The role of sleep disorders in the onset, persistence, and remission of psychotic experiences in children

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Thesis declaration form

I confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

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Overview

An association between sleep and psychotic symptoms is increasingly apparent and offers opportunities for intervention and understanding of the etiology of psychosis. This thesis explores the link between sleep and psychotic symptoms in middle childhood and preadolescence, and is presented in three parts.

Part 1 is a conceptual review of the association between nightmares and hallucinations in middle childhood. The high prevalence of nightmares and hallucinations within middle childhood is framed within the context of socio-cognitive and neural developmental changes in this period, and links are made with mechanisms relevant to both phenomena including trauma, emotion regulation, and anxiety.

Part 2 utilises a large dataset from the ongoing ABCD cohort study to investigate the relationships between sleep and distressing psychotic symptoms in 10-11 year-olds over a one year observation period. Sleep problems are found to significantly predict later distressing psychotic symptoms, and particularly strongly predict persistence of distressing psychotic symptoms across the study period. Nightmares are analysed separately and are also significantly associated with psychotic experiences, but do not significantly predict psychotic experiences above other sleep disorders. The results nevertheless support a role of sleep problems in predicting persistence of distressing psychotic experiences., for which implications are discussed.

Part 3 is a critical appraisal of both the open science methodology applied in Part 2 and the challenges still to be faced in establishing sleep as a therapeutic target in mental health.

Impact statement

This thesis explores the role of sleep as a causal factor in psychotic experiences, a question of relevance to clinicians, researchers, and policy makers.

Paper 1 explores a potential developmental framework for understanding the high prevalence of nightmares and hallucinations in middle childhood, including an examination of factors that may predict persistence of these symptoms into adolescence. This will be of use to clinicians in understanding possible presentations of these symptoms and understanding the potential contributors to persistence of symptoms, itself a key factor in predicting later mental health outcomes. For researchers the review provides a framework for understanding shared mechanisms that can be examined in future studies – for example, testing relationships between nightmares and socio-cognitive development in children. For policymakers it could provide evidence towards investment in sleep disorder screening for children, including better assessment of nightmares.

Paper 2 adds to the empirical evidence base on sleep and psychosis by demonstrating that sleep problems are common and associated with psychotic experiences in preadolescence. The results presented can therefore again inform clinical practice, wherein clinicians can be made more aware of this link and consider sleep interventions as part of preventative treatment for mental health. It can also aid policy makers in further understanding the

importance of sleep which has been historically neglected in health. Lastly the findings can be built upon by other researchers seeking to investigate mental health in children. The use of a large cohort dataset means that the associations reported are robust, but there is no causal test (as the data are observational only). Nevertheless the findings could be used to develop interventions that will allow a causal test of the relationship between sleep and psychotic experiences in childhood, and potential development of new and innovative therapies for these important issues.

In addition to this thesis the findings will be disseminated in journal outputs (an abridged version of Paper 2 is already available to readers online via a pre-print) and other academic routes, in addition to any non-academic dissemination opportunities that become available.

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Part 1: Literature Review

Nightmares and hallucinations in middle childhood: A conceptual review of developmental mechanisms

Abstract

There is a growing interest in the causal relationship between sleep disorders, including nightmares, and psychotic symptoms such as delusions and hallucinations. Both nightmares and hallucinations are highly prevalent in middle childhood (ages 7-11) and particularly in pre-adolescence (ages 9-11). In childhood both nightmares and hallucinations are relatively benign (although still associated with mental health and functional impairment), but persistence into adolescence is associated with increasingly negative mental health outcomes. Yet there has been little attention to the overlap between nightmares and hallucinations in childhood, or into what factors might predict persistence of these symptoms into adolescence. The current review firstly outlines how nightmares and hallucinations in this middle childhood could both plausibly result from co-occurring socio-cognitive development – particularly in the capacity to represent the mental states of others – and the neurophysiological changes that accompany this. The review then goes on to describe factors that may predict persistence of nightmares and hallucinations in adolescence, including trauma, anxiety, emotion dysregulation, and mutual reinforcement of hallucinations by nightmares and vice versa. The review concludes with challenges for future research on nightmares and hallucinations with a particular call for higher quality measurement within longitudinal cohort studies. Clinical implications of the findings are also discussed in terms of possible therapeutic targets for early intervention.

Nightmares and hallucinations in middle childhood: A conceptual review of developmental mechanisms

Nightmares and psychosis have had a long and vivid historical association, in part due to their similarities in being non-veridical, salient, often fearful experiences accompanied by lack of insight. Initial theories that frame hallucinations as nightmares arising in waking time have been discounted in favour of a more nuanced understanding of their distinct features and mechanisms (Waters et al., 2016). Yet interest in their overlap has been rekindled by increasing awareness of a potential causal role of sleep problems – including nightmares - in psychosis (Reeve et al., 2015; Waite et al., 2019). Nightmares are common in patients with psychosis (reported by 48.6% of patients in one study; Reeve et al., 2019)), and are associated with hallucinations in patient (Sheaves et al., 2015) and general population studies (Kammerer et al., 2021; Rek et al., 2017).

Interestingly, both nightmares and hallucinations are most prevalent within the same period of childhood – approximately between ages 7 and 11 (defined as 'middle childhood), and particularly in the latter half of this period (often referred to as 'preadolescence'). For example, a large cohort study reported almost half (46.9%) of nine-year-olds reported nightmares (Schredl et al., 2009b), declining to 30% by age 11. Thereafter the prevalence of frequent nightmares declines throughout adolescence to the adult rate of approximately 4.5% (Sandman et al., 2013). As for hallucinations, a meta-analysis reported an elevated psychotic symptom prevalence of 17% between ages 9-12, dropping to 7.5% between ages 13-18 (Kelleher et al., 2012), in a similar pattern to nightmares. This again can be contrasted with the lower adult rate of hallucinations (approximately 5%; Linscott & van Os, 2013).

Understanding why these symptoms are so common in this period, and then decline, might therefore provide valuable insights into both phenomena.

Furthermore, for both nightmares and hallucinations, their persistence across adolescence is associated with increasingly negative mental health outcomes, proportionate to age. For example, in cohort studies presence of nightmares in childhood has been associated with psychotic experiences at age 12, but nightmares at age 12 were even more strongly predictive of psychotic experiences at age 18 (Fisher et al., 2014; Jeppesen et al., 2014; Thompson et al., 2015). Nightmares in adolescence are also associated with the development of a range of other mental health problems, self-harm, and suicidality (S. Andrews & Hanna, 2020; Kirov & Brand, 2011; Pigeon et al., 2012; Scott et al., 2021). Similarly hallucinated voices in childhood (age 7-8) are only weakly associated with current psychological distress, but hearing voices at 12 or 13 was highly predictive of psychological distress (Bartels-Velthuis et al., 2010, 2011). Persistence of psychotic symptoms across adolescence is associated with increasing risk of later psychotic disorder (Healy et al., 2019), but is also a strong non-specific predictor of later mental health problems (Fisher et al., 2013). Therefore there is a clinical interest in preventing persistence of both nightmares and hallucinations across adolescence.

This review firstly aims to explore the overlap between nightmares and hallucinations in late childhood and early adolescence by framing these symptoms in the context of the socio-cognitive and neurodevelopmental changes in this period. Secondly, the review will explore mechanisms linked to nightmares or hallucinations (or both) to highlight factors that could increase risk of persistence, and that may therefore represent intervention targets.

Background and definitions

Prior to addressing these aims a brief overview of nightmares and hallucinations will be provided, with specific reference to their presentation and assessment in childhood.

