnef, M., Henry, C., Leboyer, M., Bellivier, F., and Etain, B. (2015). Sleep in patients with remitted bipolar disorders: A meta-analysis of actigraphy studies. Acta Psychiatrica Scandinavica *131*, 89–99.
86. Meyer, N., Faulkner, S.M., McCutcheon, R.A., Pillinger, T., Dijk, D.-J., and MacCabe, J.H. (2020). Sleep and Circadian Rhythm Disturbance in Remitted Schizophrenia and Bipolar Disorder: A Systematic Review and Meta-analysis. Schizophrenia Bulletin, 1–18.

87. Bauer, M., Grof, P., Rasgon, N., Bschor, T., Glenn, T., and Whybrow, P.C. (2006). Temporal relation between sleep and mood in patients with bipolar disorder. Bipolar Disorders *8*, 160–167.
88. Meyer, N., Joyce, D.W., Karr, C., De Vos, M., Dijk, D.J., Jacobson, N.C., and Maccabe, J.H. (2021). The temporal dynamics of sleep disturbance and psychopathology in psychosis: A digital sampling study. Psychological Medicine.
89. Fischer, D., Klerman, E.B., and Phillips, A.J.K. (2021). Measuring sleep regularity: Theoretical properties and practical usage of existing metrics. Sleep *44*, 1–16.
90. Bei, B., Manber, R., Allen, N.B., Trinder, J., and Wiley, J.F. (2017). Too long, too short, or too variable? sleep intraindividual variability and its associations with perceived sleep quality and mood in adolescents during naturalistically unconstrained sleep. Sleep *40*.
91. Borbély, A.A., and Wirz-Justice, A. (1982). Sleep, sleep deprivation and depression. A hypothesis derived from a model of sleep regulation. Hum Neurobiol *1*, 205–210.
92. Wirz-Justice, A., and Benedetti, F. (2019). Perspectives in affective disorders: Clocks and sleep. European Journal of Neuroscience, 1–20.
93. Takaesu, Y. (2018). Circadian rhythm in bipolar disorder: A review of the literature. Psychiatry and Clinical Neurosciences *72*, 673–682.
94. Delorme, T.C., Srivastava, L.K., and Cermakian, N. (2020). Are Circadian Disturbances a Core Pathophysiological Component of Schizophrenia? Journal of Biological Rhythms.
95. Ferguson, A., Lyall, L.M., Ward, J., Strawbridge, R.J., Cullen, B., Graham, N., Niedzwiedz, C.L., Johnston, K.J.A., MacKay, D., Biello, S.M., et al. (2018). Genome-Wide Association Study of Circadian Rhythmicity in 71,500 UK Biobank Participants and Polygenic Association with Mood Instability. EBioMedicine *35*, 279–287.
96. Wirz-Justice, A., Ajdacic, V., Rössler, W., Steinhausen, H.C., and Angst, J. (2019). Prevalence of seasonal depression in a prospective cohort study. European Archives of Psychiatry and Clinical Neuroscience *269*, 833–839.
97. Rosenthal, N.E., Sack, D.A., Gillin, J.C., Lewy, A.J., Goodwin, F.K., Davenport, Y., Mueller, P.S., Newsome, D.A., and Wehr, T.A. (1984). Seasonal affective disorder. A description of the syndrome and preliminary findings with light therapy. Arch Gen Psychiatry *41*, 72–80.
98. Wehr, T.A., Duncan, W.C., Sher, L., Aeschbach, D., Schwartz, P.J., Turner, E.H., Postolache, T.T., and Rosenthal, N.E. (2001). A circadian signal of change of season in patients with seasonal affective disorder. Archives of General Psychiatry *58*, 1108–1114.
99. Robillard, R.R., Hermens, D.F., Naismith, S.L., White, D., Rogers, N.L., Ip, T.K.C., Mullin, S.J., Alvares, G.A., Guastella, A.J., Smith, K.L., et al. (2015). Ambulatory sleep-wake patterns and variability in young people with emerging mental disorders. Journal of Psychiatry and Neuroscience *40*, 28–37.
100. Murray, G., Gottlieb, J., Hidalgo, M.P., Etain, B., Ritter, P., Skene, D.J., Garbazza, C., Bullock, B., Merikangas, K., Zipunnikov, V., et al. (2020). Measuring circadian function in bipolar disorders: Empirical and conceptual review of physiological, actigraphic, and self-report approaches. Bipolar Disorders *22*, 693–710.
101. Souêtre, E., Salvati, E., Belugou, J.L., Pringuey, D., Candito, M., Krebs, B., Ardisson, J.L., and Darcourt, G. (1989). Circadian rhythms in depression and recovery: Evidence for blunted amplitude as the main chronobiological abnormality. Psychiatry Research *28*, 263–278.
102. Li, J.Z., Bunney, B.G., Meng, F., Hagenauer, M.H., Walsh, D.M., Vawter, M.P., Evans, S.J., Choudary, P. V., Cartagena, P., Barchas, J.D., et al. (2013). Circadian patterns of gene expression in the human brain and disruption in major depressive disorder. Proc Natl Acad Sci U S A *110*, 9950–9955.
103. Emens, J., Lewy, A., Kinzie, J.M., Arntz, D., and Rough, J. (2009). Circadian misalignment in major depressive disorder. Psychiatry Research *168*, 259–261.