Sleep and nightmares

Sleep can be thought of as being governed by two processes (Borbély, 1982). The first process is homeostatic sleep pressure, which builds throughout time spent awake and is released during sleep. The second is the circadian system which synchronises sleep and wake to environmental cues such as light and meals. Sleep itself comprises several different physiological states, primarily divided into Rapid Eye Movement (REM) and Non-REM (NREM) sleep. NREM sleep can be further broken down in to three stages (NREM1-3) which represent increasingly deep sleep. Throughout the night the brain moves between these stages of sleep, completing multiple cycles with a higher proportion of NREM (especially NREM3) in the first half of the night and a higher proportion of REM sleep in the second half (Brown et al., 2012).

Sleep processes undergo many changes throughout development. Sleep duration declines rapidly throughout childhood (from 16h in infants to 9-10h by age 11-12; Tesler et al., 2013) and then more slowly throughout adolescence to approximately 7-8 hours by adulthood (Maslowsky & Ozer, 2014). Sleep timing also changes through development – for example the circadian delay shift in adolescence that promotes later sleep and wake times, causing sleep deprivation when this clashes with other demands (e.g. attending school; Crowley et al., 2007). Lastly the composition of sleep itself changes, with the proportion of time spent in REM decreasing from up to 40% in babies to 25% in middle

childhood, and then decreasing through adolescence to around 20% in adulthood (Ohayon et al., 2004).

Nightmares can be defined as a distressing and unpleasant dream that typically – but not necessarily - leads to waking (Lemyre et al., 2019). There must be at least some recollection of content on waking, and presence of dysphoric emotion which can include anger, guilt, and sadness in addition to fear – which is the most common emotion (American Psychiatric Association, 2013). Nightmares predominantly – but not exclusively – occur in REM sleep (Blaskovich et al., 2020), therefore nightmares predominantly occur in the second half of the night. A distinction is often made between post-traumatic nightmares and idiopathic nightmares (Gieselmann et al., 2019). Post-traumatic nightmares are stereotypically repetitive and replay or closely represent a traumatic experience, whereas idiopathic nightmares are not based on a specific trauma and are more likely to vary in content and emotions. Given the paucity of research differentiating these nightmare types in children this review adopts an umbrella classification of nightmares as a whole, but will specify further if research relates to only post-traumatic or idiopathic nightmares.

A major challenge for nightmare research is measurement, especially in children. Objective identification of nightmares from brain activity recording is not reliable (Paul et al., 2015) and regardless, these methods are not available to the average clinician or researcher. This means that assessment of nightmares relies on subjective report – which in turn relies both on willingness to report and recollection of the nightmare(s). This has been shown to be far from perfect in adults (Nadorff et al., 2015) These issues are further complicated in childhood with a perception of unreliability in child reporting meaning that parents are often asked to report on their child's sleep.

However, this results in further under-reporting as it adds further reliance on parents being aware and recalling the child's nightmare – in addition to the child's ability to report the nightmare (which may not be present at earlier ages) and their willingness to share their experiences with their parents (which may decline in later childhood and adolescence). This under-reporting is visible in studies which utilise both parent and child report of nightmares – for example Schredl and colleagues (2009a) found that 46.9% of children reported nightmares at least 'sometimes', but only 32% of the parents in the study reported their child as having nightmares.

Hallucinations

Hallucinations can be defined as sensory perceptions occurring the absence of an external stimulus (Maijer et al., 2019). However, this simple definition masks an extremely complex and varied phenomenon. The phenomenology of hallucinations itself is incredibly broad – stretching well beyond the most studied hallucination of voice-hearing to cover the breadth of sensory and interoceptive modalities at all grades of intensity (Pienkos et al., 2019). This is prior to considering how the appraisal of the hallucination itself (e.g. as threatening or non-threatening, meaningful or not) may itself interact with the experience (Ward et al., 2014). While hallucinations are most typically associated with psychotic disorders such as schizophrenia (where, alongside delusions, they are the cardinal 'positive symptoms' required for diagnosis), hallucinations are not specific to psychotic disorders and occur in approximately 5% of the general population (exceeding the lifetime prevalence of psychotic disorders at 3%; Johns & van Os, 2001). Hallucinations can occur following sleep deprivation, in grief, in association with other diagnoses (e.g. depression), and can occur at 'clinical' intensity levels without need for treatment (Johns et al., 2014).

As discussed already hallucinations in childhood are particularly common, but tend to be transient with up to 40% remitting within a year (Bartels-Velthuis et al., 2011; Rubio et al., 2012; Thapar et al., 2012) – this can be contrasted with their relative persistence in adulthood (Linscott & van Os, 2013). The clinical relevance of hallucinations in childhood – both in terms of distress and impairment at the time, and in relation to later psychopathology – has been the source of debate (Maijer et al., 2019). Hallucinations in childhood are less distressing, impairing, or predictive of later psychopathology than those occurring in adolescence or adulthood (Maijer et al., 2018). Furthermore, adults who hear voices but have no need for clinical care are more likely to have had childhood onset of hallucinations than those who require clinical intervention (Johns et al., 2014), and positive or benign hallucinations are reported more frequently in childhood (Maijer et al., 2019; Pignon et al., 2018). Nevertheless, childhood hallucinations can still cause distress and impaired functioning – and do still predict later psychological disorders – and therefore warrant clinical attention and monitoring (Dominguez & Garralda, 2016; Maijer et al., 2017) alongside further research attention.

Developmental context of middle childhood

The developmental context in which these hallucinations and nightmares are frequently occurring is deserving of further elaboration. Middle childhood itself (defined here as between ages 7 and 11) has historically received less attention than infancy or adolescence, being seen as a period of consolidation and gradual change in contrast to the dramatic changes of these surrounding periods (Collins, 1984). However there are significant developments in middle childhood, particularly in social and cognitive development (Del Giudice, 2017). This includes the onset of status/dominance hierarchies among peers (referred to by one authors as the 'tyranny of the peer group'; (Sandler, 1989,

p380), developments in mentalising skills including understanding multiple perspectives (Lagattuta et al., 2010; Smith & Hart, 2010), advances in imaginative and reflective capacities, and moral reasoning (Hinnant et al., 2013). As an example, advances in understanding multiple perspectives can be seen in Dumontheil, Apperly and Blakemore (2010) wherein participants viewed a set of shelves with various objects on and were asked to move them around by a 'director' who can only see some of the objects. So, for example, the director might ask them to move 'the small ball' and the participant would be required to work out that the smallest ball is not visible to the director and instead move the smallest ball that is visible to the director. Performance in this task improves across middle childhood (and continues to improve throughout adolescence), demonstrating increasing capacity to understand and manipulate representations of others' perspectives. A related capacity of 'second order' theory of mind also develops in this period, which is the ability to understand not only that person A believes X (first-order theory of mind) but that person B believes that person A believes X and to predict the actions of person B accordingly (Miller, 2009).

Possibly resulting from this increased perspective-taking, the development of fairness, reciprocity, and trust in social interactions is also notable across middle childhood and adolescence. In the 'Trust game' two players are allocated a sum of money (or equivalent resource). The first player then decides whether to divide the money, or to trust the second player with the whole sum. If they trust the second player with the whole sum, the stake triples – however, the second player then gets to decide how to distribute the winnings. In adults this second player will reciprocate (defined as splitting the total winnings fairly) around 50% of the time, adolescents in 40% of cases, and children in only 30% (Berg et al., 1995). However, there is some debate about if the increasing percentage is a result of

increasing understandings of fairness, or increasing development of cognitive control – i.e. inhibiting the selfish response (Zanolie & Crone, 2018).

Outside of the psychology lab, evidence abounds that this age is accompanied by significant developments in social role and cognitive capacity. In many historical and cultural contexts this is the age at which children start being assigned tasks (e.g. food preparation) and being considered as an independent agent themselves (Kramer, 2011; Lancy & Grove, 2011). In ontogenetically similar animals (e.g. chimpanzees) their equivalent developmental period is similarly one of social learning and growing independence, to the extent that its length is itself positively correlated with the size of the peer group (Joffe, 1997).