104. Swanson, L.M., Burgess, H.J., Huntley, E.D., Bertram, H., Mooney, A., Zollars, J., Dopp, R., Hoffmann, R., Armitage, R., and Todd Arnedt, J. (2017). Relationships between circadian measures, depression, and response to antidepressant treatment: A preliminary investigation. Psychiatry Research *252*, 262–269.
105. Moon, J.-H., Cho, C.-H., Son, G.H., Geum, D., Chung, S., Kim, H., Kang, S.-G., Park, Y.-M., Yoon, H.-K., Kim, L., et al. (2016). Advanced Circadian Phase in Mania and Delayed Circadian Phase in Mixed Mania and Depression Returned to Normal after Treatment of Bipolar Disorder. EBioMedicine *11*, 285–295.
106. Walker, W.H., Walton, J.C., DeVries, A.C., and Nelson, R.J. (2020). Circadian rhythm disruption and mental health. Translational Psychiatry *10*.
107. Moreira, J., and Geoffroy, P.A. (2016). Lithium and bipolar disorder: Impacts from molecular to behavioural circadian rhythms. Chronobiology International *33*, 351–373.
108. McCarthy, M.J., Wei, H., Nievergelt, C.M., Stautland, A., Maihofer, A.X., Welsh, D.K., Shilling, P., Alda, M., Alliey-Rodriguez, N., Anand, A., et al. (2018). Chronotype and cellular circadian rhythms predict the clinical response to lithium maintenance treatment in patients with bipolar disorder. Neuropsychopharmacology, 1.
109. Duffy, J.F., and Wright, K.P. (2005). Entrainment of the human circadian system by light. Journal of Biological Rhythms *20*, 326–338.
110. Legates, T.A., Fernandez, D.C., and Hattar, S. (2014). Light as a central modulator of circadian rhythms, sleep and affect. Nature Reviews Neuroscience *15*, 443–454.
111. Chellappa, S.L. (2021). Individual differences in light sensitivity affect sleep and circadian rhythms. Sleep *44*, 1–10.
112. Palagini, L., Bastien, C.H., Marazziti, D., Ellis, J.G., and Riemann, D. (2019). The key role of insomnia and sleep loss in the dysregulation of multiple systems involved in mood disorders: A proposed model. Journal of Sleep Research *28*, e12841.
113. Purcell, S.M., Manoach, D.S., Demanuele, C., Cade, B.E., Mariani, S., Cox, R., Panagiotaropoulou, G., Saxena, R., Pan, J.Q., Smoller, J.W., et al. (2017). Characterizing sleep spindles in 11,630 individuals from the National Sleep Research Resource. Nature Communications *8*, 1–16.
114. Lane, J.M., Liang, J., Vlasac, I., Anderson, S.G., Bechtold, D.A., Bowden, J., Emsley, R., Gill, S., Little, M.A., Luik, A.I., et al. (2017). Genome-wide association analyses of sleep disturbance traits identify new loci and highlight shared genetics with neuropsychiatric and metabolic traits. Nature Genetics *49*, 274–281.
115. Garfield, V. (2021). Sleep duration: A review of genome-wide association studies (GWAS) in adults from 2007 to 2020. Sleep Medicine Reviews *56*.
116. Blackman, J., Morrison, H.D., Lloyd, K., Gimson, A., Banerjee, L.V., Green, S., Cousins, R., Rudd, S., Harding, S., and Coulthard, E. (2022). The Past, Present and Future of Sleep Measurement in Mild Cognitive Impairment and Early Dementia - Towards a Core Outcome Set: A Scoping Review. Sleep.
117. Pagani, L., Clair, P.A.S., Teshiba, T.M., Service, S.K., Fears, S.C., Araya, C., Araya, X., Bejarano, J., Ramirez, M., Castrillon, G., et al. (2016). Genetic contributions to circadian activity rhythm and sleep pattern phenotypes in pedigrees segregating for severe bipolar disorder. Proc Natl Acad Sci U S A *113*, E754–E761.
118. O'Connell, K.S., Frei, O., Bahrami, S., Smeland, O.B., Bettella, F., Cheng, W., Chu, Y., Hindley, G., Lin, A., Shadrin, A., et al. (2021). Characterizing the Genetic Overlap Between Psychiatric Disorders and Sleep-Related Phenotypes. Biological Psychiatry *90*, 621–631.
119. O'Loughlin, J., Casanova, F., Jones, S.E., Hagenaars, S.P., Beaumont, R.N., Freathy, R.M., Watkins, E.R., Vetter, C., Rutter, M.K., Cain, S.W., et al. (2021). Using Mendelian Randomisation methods to understand whether diurnal preference is causally related to mental health. Molecular Psychiatry *26*, 6305–6316.
120. Bartsch, U., Corbin, L.J., Hellmich, C., Taylor, M., Easey, K.E., Durant, C., Marston, H.M., Timpson, N.J., and Jones, M.W. (2021). Schizophrenia-associated variation at ZNF804A correlates with altered experience-dependent dynamics of sleep slow waves and spindles in healthy young adults. Sleep *44*.

121. Merikanto, I., Utge, S., Lahti, J., Kuula, L., Makkonen, T., Lahti-Pulkkinen, M., Heinonen, K., Räikkönen, K., Andersson, S., Strandberg, T., et al. (2019). Genetic risk factors for schizophrenia associate with sleep spindle activity in healthy adolescents. Journal of Sleep Research *28*, 1–8.
122. Ang, G., Brown, L.A., Tam, S.K.E., Davies, K.E., Foster, R.G., Harrison, P.J., Sprengel, R., Vyazovskiy, V. V., Oliver, P.L., Bannerman, D.M., et al. (2021). Deletion of AMPA receptor GluA1 subunit gene (Gria1) causes circadian rhythm disruption and aberrant responses to environmental cues. Translational Psychiatry *11*.
123. Ghoshal, A., Uygun, D.S., Yang, L., McNally, J.M., Lopez-Huerta, V.G., Arias-Garcia, M.A., Baez-Nieto, D., Allen, A., Fitzgerald, M., Choi, S., et al. (2020). Effects of a patient-derived de novo coding alteration of CACNA1I in mice connect a schizophrenia risk gene with sleep spindle deficits. Translational Psychiatry *10*, 1–12.
124. Chen, K.S., Xu, M., Zhang, Z., Chang, W.C., Gaj, T., Schaffer, D. V., and Dan, Y. (2018). A Hypothalamic Switch for REM and Non-REM Sleep. Neuron *97*, 1168-1176.e4.
125. Zhang, Z., Zhong, P., Hu, F., Chung, S., Palmiter, R.D., Correspondence, Y.D., Barger, Z., Ren, Y., Ding, X., Li, S., et al. (2019). An Excitatory Circuit in the Perioculomotor Midbrain for Non-REM Sleep Control Article An Excitatory Circuit in the Perioculomotor Midbrain for Non-REM Sleep Control. Cell *177*, 1293-1307.e16.
126. Ma, C., Zhong, P., Liu, D., Barger, Z.K., Zhou, L., Chang, W.C., Kim, B., and Dan, Y. (2019). Sleep Regulation by Neurotensinergic Neurons in a Thalamo-Amygdala Circuit. Neuron *103*, 323-334.e7.
127. Palmer, C.A., and Alfano, C.A. (2017). Sleep and emotion regulation: An organizing, integrative review. Sleep Medicine Reviews *31*, 6–16.
128. Krause, A.J., Simon, E.B., Mander, B.A., Greer, S.M., Saletin, J.M., Goldstein-Piekarski, A.N., and Walker, M.P. (2017). The sleep-deprived human brain. Nat Rev Neurosci *18*, 404–418.
129. Goldstein, A.N., and Walker, M.P. (2014). The role of sleep in emotional brain function. Annual Review of Clinical Psychology *10*, 679–708.
130. Girardeau, G., Inema, I., and Buzsáki, G. (2017). Reactivations of emotional memory in the hippocampus-amygdala system during sleep. *20*.
131. Lansink, C.S., Goltstein, P.M., Lankelma, J. V, Joosten, R.N.J.M.A., McNaughton, B.L., and Pennartz, C.M.A. (2008). Preferential reactivation of motivationally relevant information in the ventral striatum. Journal of Neuroscience *28*, 6372–6382.
132. Liu, Y., Dolan, R.J., Kurth-Nelson, Z., and Behrens, T.E.J. (2019). Human Replay Spontaneously Reorganizes Experience. Cell *178*, 640-652.e14.
133. Bellesi, M., Tononi, G., Cirelli, C., and Serra, P.A. (2016). Region-Specific Dissociation between Cortical Noradrenaline Levels and the Sleep/Wake Cycle. Sleep *39*, 143–154.
134. da Silva Rocha-Lopes, J., Machado, R.B., and Suchecki, D. (2018). Chronic REM Sleep Restriction in Juvenile Male Rats Induces Anxiety-Like Behavior and Alters Monoamine Systems in the Amygdala and Hippocampus. Molecular Neurobiology *55*, 2884–2896.
135. Killgore, W.D.S. (2013). Self-Reported Sleep Correlates with Prefrontal-Amygdala Functional Connectivity and Emotional Functioning. Sleep *36*, 1597–1608.
136. Krause, A.J., Simon, E. Ben, Mander, B.A., Greer, S.M., Saletin, J.M., Goldstein-Piekarski, A.N., and Walker, M.P. (2017). Sleep disruption Attention The sleep-deprived human brain. Nature Publishing Group *18*.
137. Bian, W.J., Brewer, C.L., Kauer, J.A., and de Lecea, L. (2022). Adolescent sleep shapes social novelty preference in mice. Nature Neuroscience.
138. Tononi, G., and Cirelli, C. (2014). Sleep and the Price of Plasticity: From Synaptic and Cellular Homeostasis to Memory Consolidation and Integration. Neuron *81*, 12–34.
139. Kurth, S., Jenni, O.G., Riedner, B.A., Tononi, G., Carskadon, M.A., and Huber, R. (2010). Characteristics of sleep slow waves in children and adolescents. Sleep *33*, 475–480.