Overall this evidence supports that middle childhood is a key phase of social and cognitive development, which then continues through adolescence (J. L. Andrews et al., 2020; Blakemore & Choudhury, 2006)

Relationships between socio-cognitive development, hallucinations, and nightmares

We propose that a key factor underpinning co-occurrence of nightmares and hallucinations in middle childhood is this social and cognitive development. In this context there are several hypotheses that could be made for links to nightmares and hallucinations, based on our theoretical understanding of these phenomena.

The first hypothesis is that this developmental change produces significant stressors. For example, the introduction of social hierarchies (alongside only nascent pro-sociality) contributes to bullying

being particularly common in this period (Nansel et al., 2001). Bullying is known to increase likelihood of hallucinations (Steenkamp et al., 2021) and nightmares (Wolke & Lereya, 2014). Furthermore themes of social threat or attack are particularly prevalent in nightmares during pre-adolescence – and notably more so than for adults (45.5% of dreams recurrent dreams of 11-15yos included aggression and violence versus 19% of adults; Gauchat et al., 2015).

However, social stress is unlikely to be the sole cause of increased rates of hallucinations and nightmares as social stressors are at least as high in adolescence (Blakemore, 2019), yet in this period the majority of nightmares and hallucinations remit. A more likely possibility is that nightmares and hallucinations are a result of these socio-cognitive developmental processes themselves, for which there is some evidence.

With respect to hallucinations there has been increasing incorporation of social cognition – and development of social cognition – in theoretical accounts, particularly in relation to hearing voices (Bell, 2013). These theories leverage the agency attributed to hallucinations: that these are not just voices, but are characters with intentions that voice-hearers interact with. In this context the high prevalence of childhood hallucinations has already been associated with growing developmental capacity in social agent representation (i.e. the ability to create, use, and maintain representations of social actors for use in social cognitive functions; Bell et al., 2017; Fernyhough et al., 2019). A research literature also exists linking imaginary friends (reported by 28-65% of 5-12 year olds) and hallucinatory phenomena, mediated by a tendency to hallucinate in response to ambiguous stimuli (Davis et al., 2011; Fernyhough et al., 2007, 2019). 'Hyper theory of mind' (i.e. a tendency to infer mental states without evidence and erroneously predict behaviour as a result)has also been found to

specifically predict hallucinatory experiences in pre-adolescence in one birth cohort study (Clemmensen et al., 2016). Overall this suggests that a high prevalence of hallucinations (particularly auditory verbal hallucinations) could be a side-effect of developing social cognition in this period.

With respect to nightmares any relationship to social cognition is less well-researched, but a possible link can be made with the threat simulation theory of dreaming (Revonsuo, 2000). Threat simulation theory proposes an ambitious and active role for dreams in preparing the dreamer to react to similar threats in the waking world, thereby having an evolutionary function in improving fitness. Under this theory nightmares would be expected to mirror salient threats in particular development periods; and to provide learning on how to react to them. Therefore for the period of middle childhood, dreams and nightmares would be expected to reflect social cognition development – i.e. learning about others and threats from others.

These propositions are in part supported by the high rate of social threat nightmares in middle childhood in comparison to adulthood (Gauchat et al., 2015), and that dreamers typically take plausible defensive action towards the threat (Zadra et al., 2006). However, several lines of research contradict a role for dreaming or nightmares in learning how to respond to threat. For example, the threats in dreams themselves are rarely realistic (e.g. in childrens' dreams the threats typically come from witches, monsters, and animals; Gauchat et al., 2015), dreamers are rarely successful in evading the threat as would be expected if the dreams had a learning function (Valli & Revonsuo, 2009), and specifically in nightmares waking will usually occur at the point of greatest threat (as opposed to any resolution occurring).

Another recent theory of dreaming – the overfitting hypothesis – suggests a less literal role for dreams in learning (Hoel, 2021). This theory is based on the role of stochasticity (random, noisy, or sparse inputs) in machine learning - without this random variation in the training data it is known that models are less able to generalise their learning and therefore perform poorly. This understanding has been taken back to the human brain by Hoel (2021) who proposes that dreams fulfil this stochasticity function by providing a replay of experiences with random and remixed elements – and that therefore dreaming may have a role in improving generalisation of learning. Unfortunately the theory does not propose any particular function for nightmares or their negative emotionality (as there is no known analogue of these in the machine learning case). Nevertheless, it could be that an increased rate or novelty of social learning in middle childhood and pre-adolescence results in higher dreaming activity, which could translate to a higher frequency of nightmares. Overall, the relationship between nightmares (or dreaming) and social development in children deserves more investigation, ideally utilising similar paradigms to those applied in the hallucinations literature (e.g. investigating relationships with imaginary companions).

A third hypothesis on the relationship between hallucinations, nightmares, and socio-cognitive development could also be advanced – that in addition to socio-cognitive development influencing hallucinations and nightmares, that nightmares and hallucinations themselves impact on development, either via shared or independent mechanisms.

The impact of hallucinations on socio-cognitive development on this period is an open question with some research supporting a beneficial role of imaginary companions in e.g. developing theory of mind (Davis et al., 2011), and other research indicating that voice-hearing is associated with

behavioural problems and reduced theory of mind (Bartels-Velthuis et al., 2010; Pignon et al., 2018). It can also be noted that psychotic experiences in adulthood are associated with theory of mind deficits (Bora & Pantelis, 2013). The complexity and range of experiences is well-evidenced by a recent qualitative study with adolescent voice hearers who reported reciprocal relationships with nurturing and distressing voices; differing functions of different voices; and voices as decreasing loneliness whilst also increasing peer relationship difficulties (Parry & Varese, 2020). Current theories integrate these findings on a continuum, with hallucinations that are distressing, impairing, outside of volitional control, and/or persistent being more likely to be associated with negative developmental and psychiatric outcomes (Waters et al., 2012).

The (more sparse) evidence available for nightmares largely indicates negative impact on children. A recent review indicates that nightmares are associated with stress, anxiety, behavioural problems, and other sleep problems (Gauchat et al., 2014). Given that nightmares are by definition distressing, this negative association is not necessarily surprising – but also there has been far less research, especially in relation to links with socio-cognitive development. Given this, and the inconsistent findings from hallucinations and imaginary friends it could be hypothesised that children with nightmares have either more or less developed theory of mind or other socio-cognitive capacities. On balance it seems more likely that nightmares would be associated with sociocognitive deficits given they would appear to more closely align with distressing hallucinations than (positive experiences of) imaginary friends. Nevertheless, higher-quality studies with consistent definitions of nightmares including longitudinal measurement would be a valuable addition to test any relationship from nightmares to social development (positive or negative).

In summary, we propose that socio-cognitive developmental changes (particularly in representations of the perspectives of others) can provide one possible account of the high rates of hallucinations in middle childhood/pre-adolescence, and may also provide hypothesis for understanding the high rates of nightmares.

Neurophysiological developmental context

Supporting and interacting with this social and cognitive development are of course neurophysiological changes. The primary developmental trends in middle childhood include synaptic pruning (i.e. gradual reduction of grey matter from a peak aged 5/6) and increasing myelination (Nelson et al., 2016). These two trends permit the development and increasing integration of long-range networks in the brain, including the default mode network (Fan et al., 2021), and increased 'top down' influence including in inhibitory control. Throughout this period there is an element of 'developmental mismatch' as multiple systems (perceptual, motor, limbic) are comparatively well-developed in contrast to more frontal or associative regions (Frere et al., 2020).