140. Feinberg, I., and Campbell, I.G. (2013). Longitudinal sleep EEG trajectories indicate complex patterns of adolescent brain maturation. American Journal of Physiology - Regulatory Integrative and Comparative Physiology *304*, 296–303.
141. Plante, D.T., Goldstein, M.R., Landsness, E.C., Riedner, B.A., Guokas, J.J., Wanger, T., Tononi, G., and Benca, R.M. (2013). Altered overnight modulation of spontaneous waking EEG reflects altered sleep homeostasis in major depressive disorder: a high-density EEG investigation. J Affect Disord *150*, 1167–1173.
142. Goldschmied, J.R., Cheng, P., Armitage, R., and Deldin, P.J. (2019). A preliminary investigation of the role of slow-wave activity in modulating waking EEG theta as a marker of sleep propensity in major depressive disorder. J Affect Disord *257*, 504–509.
143. Kuhn, M., Maier, J.G., Wolf, E., Mainberger, F., Feige, B., Maywald, S., Bredl, A., Michel, M., Sendelbach, N., Normann, C., et al. (2020). Indices of cortical plasticity after therapeutic sleep deprivation in patients with major depressive disorder. Journal of Affective Disorders *277*, 425–435.
144. Irwin, M.R., Olmstead, R., and Carroll, J.E. (2016). Sleep disturbance, sleep duration, and inflammation: A systematic review and meta-analysis of cohort studies and experimental sleep deprivation. Biological Psychiatry *80*, 40–52.
145. Winders, S., Lyon, D.E., Stechmiller, J.K., and Lynch Kelly, D. Biomarkers of sleep disturbance in adults with chronic illness: A scoping review.
146. Kelly, K.M., Smith, J.A., and Mezuk, B. (2021). Depression and interleukin-6 signaling: A Mendelian Randomization study. Brain Behav Immun *95*, 106–114.
147. Ballesio, A., Zagaria, A., Ottaviani, C., Steptoe, A., and Lombardo, C. (2022). Sleep disturbance, neuro-immune markers, and depressive symptoms in older age: Conditional process analysis from the English Longitudinal Study of Aging (ELSA). Psychoneuroendocrinology *142*, 105770.
148. Späth-Schwalbe, E., Lange, T., Perras, B., Lorenz Fehm, H., and Born, J. (2000). INTERFERON-α ACUTELY IMPAIRS SLEEP IN HEALTHY HUMANS. Cytokine *12*, 518–521.
149. Han, V.X., Patel, S., Jones, H.F., Nielsen, T.C., Mohammad, S.S., Hofer, M.J., Gold, W., Brilot, F., Lain, S.J., Nassar, N., et al. (2021). Maternal acute and chronic inflammation in pregnancy is associated with common neurodevelopmental disorders: a systematic review. Translational Psychiatry *11*, 71.
150. Vanderplow, A.M., Kermath, B.A., Bernhardt, C.R., Gums, K.T., Seablom, E.N., Radcliff, A.B., Ewald, A.C., Jones, M. V., Baker, T.L., Watters, J.J., et al. (2022). A feature of maternal sleep apnea during gestation causes autism-relevant neuronal and behavioral phenotypes in offspring. PLoS Biol *20*.
151. Huang, W.Y., Huang, C.C., Chang, C.C., Kor, C.T., Chen, T.Y., and Wu, H.M. (2017). Associations of Self-Reported Sleep Quality with Circulating Interferon Gamma-Inducible Protein 10, Interleukin 6, and High-Sensitivity C-Reactive Protein in Healthy Menopausal Women. PLOS ONE *12*, e0169216.
152. Kramer, A., Lange, T., Spies, C., Finger, A.M., Berg, D., and Oster, H. (2022). Foundations of circadian medicine. PLoS Biology *20*.
153. Kervezee, L., Kosmadopoulos, A., and Boivin, D.B. (2020). Metabolic and cardiovascular consequences of shift work: The role of circadian disruption and sleep disturbances. European Journal of Neuroscience *51*, 396–412.
154. Dolsen, M.R., Crosswell, A.D., and Prather, A.A. (2019). Links Between Stress, Sleep, and Inflammation: Are there Sex Differences? Current Psychiatry Reports 2019 21:2 *21*, 1–6.
155. Ghilotti, F., Bellocco, R., Lagerros, Y.T., Thorson, A., Theorell-Haglöw, J., Torbjörn Åkerstedt, |, and Lindberg, E. (2021). Relationship between sleep characteristics and markers of inflammation in Swedish women from the general population. J Sleep Res *30*.
156. Irwin, M.R., and Piber, D. (2018). Insomnia and inflammation: a two hit model of depression risk and prevention. World Psychiatry *17*, 359–361.