Hallucinations are particularly characterised by reduced inhibitory control and abnormalities in resting state network activity (Alderson-Day et al., 2016; Jacobson McEwen et al., 2014), and these same tendencies have furthermore been linked to sleep dysfunction (Lunsford-Avery et al., 2013). Given that long-range networks are still developing across middle childhood, including the resting-state network, this could provide a neurophysiological underpinning for the increased rate of hallucinations in this period.

The neurobiology of nightmares is relatively under-investigated, especially in children. It is known dreaming activity in general is characterised by high activity in limbic and sensory areas and relatively

low pre-frontal modulation (Levin & Nielsen, 2009; Nir & Tononi, 2010). This picture would match the typical imbalances within development in middle childhood (e.g. sensory areas developing prior to top-down association areas such as the pre-frontal cortex; Casey et al., 2005).

As a simplified summary, during middle childhood the bottom-up systems known to generate hallucinations and nightmares are present, but the systems required for top-down control of these experiences are still developing. Therefore the neurophysiological context also supports that this period is one of higher vulnerability to nightmares and hallucinations.

What factors predict persistence of nightmares and hallucinations in adolescence?

As discussed previously, this high rate of hallucinations and nightmares in middle childhood/pre-adolescence is followed by a relatively high rate of remission over adolescence (around 40% yearly; de Leede-Smith & Barkus, 2013). The persistence of psychotic experiences across adolescence is associated with particularly negative outcomes in terms of mental health and general functioning (Dominguez et al., 2011; Healy et al., 2018, 2019). Further understanding of predictive factors or mechanisms that contribute to the persistence of these psychotic experiences may therefore lead to improved identification and treatment.

Trauma

A key factor for predicting persistence is presence of trauma. Traumatic experiences are strongly associated with a higher likelihood of nightmares and childhood hallucinations. For example, in one study 75% of children hearing voices reported some kind of trauma (Escher et al., 2004). Presence of

trauma also predicts more persistent hallucinations (Kelleher et al., 2013; Wigman et al., 2012) and nightmares (Nielsen, 2017), although in the latter case this has not been investigated specifically across adolescence. However, it is worth noting that not all individuals reporting nightmares or hallucinations have been exposed to trauma, and children who are exposed to trauma do not necessarily go on to develop nightmares or hallucinations (Abajobir et al., 2017; Maijer et al., 2019).

Interestingly Nielsen (2017) does discuss a specific model linking childhood adversity and nightmares specifically in the context of their 'stress acceleration hypothesis'. This proposes that adverse experiences in a critical window of infancy (i.e. prior to the formation of autobiographical memories at approximately age 3-4) sensitises neural systems relating to emotion regulation, leading to the later emergence of nightmares in response to stressors. However, childhood adversity is defined extremely broadly under this theory – incorporating for example, family arguments. Lack of recollection of trauma also does not disprove the theory (given a memory cut-off is incorporated within the rationale), therefore it is challenging to empirically test.

With respect to hallucinations, childhood trauma has a strong and well-researched relationship to hallucinations, with high proportions of voice hearers reporting childhood trauma, and often a content or experiential overlap between the trauma and the hallucination (Daalman et al., 2012; Hardy et al., 2005). Trauma – prior or ongoing – is also known to increase risk of persistence of psychotic experiences across adolescence (e.g. Mackie et al., 2011). Many different mechanisms have been proposed to explain this link including sensitisation of stress responses (similar to the Nielsen model reported above), disruption of memory encoding (which is proposed to increase rates of

intrusive thoughts), and inducement of negative schematic beliefs about self and others (Hardy et al., 2016).

Overall this research supports a well-evidenced role for trauma as a factor in predicting persistence of hallucinations across adolescence; and a highly plausible but less well-evidenced factor predicting persistence of nightmares.

Anxiety

Anxiety in middle childhood has been associated with a high likelihood of reporting nightmares (Reynolds & Alfano, 2016; Schredl et al., 1996). In one cohort of children with anxiety disorders nightmares were the most commonly reported sleep complaint (by 52% of children; Alfano et al., 2006). This is not surprising, as anxiety is often closely linked to nightmares in theoretical accounts due to overlapping basis in threat systems and threat processes (Nielsen & Levin, 2007), and it is highly plausible it contributes to persistence of nightmares – yet no longitudinal studies could be found that explored anxiety as a predictor of persistence of nightmares across adolescence.

Childhood anxiety has been associated with a higher likelihood of reporting hallucinations (Bartels-Velthuis et al., 2010), and with higher likelihood of persistence of hallucinations (Rubio et al., 2012). As with nightmares, anxiety can be easily theoretically linked to persistence of hallucinations by contribution to distress and impairment – for example, a tendency to worry may result in ruminating or catastrophising over hallucination content, thereby increasing the likelihood of the issue persisting.

In summary anxiety is another highly likely predictor of persistence of nightmares and hallucinations across adolescence, but further research with respect to nightmares is required to verify this association.

Emotion regulation difficulties

Emotion regulation is broadly defined as the ability to resist and manage emotional intrusions, a capacity which itself develops over childhood and adolescence (McRae et al., 2012). Emotion regulation difficulties have been incorporated as both a cause and consequence of nightmares; in one theory dream processes are hypothesised to function as mood-regulators in extinguishing fear memories, with nightmares representing disruption of this process due to elevated distress which then itself maintains the dysregulated mood (Levin & Nielsen, 2009). Emotion regulation difficulties have also been proposed to mediate the established link between nightmares and suicidal ideation (S. Andrews & Hanna, 2020). It is also known that sleep loss – such as that that might occur as a result of nightmares - increases emotion regulation difficulties during adolescence (Baum et al., 2014). Emotion regulation difficulties have also been linked with hallucinations (Maijer et al., 2019), including mediating a link between childhood trauma and psychotic experiences (Lincoln et al., 2017), and seems a highly plausible predictor of persistence of hallucinations through adolescence.

Emotion regulation difficulties are therefore likely to be a predictor of persistence of both nightmares and hallucinations, but this is based largely on theoretical work and empirical confirmation is required.

Cognitive appraisals

Appraisals of both nightmares and hallucinations can influence the distress or impairment associated with them – for example, a nightmare which involves an attack will be more distressing if one believes that nightmares predict the future. Despite the relevance of such appraisals in nightmares, they have historically been under-researched and only recently included within cognitive models and treatment (Gieselmann et al., 2019), and not investigated specifically within adolescence. For hallucinations the appraisal of the experience as external and uncontrollable predicts distress and persistence across adolescence (de Leede-Smith & Barkus, 2013; Ward et al., 2014; Waters et al., 2012).

Another cognitive factor can be the response to the experience. One particularly relevant cognitive response is the attempt to suppress the experience. For both nightmares and hallucinations it is known that attempts to suppress the experience or the memory of the experience tends to lead to rumination and further exacerbation (Badcock et al., 2007; Kröner-Borowik et al., 2013). Therefore there is a highly plausible joint factor of a tendency to suppress unpleasant or distressing thoughts (whether about the hallucination or the nightmare) as predicting persistence of these experiences over adolescence.

Cognitive appraisals or responses are therefore another likely factor in predicting persistence of hallucinations and nightmares; however far more attention is required to them in both cases and especially in nightmares.

Mutual exacerbation

A final factor worth considering in predicting persistence of nightmares or hallucinations would be that these symptoms are highly likely to influence one another.

It is highly plausible that nightmares may directly contribute to hallucinations. Longitudinal studies have shown that nightmares in childhood predict hallucinations and persistence of hallucinations in adolescence (Fisher et al., 2014; Thompson et al., 2015). The experiences and content of nightmares themselves – especially when they involve being threatened by others– could easily be understood to reinforce and exacerbate the distress from any similar themes in hallucinations. Nightmares are related with increased feelings of entrapment and hopelessness (with this effect in part mediating their association with suicidality; S. Andrews & Hanna, 2020); again in as far as this conceptually overlap with beliefs that voices are outside of control, it could be expected that nightmares contribute to distress and persistence of hallucinations in this developmental period.

Nightmares could also indirectly contribute to hallucinations via increasing distress, anxiety and emotion dysregulation (Gauchat et al., 2014). These factors would also contribute to distress and persistence of hallucinations as already discussed. Nightmares are also one cause of disturbed sleep (e.g. waking during the night, anxiety at bed time, early morning waking, daytime fatigue; Lancee & Schrijnemaekers, 2013).Therefore the known causal effect of disturbed sleep on hallucinations (partially itself mediated by negative affect; Reeve, Emsley, et al., 2018) would be another indirect pathway linking nightmares to hallucinations.

Hallucinations may also directly contribute to nightmares by specifically promoting or reinforcing threatful nightmare content in the same way as nightmares may reinforce hallucinations. A recent

survey study of nightmares and psychotic experiences in young adults indicated specific thematic overlap between contents or themes of nightmares and hallucinations (Kammerer et al., 2021). Indirect pathways from hallucinations to nightmares are also plausible – for example, hallucinations also contribute to anxiety (Hartley et al., 2013). Furthermore, insofar as hallucinations are associated with social or academic problems this could provide additional stressors and thereby increase nightmares.

In both directions (nightmares influencing hallucinations and hallucinations influencing nightmares) there are therefore plausible mechanisms. However further studies will be required to unpack the predominant directions of causal influence, particularly studies that utilise longitudinal data across middle childhood and adolescence. When similar analyses have been done with generic sleep problems and psychotic experiences it has generally been shown that sleep problems influence psychotic experiences more than vice versa (Hennig et al., 2019; Reeve, Nickless, et al., 2018) however this has not yet been investigated with nightmares or across this developmental period.

Discussion

In this review we have highlighted that nightmares and hallucinations have an overlapping period of high prevalence in middle childhood, and that while in many cases they naturally remit over adolescence, their persistence is associated with later mental health problems (most notably psychosis alongside other disorders). By focusing on the key developmental changes of this period several possible hypotheses have been developed. The first is that this period is one of increased stress and anxiety, which is then reflected in nightmare and hallucination occurrence and content - but evidence is lacking that this period is uniquely stressful. The second is that nightmares and hallucinations are

both results of the social and neural development which seems highly plausible based on the studies reviewed. An extension of this is that nightmares and hallucinations are affected by and themselves influence this development – in the case of hallucinations there is some evidence of positive and negative impacts, but for nightmares the impact is mostly negative where it has been researched.

A second question explored is the factors that predict persistence of hallucinations and nightmares across development. Several likely predictors have been discussed in this review, including trauma, anxiety, emotion regulation difficulties, cognitive appraisals, and a mutual exacerbation of hallucinations by nightmares and vice versa. Investigating the inter-relationships between these symptoms in high-quality longitudinal studies will be required to disentangle directions of effect, which will in turn allow identification of key therapeutic intervention points. For example, it may be possible to apply existing interventions that reduce anxiety to reduce persistence of nightmares and hallucinations across adolescence. Many of the mechanistic factors noted here (e.g. anxiety) have existing or adaptable interventions that could already be implemented by clinicians and assessed in research.

It is also worth noting that interventions for nightmares in childhood have been developed, including adaptations to imagery rehearsal therapy (Simard & Nielsen, 2009; St-Onge et al., 2009). Further testing of the impact of nightmare interventions on hallucinations (or the proposed mechanisms discussed here) would be highly valuable to test a causal relationship. Tailored interventions for hallucinations in childhood and adolescence are currently under investigation (e.g. Jolley et al., 2018), and again it would be useful to investigate the impact of improving hallucinations on nightmares and sleep in general, particularly with follow up over adolescence.

In this review we have focused on nightmares and hallucinations due to phenomenological overlap and data being available on both symptoms for this age group. However, paranoia – unfounded beliefs that others mean you harm - is a related psychotic experience that is also common in early adolescence (Bird et al., 2019), has been associated with social cognition (Raihani & Bell, 2019) and has been specifically linked with nightmares in young adults (Kammerer et al., 2021). Around half of adults with persecutory delusions in one study identified nightmares as occurring in the weeks prior to onset of delusion (Freeman et al., 2019), alongside nightmares being closely correlated with hallucinatory experiences. A recent trial investigating nightmare treatment in individuals with persecutory delusions also noted a content overlap between paranoid beliefs and nightmares, and treatment of nightmares was associated with improvements in paranoia (Sheaves et al., 2019).

Limitations and challenges for future research

Throughout this review we have discussed various limitations of the research it draws on. For nightmares in particular challenges in measurement have been highlighted, such as reliance on parental report resulting in under-reporting. Another issue is in timing of reports – many studies rely on retrospective recall of nightmares, however this has been shown to particularly affected by state anxiety. For example in Reynolds & Alfano (2016) the higher prevalence of nightmares among children with anxiety was only found in retrospective reports, and prospectively recorded rates of nightmares did not differ between anxious or non-anxious children. However, there may be concerns about prospective recording given that dream journaling is known to increase the frequency of reported dreaming (Aspy, 2016) – therefore perhaps prospective recording of nightmares will itself increase the rate of nightmares, posing ethical and scientific challenges. This issue might be avoided

by use of appropriately validated symptom or diagnostic questionnaires for nightmares– these could also easily have extended sections for indicating typical nightmare content, measuring associated distress, and exploring appraisals (without requiring collection or analysis of lengthy and unreliable dream journals). This would also aid in discriminating dreams and nightmares in this period (which are often conflated by only measuring e.g. 'bad dreams', and allow an assessment of – for example - whether high nightmare prevalence in this period is a reflection of higher rates of dreaming activity or if nightmares are specifically more common.

A broader limitation across the sleep literature is typicality of assessing 'sleep disturbance' or 'low sleep quality', without assessment of any symptoms underlying these reports (Reeve et al., 2015). For example, both nightmares and insomnia could cause night awakening. Without carefully assessing for presence of nightmares or other disorders that can cause awakening (e.g. sleep walking) it is likely that the conclusions of such research will not be as accurate as they could be. In order to resolve these issues improved measures of nightmares and sleep need to be developed, particularly for use by children – ideally these would be self-report, as is used for psychotic experiences, and include indices of distress, impact, and content as applied by Kammerer and colleagues (2021).

Measurement of psychotic experiences in children also poses challenges. Unlike with nightmares the norm is to ask the child, but this induces a floor-age on investigations, as evidenced by few studies reporting data before age 9 (and those that do providing caveats about whether the measured experiences should all be classified as psychotic e.g. Pignon et al., 2018). This measurement issue is further complicated by the diversity of measures of hallucinatory experiences – and that many measures compound hallucinations with other psychotic-like experiences - meaning that it is difficult

to gain consensus figures even on basic figures like the prevalence of hallucinations (Maijer et al., 2019). Recent work, for example from Gundersen and colleagues (2019) in validating self-report measures against interview measures in children and adolescents is especially valuable in this context.

Another limitation is that the majority of research discussed is cross-sectional and observational (especially with respect to nightmares). In order to investigate directions of effect high-quality longitudinal data sets at the least are required, and ideally intervention studies to confirm causal roles of different factors. This is especially the case when considering the naturally shifting developmental landscape of this period, and the need to contrast if an intervention or variable predicts persistence or remittance of a particular symptom. Statistical approaches such as directed acyclic graphs may be especially useful in illuminating the predominant directions of influence between the symptoms discussed here, thereby narrowing down the causal space for intervention development – for example Bird and colleagues recently applied this technique to understanding paranoia in adolescence (Bird et al., 2019).