157. Radmanish, M., Khalfallah, O., Glaichenhaus, N., Forhan, A., Heude, B., Charles, M.-A., Davidovic, L., and Plancoulaine, S. (2022). Sleep duration trajectories associated with levels of specific serum cytokines at age 5: A longitudinal study in preschoolers from the EDEN birth cohort. Brain, Behavior, & Immunity - Health *21*, 100429.
158. Cook, F., Conway, L.J., Giallo, R., Gartland, D., Sciberras, E., Brown, S., and Health, I. (2020). Infant sleep and child mental health: a longitudinal investigation. Arch Dis Child *105*, 655–660.
159. Park, H., Chiang, J.J., Bower, J.E., Irwin, M.R., Almeida, D.M., Seeman, T.E., McCreath, H., and Fuligni, A.J. (2020). Sleep and Inflammation During Adolescents' Transition to Young Adulthood. Journal of Adolescent Health *67*, 821–828.
160. Fernandez-Mendoza, J., Baker, J.H., Vgontzas, A.N., Gaines, J., Liao, D., and Bixler, E.O. (2017). Insomnia symptoms with objective short sleep duration are associated with systemic inflammation in adolescents. Brain, Behavior, and Immunity *61*, 110–116.
161. Bakour, C., Schwartz, S., O'rourke, K., Wang, W., Sappenfield, W., Couluris, M., and Chen, H. (2017). Sleep Duration Trajectories and Systemic Inflammation-Bakour et al. SLEEP *40*.
162. Mitchell, R.H.B., and Goldstein, B.I. (2014). Inflammation in children and adolescents with neuropsychiatric disorders: A systematic review. J Am Acad Child Adolesc Psychiatry *53*, 274–296.
163. Reddy, A., Thootkur, M., and Li, L. (2020). Association Between Major Depressive Disorder and Sleep Disturbances Through Inflammation in Adolescents. Frontiers in Psychiatry *11*, 1.
164. Quidé, Y., Bortolasci, C.C., Spolding, B., Kidnapillai, S., Watkeys, O.J., Cohen-Woods, S., Berk, M., Carr, V.J., Walder, K., and Green, M.J. (2019). Association between childhood trauma exposure and pro-inflammatory cytokines in schizophrenia and bipolar-I disorder. Psychological Medicine *49*, 2736–2744.
165. Fang, S.H., Suzuki, K., Lim, C.L., Chung, M.S., Ku, P.W., and Chen, L.J. (2016). Associations between sleep quality and inflammatory markers in patients with schizophrenia. Psychiatry Research *246*, 154–160.
166. Lee, E.E., Ancoli-Israel, S., Eyler, L.T., Tu, X.M., Palmer, B.W., Irwin, M.R., and Jeste, D. V. (2019). Sleep Disturbances and Inflammatory Biomarkers in Schizophrenia: Focus on Sex Differences. American Journal of Geriatric Psychiatry *27*, 21–31.
167. Xie, L., Kang, H., Xu, Q., Chen, M.J., Liao, Y., Thiyagarajan, M., O'Donnell, J., Christensen, D.J., Nicholson, C., Iliff, J.J., et al. (2013). Sleep drives metabolite clearance from the adult brain. Science (1979) *342*, 373–377.
168. Reddy, O.C., and van der Werf, Y.D. (2020). The sleeping brain: Harnessing the power of the glymphatic system through lifestyle choices. Brain Sciences *10*, 1–16.
169. Zhang, R., Liu, Y., Chen, Y., Li, Q., Marshall, C., Wu, T., Hu, G., and Xiao, M. (2020). Aquaporin 4 deletion exacerbates brain impairments in a mouse model of chronic sleep disruption. CNS Neuroscience and Therapeutics *26*, 228–239.
170. Yan, T., Qiu, Y., Yu, X., and Yang, L. (2021). Glymphatic Dysfunction: A Bridge Between Sleep Disturbance and Mood Disorders. Frontiers in Psychiatry *12*, 1–13.
171. Wirth, M.D., Jessup, A., Turner-McGrievy, G., Shivappa, N., Hurley, T.G., and Hébert, J.R. (2020). Changes in dietary inflammatory potential predict changes in sleep quality metrics, but not sleep duration. Sleep *43*.
172. Wang, Z., Chen, W.-H., Li, S.-X., He, Z.-M., Zhu, W.-L., Ji, Y.-B., Wang, Z., Zhu, X.-M., Yuan, K., Bao, Y.-P., et al. (2021). Gut microbiota modulates the inflammatory response and cognitive impairment induced by sleep deprivation. Molecular Psychiatry *26*, 6277–6292.
173. Talbot, L.S., Stone, S., Gruber, J., Hairston, I.S., Eidelman, P., and Harvey, A.G. (2012). A test of the bidirectional association between sleep and mood in bipolar disorder and insomnia. J Abnorm Psychol *121*, 39–50.
174. NICE (2022). NICE clinical knowledge summary - Insomnia. https://cks.nice.org.uk/topics/insomnia/.

175. Wilson, S., Anderson, K., Baldwin, D., Dijk, D.J., Espie, A., Espie, C., Gringras, P., Krystal, A., Nutt, D., Selsick, H., et al. (2019). British Association for Psychopharmacology consensus statement on evidence-based treatment of insomnia, parasomnias and circadian rhythm disorders: An update. Journal of Psychopharmacology *33*, 923–947.
176. Riemann, D., Baglioni, C., Bassetti, C., Bjorvatn, B., Dolenc Groselj, L., Ellis, J.G., Espie, C.A., Garcia-Borreguero, D., Gjerstad, M., Gonçalves, M., et al. (2017). European guideline for the diagnosis and treatment of insomnia. Journal of Sleep Research *26*, 675–700.
177. Trauer, J.M., Qian, M.Y., Doyle, J.S., Rajaratnam, S.M.W., and Cunnington, D. (2015). Cognitive behavioral therapy for chronic insomnia: A systematic review and meta-analysis. Annals of Internal Medicine *163*, 191–204.
178. Benz, F., Knoop, T., Ballesio, A., Bacaro, V., Johann, A.F., Rücker, G., Feige, B., Riemann, D., and Baglioni, C. (2020). The efficacy of cognitive and behavior therapies for insomnia on daytime symptoms: A systematic review and network meta-analysis. Clinical Psychology Review *80*, 101873.
179. Wu, J.Q., Appleman, E.R., Salazar, R.D., and Ong, J.C. (2015). Cognitive behavioral therapy for insomnia comorbid with psychiatric and medical conditions a meta-analysis. JAMA Internal Medicine *175*, 1461–1472.
180. Gee, B., Orchard, F., Clarke, E., Joy, A., Clarke, T., and Reynolds, S. (2019). The effect of non-pharmacological sleep interventions on depression symptoms: A meta-analysis of randomised controlled trials. Sleep Medicine Reviews *43*, 118–128.
181. Scott, A.J., Webb, T.L., Martyn-St James, M., Rowse, G., and Weich, S. (2021). Improving sleep quality leads to better mental health: A meta-analysis of randomised controlled trials. Sleep Medicine Reviews *60*, 101556.
182. Harvey, Allison., Soehner, A.M., Kaplan, K.A., Hein, K., Lee, J., Kanady, J., Li, D., Rabe-Hesketh, S., Ketter, T.A., Neylan, T.C., et al. (2015). Treating insomnia improves mood state, sleep, and functioning in bipolar disorder: A pilot randomized controlled trial. Journal of Consulting and Clinical Psychology *83*, 564–577.
183. Freeman, D., Waite, F., Startup, H., Myers, E., Lister, R., McInerney, J., Harvey, A.G., Geddes, J., Zaiwalla, Z., Luengo-Fernandez, R., et al. (2015). Efficacy of cognitive behavioural therapy for sleep improvement in patients with persistent delusions and hallucinations (BEST): A prospective, assessor-blind, randomised controlled pilot trial. The Lancet Psychiatry *2*, 975–983.
184. Espie, C.A., Emsley, R., Kyle, S.D., Gordon, C., Drake, C.L., Siriwardena, A.N., Cape, J., Ong, J.C., Sheaves, B., Foster, R., et al. (2019). Effect of Digital Cognitive Behavioral Therapy for Insomnia on Health, Psychological Well-being, and Sleep-Related Quality of Life: A Randomized Clinical Trial. JAMA Psychiatry *76*, 21–30.
185. Christensen, H., Batterham, P.J., Gosling, J.A., Ritterband, L.M., Griffiths, K.M., Thorndike, F.P., Glozier, N., O'Dea, B., Hickie, I.B., and Mackinnon, A.J. (2016). Effectiveness of an online insomnia program (SHUTi) for prevention of depressive episodes (the GoodNight Study): a randomised controlled trial. Lancet Psychiatry *3*, 333–341.
186. Cheng, P., Kalmbach, D.A., Tallent, G., Joseph, C.L.M., Espie, C.A., and Drake, C.L. (2019). Depression prevention via digital cognitive behavioral therapy for insomnia: A randomized controlled trial. Sleep *42*, 1–9.
187. Morin, C.M., Edinger, J.D., Beaulieu-Bonneau, S., Ivers, H., Krystal, A.D., Guay, B., Bélanger, L., Cartwright, A., Simmons, B., Lamy, M., et al. (2020). Effectiveness of Sequential Psychological and Medication Therapies for Insomnia Disorder: A Randomized Clinical Trial. JAMA Psychiatry *77*, 1107–1115.
188. Harvey, A.G., Dong, L., Hein, K., Yu, S., Martinez, A., Gumport, N., Smith, F.L., Chapman, A., Lisman, M., Mirzadegan, I.A., et al. (2021). A randomized controlled trial of the Transdiagnostic Intervention for Sleep and Circadian Dysfunction (TranS-C) to improve serious mental illness outcomes in a community setting. Journal of Consulting and Clinical Psychology *In press*.