Conclusion

In this review the high prevalence of nightmares and hallucinations in middle childhood and pre-adolescence has been explored within a developmentally informed framework. This has highlighted that the socio-cognitive development of this period – particularly increased representation of the states of others – may itself provide the capacity for nightmares and hallucinations, and therefore underly their high prevalence at this point. For both nightmares and hallucinations their persistence into adolescence is strongly associated with distress, impairment, and later mental ill-health. Factors that might predict persistence of both nightmares and hallucinations into adolescence were described

including trauma, anxiety, emotion dysregulation, cognitive appraisals, and mutual reinforcement (e.g. nightmares contributing to persistence of hallucinations and/or vice versa). Overall this review hopes to increase understanding of these two phenomena and their potential shared mechanisms, and develop clinicians' ability to understand their relevance in this developmental period.

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Part 2: Empirical paper

Sleep disorders predict the occurrence and persistence, but not remission, of psychotic experiences in preadolescence: A longitudinal analysis of the ABCD cohort data

Abstract

The relationship between sleep disorder and psychotic experiences in preadolescence has not been extensively studied despite the potential for intervention. The current study addresses this relationship using the Adolescent Brain and Cognitive Development (ABCD) cohort, which currently provides baseline data from 11,830 10 to 11-year-olds; for 4910 of these 1-year follow-up data is also available. A set of pre-registered multi-level regression models were applied to test whether a) sleep disorder is associated with psychotic experiences at baseline; b) baseline sleep disorder predicts psychotic experiences at follow-up; c) the persistence of sleep disorder predicts persistence of psychotic experiences at follow-up; d) the remission of sleep disorder predicts the remission of psychotic experiences at follow-up. Further exploratory models tested a specific relationship between nightmares and psychotic experiences. After controlling for sociodemographic variables, stimulant medication, and IQ sleep disorder was significantly associated with psychotic experiences cross-sectionally (OR=1.39, 95% CI 1.20-1.60), at one-year follow-up (OR=1.33, 95% CI 1.12-1.58), and the persistence of sleep disorder predicted the persistence of psychotic experiences (OR=1.62, 95% CI 1.34-1.97). However, remission of sleep disorders did not predict remission of psychotic experiences (OR=1.06, 95% CI 0.84-1.33). Similar relationships were found between nightmares and psychotic experiences, but no specific relationship with psychotic experiences was found for nightmares above other sleep disorders. The results indicate that sleep disorders in preadolescence are common and associated with psychotic experiences, although the lack of co-remission raises questions about the mechanism of association. However given these findings, and existing evidence in later adolescence and adults, further investigation of sleep as a preventative mental health intervention target in this age group is warranted.

Sleep disorders predict the occurrence and persistence, but not remission, of psychotic experiences in preadolescence: A longitudinal analysis of the ABCD cohort data

Sleep disorders are hypothesised to be a significant causal factor in the development and maintenance of psychosis (Reeve et al., 2015; Waite et al., 2019). Experimental research in adults supports that sleep disruption increases psychotic experiences (Reeve, Emsley, et al., 2018), and that treating sleep disorders reduces psychotic experiences in adults (Freeman et al., 2017). While the relationship between sleep and psychotic symptoms is thought to be bidirectional, longitudinal studies in adults have indicated that sleep disorders predict later psychotic symptoms to a greater extent than vice versa (Hennig & Lincoln, 2017; Reeve, Nickless, et al., 2018). These and other findings have raised the possibility of targeting sleep disorders as a preventative intervention in mental health (Freeman et al., 2017). This proposal is further supported by sleep disorders acting as a generic contributor to a range of mental health problems in addition to (or perhaps as part of) their relationship with psychosis (Freeman et al., 2020), including during childhood and adolescence (Gradisar et al., 2020).

This drive towards sleep as a preventative intervention raises the question of how early a relationship between sleep and psychosis exists. Psychotic experiences are roughly 10x more common in children than they are in adults (reported by 66% of 7-8 year old children compared to 5.8-7.2% of adults; Laurens et al., 2012; Linscott & van Os, 2013; McGrath et al., 2015). Not all childhood psychotic experiences are pathological (Maijer et al., 2019), nevertheless persistence, distress, and amount of different psychotic experiences reported in

childhood is associated with higher risk of developing adult psychotic disorder (Dominguez et al., 2011; Fisher et al., 2013) and is a general predictor of poor physical and mental health later in life (Davies et al., 2018; Kelleher et al., 2012; Trotta et al., 2020). As discussed in Part 1, the age at which psychotic experiences are reported is also positively related to risk of later psychotic disorder. Reporting psychotic experiences at age 10-11 is associated with a 5x increased likelihood of developing a later psychotic disorder (Fisher et al., 2013), whereas reporting these experiences at ages 14-17 is associated with a 10x increased likelihood (Dominguez et al., 2011). This set of findings have been encompassed under a 'proneness to persistence' model of psychosis, with these non-clinical psychotic experiences existing on a continuum with psychotic disorders (Linscott & van Os, 2013).

The relationship between sleep disorders and psychotic experiences in children is less well-researched than in adults (Reeve et al., 2015). However, many studies have demonstrated that children or adolescents with sleep disturbances are more likely to report psychotic experiences (Jeppesen et al., 2014; Koopman-Verhoeff et al., 2018; Y. J. Lee et al., 2012). Several large population cohort studies have reported that sleep problems during childhood – particularly nightmares, as discussed in Part 1 - predict psychotic experiences contemporaneously and across adolescence (Fisher et al., 2014; Koopman-Verhoeff et al., 2018; Morales-Muñoz et al., 2020; Thompson et al., 2015). Furthermore, as in adults, sleep problems in children are linked to a wide range of other negative mental and physical health outcomes (Dong et al., 2019; Gregory & Sadeh, 2012; Zhang et al., 2017).

Despite this evidence indicating that sleep disorders have an important role in the onset of psychotic experiences during childhood and adolescence, it is less clear whether sleep disorders contribute to persistence of psychotic experiences across this age group. This is particularly important given that persistence is a particularly strong predictor of poor outcome as raised in Part 1. It is also notable that a high proportion of both sleep problems and psychotic experiences remit during adolescence (Rubio et al., 2012)– yet as with persistence, whether sleep problems have an influence on remission of psychotic experiences is unknown. If improvements in sleep are associated with a reduction in psychotic experiences, this would provide evidence suggesting sleep interventions to reduce psychotic experiences could be viable. The large cohort studies listed above have rarely measured both sleep and psychotic experiences at multiple time points (with sleep being assessed usually only at younger ages and psychotic experiences assessed usually only assessed in adolescence) making it difficult to explore their concurrent interaction.

The current study

The Adolescent Brain and Cognitive Development study cohort data (release 2.0.1) was used to investigate the relationship between sleep and psychotic experiences in a cohort of 9-11 year-olds to address a set of pre-registered research questions:

1. Do sleep disorders and psychotic experiences co-occur in this cohort?
2. Do sleep disorders predict later psychotic experiences in this cohort?
3. Do sleep disorders predict persistence of psychotic experiences in this cohort?

4. Does remission of sleep disorders predict remission of psychotic experiences in this cohort?

These were examined using set of linear and logistic regression models applied to the baseline and one-year follow up data using a pre-registered analysis plan with all analysis available as open code: https://osf.io/8ks72/ and provided in Appendix 1.

Two further exploratory research questions were generated following the conceptual review in Part 1. These questions are derived from the evidence of a possible specific association between nightmares and psychotic experiences (as indicated in e.g. Fisher et al., 2014), and they aim to begin addressing a current lack of longitudinal studies investigating this relationship in preadolescence.

5. Do nightmares predict a higher likelihood of psychotic experiences co-occurring, being present at follow-up, persisting across the study, or remitting across the study?
6. Do nightmares (compared to other sleep disorders) predict a higher likelihood of psychotic experiences co-occurring, being present at follow-up, persisting across the study, or remitting across the study?