189. Schneider, C.L., Hertenstein, E., Fehér, K., Maier, J.G., Cantisani, A., Moggi, F., Berger, T., and Nissen, C. (2020). Become your own SLEEPexpert : design, implementation, and preliminary evaluation of a pragmatic behavioral treatment program for insomnia in inpatient psychiatric care . SLEEP Advances *1*, 1–8.
190. Sheaves, B., Freeman, D., Isham, L., McInerney, J., Nickless, A., Yu, L.-M., Rek, S., Bradley, J., Reeve, S., Attard, C., et al. (2017). Stabilising sleep for patients admitted at acute crisis to a psychiatric hospital (OWLS): an assessor-blind pilot randomised controlled trial. Psychol Med, 1–11.
191. Gottlieb, J.F., Benedetti, F., Geoffroy, P.A., Henriksen, T.E.G., Lam, R.W., Murray, G., Phelps, J., Sit, D., Swartz, H.A., Crowe, M., et al. (2019). The chronotherapeutic treatment of bipolar disorders: A systematic review and practice recommendations from the ISBD task force on chronotherapy and chronobiology. Bipolar Disorders *21*, 741–773.
192. Bisdounis, L., Saunders, K.E.A., Farley, H.J., Lee, C.K., McGowan, N.M., Espie, C.A., and Kyle, S.D. (2022). Psychological and behavioural interventions in bipolar disorder that target sleep and circadian rhythms: A systematic review of randomised controlled trials. Neuroscience and Biobehavioral Reviews *132*, 378–390.
193. Faulkner, S.M., Bee, P.E., Meyer, N., Dijk, D.-J., and Drake, R.J. (2019). Light therapies to improve sleep in intrinsic circadian rhythm sleep disorders and neuro-psychiatric illness: a systematic review and meta-analysis. Sleep Medicine Reviews *46*, 108–123.
194. Boland, E.M., Rao, H., Dinges, D.F., Smith, R. V., Goel, N., Detre, J.A., Basner, M., Sheline, Y.I., Thase, M.E., and Gehrman, P.R. (2017). Meta-analysis of the antidepressant effects of acute sleep deprivation. Journal of Clinical Psychiatry *78*, e1020–e1034.
195. Boland, E.M., Rao, H., Dinges, D.F., Smith, R. V., Goel, N., Detre, J.A., Basner, M., Sheline, Y.I., Thase, M.E., and Gehrman, P.R. (2017). Meta-analysis of the antidepressant effects of acute sleep deprivation. Journal of Clinical Psychiatry *78*, e1020–e1034.
196. Humpston, C., Benedetti, F., Serfaty, M., Markham, S., Hodsoll, J., Young, A.H., and Veale, D. (2020). Chronotherapy for the rapid treatment of depression: A meta-analysis. Journal of Affective Disorders *261*, 91–102.
197. Rajaratnam, S.M.W., Middleton, B., Stone, B.M., Arendt, J., and Dijk, D.-J. (2004). Melatonin advances the circadian timing of EEG sleep and directly facilitates sleep without altering its duration in extended sleep opportunities in humans. J Physiol *561*, 339–351.
198. Palagini, L., Manni, R., Aguglia, E., Amore, M., Brugnoli, R., Bioulac, S., Bourgin, P., Micoulaud Franchi, J.A., Girardi, P., Grassi, L., et al. (2021). International Expert Opinions and Recommendations on the Use of Melatonin in the Treatment of Insomnia and Circadian Sleep Disturbances in Adult Neuropsychiatric Disorders. Frontiers in Psychiatry *12*, 1–15.
199. Frank, E., Swartz, H.A., and Boland, E. (2007). Interpersonal and social rhythm therapy: An intervention addressing rhythm dysregulation in bipolar disorder. Dialogues in Clinical Neuroscience *9*, 325–332.
200. Harvey, A.G., and Buysse, D.J. (2018). Treating sleep problems: A transdiagnostic approach. (The Guilford Press).
201. Buysse, D.J. (2014). Sleep health: can we define It? does it matter? Sleep *37*, 9–17.
202. Moussavi, S., Chatterji, S., Verdes, E., Tandon, A., Patel, V., and Ustun, B. (2007). Depression, chronic diseases, and decrements in health: results from the World Health Surveys. Lancet *370*, 851–858.
203. Long, Q., Jin, H., You, X., Liu, Y., Teng, Z., Chen, Y., Zhu, Y., and Zeng, Y. (2022). Eczema is a shared risk factor for anxiety and depression: A meta-analysis and systematic review. PLoS ONE *17*, 1–15.
204. Van Dyne, A., Moy, J., Wash, K., Thompson, L., Skow, T., Roesch, S.C., and Cronan, T. (2022). Health, Psychological and Demographic Predictors of Depression in People