Method

Recruitment

The Adolescent Brain and Cognitive Development (ABCD; https://abcdstudy.org/) 2.0.1 release study data was used in the current analysis (Feldstein Ewing & Luciana, 2018; Volkow

et al., 2018). The ABCD study is an ongoing longitudinal cohort study aimed at recruiting a representative sample of US children. At the initial stage, all families of children aged 9-10 in geographic catchment area of study sites across the USA were contacted via schools with information about the study. Families that volunteered were then contacted by the research team and screened for inclusion. Participants were purposively recruited to fulfil specific representativeness requirements to match national US sociodemographic factors, for example utilising targets for each of five major race/ethnicity classifications (White, African-American, Hispanic, Asian All Other). The 2.0.1 release includes baseline data on 11,873 individuals, and one year follow-up from 4,951 of those participants, with follow up data from the remainder of the cohort to be released at a future date. Full details of the ABCD study design are available in a special issue of Developmental Cognitive Neuroscience (Feldstein Ewing & Luciana, 2018), and the approval for access to the data for the current study is available in Appendix 2. The Data Statement at the end of this chapter provides further details on funding and access.

Measures

Psychotic experiences

Participants' psychotic experiences were assessed using the Prodromal Questionnaire – Brief Child version (PQ-BC), provided in Appendix 3 for reference. This measure was adapted for and validated within the current ABCD dataset showing high reliability (Cronbach's alpha = 0.863 for total score and 0.873 for distress subscale; Karcher et al., 2018). The PQ-BC is a self-report questionnaire assessing presence and distress associated with

psychotic like symptoms in children. For each psychotic experience the child is asked if they experience it (yes/no), and if they do, how much it bothers them on a pictographic 1 to 5 scale showing a human cartoon figure in various levels of distress. This questionnaire yields two outcome variables – the sum of symptoms endorsed (range 0-21) and the sum of distress reported for those symptoms (range 0-126).

Continuous and dichotomous outcomes of the sum of distress were used, rather than the pre-registered symptom approach (see Alterations to the pre-registered statistical plan for further details and rationale). For the dichotomous outcome the distress score was transformed to a categorical 0-1 variable where 1 indicates presence of at least one distressing psychotic symptom (at least one distressing symptom scored ≥2 score on distress) and 0 indicates no distressing psychotic symptoms present. When applied to baseline and follow up this was then used to further derive variables indicating 'onset' of psychotic symptoms (i.e. 0 at baseline, 1 at follow up) 'persistence' of psychotic symptoms (i.e. 1 at both time points), and 'remission' (1 at baseline, 0 at follow up).

Sleep Disorders

Presence of sleep disorders was assessed using the Sleep Disorder Scale for Children (SDSC), which is a parent-reported questionnaire assessing the presence of a range of sleep disorder symptoms in children (Bruni et al., 1996). The SDSC is provided in Appendix 3 for reference. It is composed of 26 Likert items assessing the frequency of various disturbances over the past 6 months on a 1 to 5 Likert scale (1 = never, 5 = always/daily experiencing a particular issue). All items can be summated for a total measure of sleep disturbance, for

which a cut-off point at 39 has sensitivity of 0.89 and specificity of 0.74, correctly identifying 73.4% of a control group and 89.1% of sleep disordered participants (Bruni et al., 1996).

This cut-off was used in the current study to categorise participants according to absence or presence of disturbed sleep. The categorical score at baseline and follow up was then used to derive variables relating to onset, persistence, and remission of sleep disorders following the template for psychotic experiences above.

Nightmares

For the additional exploratory analyses item 21 of the SDSC: '*The child has nightmares which he/she doesn't remember the next day*' was used to assess presence of nightmares. As with all SDSC items this was rated on by parents a 1-5 scale (1 = never, 5 = always/daily experiencing a particular issue).

For investigating research question 5 both the item score and a dichotomised score (any response above 'never' coded as nightmares present (1), otherwise coded as absent (0)), with onset, persistence, and remission variables calculated as already described for use in descriptive statistics.

A further dichotomised variable was then calculated to compare nightmares (nightmares present = 1) to other sleep disorders (nightmares absent, other sleep disorders present = 0) for research question 6, with participants reporting no sleep disorders excluded from analyses.

Potential confounders: Socio-demographic, IQ, and medication variables

Further variables were used from the ABCD dataset to index potential confounders, defined as factors that can independently influence each of the variables of interest (sleep and psychotic experiences).

Male gender and non-white ethnicity are associated with a higher likelihood of reporting both sleep problems (Biggs et al., 2013) and psychotic experiences (Jongsma et al., 2020). Gender (Male/Female), ethnicity (White/Black/Hispanic/Asian/Other) were reported within the basic demographic questionnaires of the study. Ethnicity was re-coded in to white/non-white for the purposes of all analyses.

Lower socioeconomic status is also associated with increased likelihood of psychiatric disorder (Kivimäki et al., 2020) and shorter sleep duration (Tomfohr-Madsen et al., 2020). Socioeconomic status was indexed by using the sum score (range = 0-7) of seven yes/no items in the parent demographic survey questions relating to experiences of family hardship (e.g. "*in the past 12 months has there been a time when you and your immediate family needed food but couldn't afford to buy it or couldn't afford to go out to get it?*"), with higher scores on this sum scale indicating lower socioeconomic status. Neighbourhood deprivation was also assessed using the area deprivation index of the home address, which provides a national percentile value (range = 1-100) with higher values indicating higher levels of deprivation.

Family conflict is also associated with sleep problems (Gregory et al., 2006) and psychotic experiences (Cechnicki et al., 2013). Family conflict was indexed by the 9-item family conflict

subscale of the family experiences. Each item is reported by parents as true or false (e.g. *"We fight a lot in our family"*), with higher values indicating higher levels of conflict (range = 0-9).

Lower IQ scores and prescription of stimulant medications have been reported to have associations with psychotic experiences (Horwood et al., 2008) and, especially for stimulant medications, with sleep problems (Kidwell et al., 2015). Child IQ was assessed using the WISC-V matrix reasoning subscale score (range = 1-19), with higher values indicating higher IQ. Medication fields were searched for any stimulant medications (e.g. *"Methylphenidate"*) and their trade names (e.g. *"Ritalin"*) with absence or presence coded as a dichotomous 0/1 variable.

Notably, depression and anxiety were not included as potential confounders as these are consistently found to act as mediators in the causal pathway between sleep and psychotic experiences (e.g. (Reeve, Emsley, et al., 2018)). Therefore, if included in statistical models as confounders this would likely result in an underestimate of the relationship between sleep and psychotic experiences which was the primary focus of the current investigation.

Analysis

The pre-registration document outlining the hypotheses and analysis plan, and the analysis code used in this study are available online at the following link: https://osf.io/8ks72/ and provided in Appendix 3. R Studio version 3.6.2 was used for all analyses. Appendix 4 contains a list of packages and version numbers, and Appendix 5 contains the code utilised in analysis.

For each research question a set of planned regression analyses were pre-specified. The pre-registration was completed before the ABCD 2.0 data release, i.e. before the one-year follow-up data was made available. In each case, the regression model was first estimated with only the key explanatory (sleep) and dependent (psychosis) variables, and if a significant association was found, the process was repeated with potential confounders (added simultaneously) included to test robustness of the hypothesised association between sleep and psychosis.

A logistic regression approach was used for the majority of the analysis. This imposes a categorical classifier approach on to the (dimensional) variables of sleep and psychosis, hence the development of dichotomous variables as specified previously. This allows the analysis to provide an estimate of how much the presence of A (e.g. sleep disturbance) predicts the likelihood of B (e.g. psychotic experiences) also being present, with the odds ratios produced indicating the strength of the relationship.