with Fibromyalgia and Osteoarthritis. International Journal of Environmental Research and Public Health 2022, Vol. 19, Page 3413 *19*, 3413.
205. Krishnan, S., Chai-Coetzer, C.L., Grivell, N., Lovato, N., Mukherjee, S., Vakulin, A., Adams, R.J., and Appleton, S.L. (2022). Comorbidities and quality of life in Australian men and women with diagnosed and undiagnosed high risk obstructive sleep apnea. Journal of Clinical Sleep Medicine.
206. MacAulay, G.C., Galland, B.C., Boucher, S.E., Wiltshire, E.J., Haszard, J.J., Campbell, A.J., Black, S.M., Smith, C., Elder, D., and Wheeler, B.J. (2020). Impact of type 1 diabetes mellitus, glucose levels, and glycemic control on sleep in children and adolescents: A case-control study. Sleep *43*, 1–11.
207. Tyring, S., Gottlieb, A., Papp, K., Gordon, K., Leonardi, C., Wang, A., Lalla, D., Woolley, M., Jahreis, A., Zitnik, R., et al. (2006). Etanercept and clinical outcomes, fatigue, and depression in psoriasis: Double-blind placebo-controlled randomised phase III trial. Lancet *367*, 29–35.
208. Martins, D., Dipasquale, O., Davies, K., Cooper, E., Tibble, J., Veronese, M., Frigo, M., Williams, S.C.R., Turkheimer, F., Cercignani, M., et al. (2022). Transcriptomic and cellular decoding of functional brain connectivity changes reveal regional brain vulnerability to pro- and anti-inflammatory therapies. Brain, Behavior, and Immunity *102*, 312–323.
209. Simonelli, G., Marshall, N.S., Grillakis, A., Miller, C.B., Hoyos, C.M., and Glozier, N. (2018). Sleep health epidemiology in low and middle-income countries: a systematic review and meta-analysis of the prevalence of poor sleep quality and sleep duration. Sleep Health *4*, 239–250.
210. Manzar, M.D., Bekele, B.B., Noohu, M.M., Salahuddin, M., Albougami, A., Spence, D.W., Pandi-Perumal, S.R., and Bahammam, A.S. (2020). Prevalence of poor sleep quality in the Ethiopian population: a systematic review and meta-analysis. Sleep and Breathing *24*, 709–716.
211. Stranges, S., Tigbe, W., Gómez-Olivé, F.X., Thorogood, M., and Kandala, N.B. (2012). Sleep problems: An emerging global epidemic? Findings from the INDEPTH WHO-SAGE study among more than 40,000 older adults from 8 countries across Africa and Asia. Sleep *35*, 1173–1181.
212. Chaput, J.-P., Katzmarzyk, P.T., LeBlanc, A.G., Tremblay, M.S., Barreira, T. V, Broyles, S.T., Fogelholm, M., Hu, G., Kuriyan, R., Kurpad, A., et al. (2015). Associations between sleep patterns and lifestyle behaviors in children: an international comparison. International Journal of Obesity Supplements *5*, S59–S65.
213. Hill, T.D., Trinh, H.N., Wen, M., and Hale, L. (2016). Perceived neighborhood safety and sleep quality: A global analysis of six countries. Sleep Medicine *18*, 56–60.
214. Alonzo, R., Hussain, J., Stranges, S., and Anderson, K.K. (2021). Interplay between social media use, sleep quality, and mental health in youth: A systematic review. Sleep Medicine Reviews *56*.
215. Kieling, C., Baker-Henningham, H., Belfer, M., Conti, G., Ertem, I., Omigbodun, O., Rohde, L.A., Srinath, S., Ulkuer, N., and Rahman, A. (2011). Child and adolescent mental health worldwide: evidence for action. The Lancet *378*, 1515–1525.
216. Patel, V., Saxena, S., Lund, C., Thornicroft, G., Baingana, F., Bolton, P., Chisholm, D., Collins, P.Y., Cooper, J.L., Eaton, J., et al. (2018). The Lancet Commission on global mental health and sustainable development. The Lancet *392*, 1553–1598.
217. Kearns, J.C., Kittel, J.A., Schlagbaum, P., Pigeon, W.R., and Glenn, C.R. (2021). Worry-related sleep problems and suicidal thoughts and behaviors among adolescents in 88 low-, middle-, and high-income countries: an examination of individual- and country-level factors. European Child and Adolescent Psychiatry *1*, 1–17.
218. Van Kamp, I., and Davies, H. (2013). Noise and Health. Noise and Health *15*, 153.
219. Paksarian, D., Rudolph, K.E., Stapp, E.K., Dunster, G.P., He, J., Mennitt, D., Hattar, S., Casey, J.A., James, P., and Merikangas, K.R. (2020). Association of Outdoor

Artificial Light at Night With Mental Disorders and Sleep Patterns Among US Adolescents. JAMA Psychiatry *77*, 1266–1275.
220. Vollmer, C., Michel, U., and Randler, C. (2012). Outdoor Light at Night (LAN) Is Correlated With Eveningness in Adolescents. https://doi.org/10.3109/07420528.2011.635232 *29*, 502–508.
221. Wang, L.-B., Gong, Y.-C., Fang, Q.-L., Cui, X.-X., Dharmage, S.C., Jalaludin, B., Knibbs, L.D., Bloom, M.S., Guo, Y., Lin, L.-Z., et al. (2022). Association Between Exposure to Outdoor Artificial Light at Night and Sleep Disorders Among Children in China. JAMA Network Open *5*, e2213247–e2213247.
222. Smolensky, M.H., Sackett-Lundeen, L.L., and Portaluppi, F. (2015). Nocturnal light pollution and underexposure to daytime sunlight: Complementary mechanisms of circadian disruption and related diseases. Chronobiology International *32*, 1029–1048.
223. Cao, M., Xu, T., and Yin, D. (2022). Understanding light pollution: recent advances on its health threats and regulations. Journal of Environmental Sciences.
224. Bedrosian, T.A., and Nelson, R.J. (2017). Timing of light exposure affects mood and brain circuits. Translational Psychiatry 2017 7:1 *7*, e1017–e1017.
225. Reiter, R.J., Rosales-Corral, S., and Sharma, R. (2020). Circadian disruption, melatonin rhythm perturbations and their contributions to chaotic physiology. Advances in Medical Sciences *65*, 394–402.
226. Fisk, A.S., Tam, S.K.E., Brown, L.A., Vyazovskiy, V. V., Bannerman, D.M., and Peirson, S.N. (2018). Light and cognition: Roles for circadian rhythms, sleep, and arousal. Frontiers in Neurology *9*, 56.
227. Brown, T.M., Brainard, G.C., Cajochen, C., Czeisler, C.A., Hanifin, J.P., Lockley, S.W., Lucas, R.J., Münch, M., OHagan, J.B., Peirson, S.N., et al. (2022). Recommendations for daytime, evening, and nighttime indoor light exposure to best support physiology, sleep, and wakefulness in healthy adults. PLoS Biology *20*, 1–24.
228. Münch, M., Wirz-Justice, A., Brown, S.A., Kantermann, T., Martiny, K., Stefani, O., Vetter, C., Wright, K.P., Wulff, K., and Skene, D.J. (2020). The Role of Daylight for Humans: Gaps in Current Knowledge. Clocks & Sleep *2*, 61–85.
229. Spitschan, M. (2019). Future-proofing circadian research. Light Res Technol *51*, 818–819.
230. European Environment Agency (2020). Health risks caused by environmental noise in Europe — European Environment Agency. https://www.eea.europa.eu/publications/health-risks-caused-by-environmental.
231. Hegewald, J., Schubert, M., Freiberg, A., Starke, K.R., Augustin, F., Riedel-Heller, S.G., Zeeb, H., and Seidler, A. (2020). Traffic Noise and Mental Health: A Systematic Review and Meta-Analysis. International Journal of Environmental Research and Public Health 2020, Vol. 17, Page 6175 *17*, 6175.
232. Thompson, R., Smith, R.B., Bou Karim, Y., Shen, C., Drummond, K., Teng, C., and Toledano, M.B. (2022). Noise pollution and human cognition: An updated systematic review and meta-analysis of recent evidence. Environment International *158*.
233. Bao, W.-W., Xue, W.-X., Jiang, N., Huang, S., Zhang, S.-X., Zhao, Y., Chen, Y.-C., Dong, G.-H., Cai, M., and Chen, Y.-J. (2022). Exposure to road traffic noise and behavioral problems in Chinese schoolchildren: A cross-sectional study. Science of The Total Environment *837*, 155806.
234. Cao, B., Chen, Y., and McIntyre, R.S. (2021). Comprehensive review of the current literature on impact of ambient air pollution and sleep quality. Sleep Medicine *79*, 211–219.
235. Liu, J., Wu, T., Liu, Q., Wu, S., and Chen, J.C. (2020). Air pollution exposure and adverse sleep health across the life course: A systematic review. Environmental Pollution *262*.
236. Kalmbach, D.A., Anderson, J.R., and Drake, C.L. (2018). The impact of stress on sleep: Pathogenic sleep reactivity as a vulnerability to insomnia and circadian disorders. Journal of Sleep Research *27*.

237. Kalmbach, D.A., Pillai, V., Arnedt, J.T., Anderson, J.R., and Drake, C.L. (2016). Sleep system sensitization: Evidence for changing roles of etiological factors in insomnia. Sleep Medicine *21*, 63–69.
238. Riemann, D., Spiegelhalder, K., Feige, B., Voderholzer, U., Berger, M., Perlis, M., and Nissen, C. (2010). The hyperarousal model of insomnia: A review of the concept and its evidence. Sleep Medicine Reviews *14*, 19–31.
239. Van Someren, E.J.W. (2021). Brain mechanisms of insomnia: new perspectives on causes and consequences. Physiol Rev *101*, 995–1046.
240. Riberio, A., Rachel, G., Bernardo, G., Casey, C., William, A., Alejandro, M., Colby, L., Arlene, H., Neil, K., and Pfaff, D. (2022). Temporal relations between peripheral and central arousals in good and poor sleepers. Proceedings of the National Academy of Sciences *119*, e2201143119.
241. Feder, A., Fred-Torres, S., Southwick, S.M., and Charney, D.S. (2019). The Biology of Human Resilience: Opportunities for Enhancing Resilience Across the Life Span. Biological Psychiatry *86*, 443–453.
242. Arora, T., Grey, I., Östlundh, L., Alamoodi, A., Omar, O.M., Hubert Lam, K.B., and Grandner, M. (2022). A systematic review and meta-analysis to assess the relationship between sleep duration/quality, mental toughness and resilience amongst healthy individuals. Sleep Medicine Reviews *62*.
243. Collop, N.A. (2002). Scoring variability between polysomnography technologists in different sleep laboratories. Sleep Medicine *3*, 43–47.
244. Grandner, M.A., Lujan, M.R., and Ghani, S.B. (2021). Sleep-tracking technology in scientific research: Looking to the future. Sleep *44*, 1–3.
245. Ancoli-Israel, S., Cole, R., Alessi, C., Chambers, M., Moorcroft, W., and Pollak, C.P. (2003). The role of actigraphy in the study of sleep and circadian rhythms. Sleep *26*, 342–392.
246. Lujan, M.R., Perez-Pozuelo, I., and Grandner, M.A. (2021). Past, Present, and Future of Multisensory Wearable Technology to Monitor Sleep and Circadian Rhythms. Frontiers in Digital Health *3*, 1–20.
247. Depner, C.M., Cheng, P.C., Devine, J.K., Khosla, S., De Zambotti, M., Robillard, R., Vakulin, A., and Drummond, S.P.A. (2020). Wearable technologies for developing sleep and circadian biomarkers: A summary of workshop discussions. Sleep *43*, 1–13.
248. Perez-Pozuelo, I., Zhai, B., Palotti, J., Mall, R., Aupetit, M., Garcia-Gomez, J.M., Taheri, S., Guan, Y., and Fernandez-Luque, L. (2020). The future of sleep health: a data-driven revolution in sleep science and medicine. npj Digital Medicine *3*, 1–15.
249. Zhang, Y., Folarin, A.A., Sun, S., Cummins, N., Bendayan, R., Ranjan, Y., Rashid, Z., Conde, P., Stewart, C., Laiou, P., et al. (2021). Relationship between major depression symptom severity and sleep collected using a wristband wearable device: Multicenter longitudinal observational study. JMIR Mhealth Uhealth *9*, 1–15.
250. De Angel, V., Lewis, S., White, K., Oetzmann, C., Leightley, D., Oprea, E., Lavelle, G., Matcham, F., Pace, A., Mohr, D.C., et al. (2022). Digital health tools for the passive monitoring of depression: a systematic review of methods. npj Digital Medicine *5*.
251. Melbye, S.A., Stanislaus, S., Vinberg, M., Frost, M., Bardram, J.E., Sletved, K., Coello, K., Kjærstad, H.L., Christensen, E.M., Faurholt-Jepsen, M., et al. (2021). Mood, activity, and sleep measured via daily smartphone-based self-monitoring in young patients with newly diagnosed bipolar disorder, their unaffected relatives and healthy control individuals. European Child and Adolescent Psychiatry *30*, 1209–1221.
252. Merikangas, K.R., Swendsen, J., Hickie, I.B., Cui, L., Shou, H., Merikangas, A.K., Zhang, J., Lamers, F., Crainiceanu, C., Volkow, N.D., et al. (2019). Real-time Mobile Monitoring of the Dynamic Associations among Motor Activity, Energy, Mood, and Sleep in Adults with Bipolar Disorder. JAMA Psychiatry *76*, 190–198.

253. Meyer, N., Kerz, M., Folarin, A., Joyce, D.W., Jackson, R., Karr, C., Dobson, R., and Maccabe, J. (2018). Capturing rest-activity profiles in schizophrenia using wearable and mobile technologies: Development, implementation, feasibility, and acceptability of a remote monitoring platform. JMIR Mhealth Uhealth *6*, e188.
254. Barnett, I., Torous, J., Staples, P., Sandoval, L., Keshavan, M., and Onnela, J.P. (2018). Relapse prediction in schizophrenia through digital phenotyping: A pilot study. Neuropsychopharmacology *43*, 1660–1666.
255. Lujan, M.R., Perez-Pozuelo, I., and Grandner, M.A. (2021). Past, Present, and Future of Multisensory Wearable Technology to Monitor Sleep and Circadian Rhythms. Frontiers in Digital Health *3*, 1–20.
256. Chinoy, E.D., Cuellar, J.A., Huwa, K.E., Jameson, J.T., Watson, C.H., Bessman, S.C., Hirsch, D.A., Cooper, A.D., Drummond, S.P.A., and Markwald, R.R. (2021). Performance of seven consumer sleep-tracking devices compared with polysomnography. Sleep *44*, 1–16.
257. de Zambotti, M., Goldstone, A., Claudatos, S., Colrain, I.M., and Baker, F.C. (2017). A validation study of Fitbit Charge 2 compared with polysomnography in adults. Chronobiology International, 1–12.
258. Arnal, P.J., Thorey, V., Debellemaniere, E., Ballard, M.E., Hernandez, A.B., Guillot, A., Jourde, H., Harris, M., Guillard, M., van Beers, P., et al. (2020). The dreem headband compared to polysomnography for electroencephalographic signal acquisition and sleep staging. Sleep *43*, 1–13.
259. Kwon, S., Kim, H., and Yeo, W.H. (2021). Recent advances in wearable sensors and portable electronics for sleep monitoring. iScience *24*, 102461.
260. de Zambotti, M., Menghini, L., Grandner, M.A., Redline, S., Zhang, Y., Wallace, M.L., and Buxton, O.M. (2022). Rigorous performance evaluation (previously, “validation”) for informed use of new technologies for sleep health measurement. Sleep Health *8*.
261. Menghini, L., Cellini, N., Goldstone, A., Baker, F.C., and de Zambotti, M. (2021). A standardized framework for testing the performance of sleep-tracking technology: step-by-step guidelines and open-source code. Sleep *44*, 1–12.
262. Depner, C.M., Cheng, P.C., Devine, J.K., Khosla, S., De Zambotti, M., Robillard, R., Vakulin, A., and Drummond, S.P.A. (2020). Wearable technologies for developing sleep and circadian biomarkers: A summary of workshop discussions. Sleep *43*, 1–13.
263. Hastings, M.H., Reddy, A.B., and Maywood, E.S. (2003). A clockwork web: Circadian timing in brain and periphery, in health and disease. Nature Reviews Neuroscience *4*, 649–661.
264. Arendt, J. (2005). Melatonin: Characteristics, concerns, and prospects. Journal of Biological Rhythms *20*, 291–303.
265. Slyepchenko, A., Allega, O.R., Leng, X., Minuzzi, L., Eltayebani, M.M., Skelly, M., Sassi, R.B., Soares, C.N., Kennedy, S.H., and Frey, B.N. (2019). Association of functioning and quality of life with objective and subjective measures of sleep and biological rhythms in major depressive and bipolar disorder. Aust N Z J Psychiatry, 4867419829228.
266. Robillard, R., Carpenter, J.S., Rogers, N.L., Fares, S., Grierson, A.B., Hermens, D.F., Naismith, S.L., Mullin, S.J., Feilds, K.-L., Glozier, N., et al. (2018). Circadian rhythms and psychiatric profiles in young adults with unipolar depressive disorders. Transl Psychiatry *8*, 213.
267. Wulff, K., Dijk, D.-J.J., Middleton, B., Foster, R.G., and Joyce, E.M. (2012). Sleep and circadian rhythm disruption in schizophrenia. British Journal of Psychiatry *200*, 308–316.
268. Bromundt, V., Köster, M., Georgiev-Kill, A., Opwis, K., Wirz-Justice, A., Stoppe, G., and Cajochen, C. (2011). Sleep - Wake cycles and cognitive functioning in schizophrenia. British Journal of Psychiatry *198*, 269–276.
269. Dijk, D.J., and Duffy, J.F. (2020). Novel Approaches for Assessing Circadian Rhythmicity in Humans: A Review. Journal of Biological Rhythms *35*, 421–438.

270. Laing, E.E., Möller-Levet, C.S., Poh, N., Santhi, N., Archer, S.N., and Dijk, D.J. (2017). Blood transcriptome based biomarkers for human circadian phase. Elife *6*, 1–26.
271. Hughey, J.J. (2017). Machine learning identifies a compact gene set for monitoring the circadian clock in human blood. Genome Medicine *9*, 1–11.
272. Stone, J.E., Phillips, A.J.K., Ftouni, S., Magee, M., Howard, M., Lockley, S.W., Sletten, T.L., Anderson, C., Rajaratnam, S.M.W., and Postnova, S. (2019). Generalizability of A Neural Network Model for Circadian Phase Prediction in Real-World Conditions. Scientific Reports *9*, 1–17.
273. Cheng, P., Walch, O., Huang, Y., Mayer, C., Sagong, C., Cuamatzi Castelan, A., Burgess, H.J., Roth, T., Forger, D.B., and Drake, C.L. (2021). Predicting circadian misalignment with wearable technology: validation of wrist-worn actigraphy and photometry in night shift workers. Sleep *44*, 1–8.
274. Huang, Y., Mayer, C., Cheng, P., Siddula, A., Burgess, H.J., Drake, C., Goldstein, C., Walch, O., Forger, D.B., and Forger, D.B. (2021). Predicting circadian phase across populations: A comparison of mathematical models and wearable devices. Sleep *44*, 1–11.
275. Skeldon, A.C., Dijk, D.-J., Meyer, N., and Wulff, K. (2021). Extracting Circadian and Sleep Parameters from Longitudinal Data in Schizophrenia for the Design of Pragmatic Light Interventions. Schizophrenia Bulletin, 1–10.

Appendix 1

We gratefully acknowledge the generous contribution of leading experts in the field, who kindly agreed to be interviewed for the purposes of this scoping report. These include:

Melanie Abbass, King's College London
Massimiliano Di Zambotti, SRI international, California
Daniel Buysse, University of Pittsburgh
Sarah Chellappa, University of Cologne
Sean Drummond, Monash University
Alice Gregory, Goldsmiths, University of London
Ian Hickie, University of Sydney
Andrew Krystal, University of California San Francisco
Simon Kyle, University of Oxford
Monique Lebourgeois, Unversity of Colorado Boulder
Hugh Marston, Boehringer Ingelheim
Greg Murray, Swinburne University of Technology
Christoph Nissen, University of Geneva
Jan Scott, University of Newcastle
Danny Smith, University of Edinburgh
Adriane Soehner, University of Pittsburgh
Leila Tarokh, University of Bern
Jonathan Winkelman, Harvard University