The following four research questions were pre-registered:

RQ1: Do sleep disorders and psychotic experiences co-occur?

This was Tested cross-sectionally at baseline with a) a linear regression to test continuous association between sleep symptoms and psychotic experiences b) a logistic regression to test if sleep symptoms (continuous) predicted presence of psychotic experiences (dichotomous) and c) a logistic regression to test if presence of sleep disorder (dichotomous) predicted presence of psychotic experiences (dichotomous). If significant this would then be repeated with confounding variables added simultaneously (models d-f)

RQ2: Do sleep disorders predict later psychotic experiences?

This was investigated by logistic regression models testing if the presence of sleep disorder a) at baseline and b) at both baseline and follow-up predicted psychotic experiences at one year follow up. If significant, this analysis would then be repeated with confounding variables added (c-d)

RQ3: Do sleep disorders predict persistence of psychotic experiences?

This was investigated by logistic regression models testing if the presence or persistence of sleep disorder predicted persistence (i.e. presence at both baseline and follow-up) of psychotic experiences. If significant, this analysis would then be repeated with confounding variables added (c-d)

RQ4: Does remission of sleep disorders predict remission of psychotic experiences?

This was investigated by logistic regression models testing if the remission of sleep disorders (i.e. present at baseline, absent at follow up) also predicted remission of psychotic experiences using logistic regression (a). If significant, this analysis would then be repeated with confounding variables added (b)

Alterations to the pre-registered statistical plan

One major alteration to the pre-registered statistical plan is the alteration of our primary outcome variable for logistic regressions from presence / absence of at least one psychotic experience to presence/absence of at least one *distressing* psychotic experience. This followed further published analyses of the PQ-BC responses in the ABCD dataset which advised that our symptom count variable (without incorporating distress) may result in inclusion of 'false

alarm' responses, and that the addition of requiring the child to report being 'bothered' by the experience increases the validity by removing some erroneous responding (Karcher et al., 2018, 2020).

Other alterations to our analysis plan were made according to subsequently published guidance on analysis of the ABCD cohort (Heeringa & Berglund, 2020), namely introducing multi-level clustering by site and family. The planned unweighted results are reported here, but population weighted demographic and descriptive variables and weighted analyses (where population weights have been converted to scaling weights to allow their inclusion in the multi-level regression model using the 'Method A' and 'Method B' algorithm proposed by Carle (2009)), are available in Appendix 6.

The primary outcome statistic for our analyses is the odds-ratio, in keeping with epidemiological analysis norms. However, odds-ratios have been criticised under the grounds that they are often misinterpreted and do not provide a straightforward understanding of risk in relation to exposure (Norton et al., 2018; Ranganathan et al., 2015)– therefore additional approximate risk ratios for the primary predictive sleep variable in all models has been calculated following guidance by Grant (2014). These are reported in Appendix 7.

Exploratory nightmare analysis

Following the hypotheses generated from Paper 1 the analyses below were applied to our exploratory hypotheses (research questions 5 and 6). These were addressed by a similar but simplified approach as that taken with the pre-registered analyses – i.e. by building a stepped set of linear and logistic regression models. One difference is the lack of addition of

confounding factors within the models, both due to the exploratory nature of the analysis but also because there is not an equivalent literature supporting a specific relationship between, for example, stimulant medication and nightmares (in comparison to stimulant medication and broadly-measured sleep disturbance). . The analysis code for the exploratory research questions is included at the end of Appendix 5.

RQ5: Do nightmares predict a higher likelihood of psychotic experiences co-occurring, being present at follow-up, persisting across the study, or remitting across the study??

The association between nightmares and psychotic experiences was tested using a) a linear regression to test continuous association between nightmare symptom frequency and number of psychotic experiences b) a logistic regression to presence of nightmares (dichotomous) predicted presence of psychotic experiences (dichotomous) within baseline. Prediction of presence of psychotic experiences at follow up (d), persistence of psychotic experiences (d), and remission of psychotic experiences (e) was then tested by logistic regression.

RQ6: Do nightmares predict a higher likelihood of onset, persistence, or remission of psychotic experiences compared to other sleep disorders?

To test this more conservative association the logistic regression models from 5) were repeated utilising the dichotomous nightmares (1) versus other sleep disorders (0) variable. Participants who had no sleep disorders were excluded from this analysis.

Results

Demographic and descriptive results

Table 1 displays descriptive statistics of the study. Most descriptive variables remained consistent between baseline and follow-up, however the follow-up group has a preponderance of White participants (59.5% compared to 52.1%) and fewer Black participants (9.3% at follow up compared to 15.0% at baseline).

Table 1: Demographic variables and descriptive statistics

Descriptive statistic	Baseline n = 11830	12-month follow-up n = 4910
Age – mean (SD)	9y10m (7.4m)	11y0m (7.6m)
Gender – n male (%)	6162 (52.1%)	2565 (52.2%)
Ethnicity – n(%)		
White	6161 (52.1%)	2923 (59.5%)
Black	1769 (15.0%)	457 (9.3%)
Hispanic	2391 (20.2%)	930 (18.9%)
Asian	250 (2.1%)	115 (2.3%%)
Other	1238 (10.5%)	485 (9.9%)
Socioeconomic status scale – mean (SD)	0.47 (1.1)	0.38 (1.0)
Child IQ Scaled Score – mean (SD)	9.86 (3.0)	10.14(2.9)
Neighbourhood deprivation percentile – mean (SD)	39.22 (27.3)	36.23 (25.3)
Family conflict scale – mean (SD)	2.54 (2.0)	2.47 (1.9)
Stimulant medication prescribed – n (%)	722 (6.1%)	322 (5.6%)
PQ-BC total – mean (SD)	2.63 (3.6)	1.71 (3.0)
PQ-BC distress – mean (SD)	6.31 (10.6)	4.05 (8.7)
SDSC total– mean (SD)	36.53 (8.2)	36.35 (7.9)
Nightmare (SDSC Item 21) - mean(SD)	1.22 (0.49)	1.17 (0.42)
Derived variable counts	**Baseline n = 11930**	**12-month follow up n = 4910**
Sleep disorders present *(≥39 cut off on SDSC)* – n (%)	3602 (30.4%)	1391 (28.4%)
Sleep disorders onset *(absent at baseline, present at follow up)* – n(%)		482 (9.8%)
Sleep disorders persist *(present at both baseline and follow up)* – n (%)		909 (18.5%)
Sleep disorders remit *(present at baseline, absent at follow up)* – n (%)		490 (10.0%)
Psychotic experiences *(≥1 distress on ≥1 item)* – n (%)	5109 (43.2%))	1512 (30.8%)
Psychotic experiences onset – n (%)		483 (9.8%)
Psychotic experiences persist – n (%)		1029 (21.0%)
Psychotic experiences remit – n (%)		1067 (21.7%)
Nightmares present *(at least 'Occasionally')*– n (%)	2323 (19.6%)	776 (15.8%)
Nightmares onset – n (%)		404 (8.2%)
Nightmares persist – n (%)		372 (7.6%)
Nightmares remit – n (%)		580 (11.8%)

SDSC: Sleep Disorder Scale for Children, PQ-BC: Prodromal Questionnaire – Brief Child version ; SD = standard deviation

Distressing psychotic experiences reported by the cohort decline over the observation period (43.2% of cohort reporting at least one at baseline, versus 30.8% at follow-up), a result of the high remittance rate (21.7%) compared to new onset (9.8%). This is also reflected in the reduced average PQ-BC symptom and distress scores at follow-up versus baseline.

Nevertheless, where sleep disorders and psychotic experiences were present at follow up the majority – around two thirds – were persistent for both sleep disorders and psychotic experiences. This is supported by cross-tabulation of sleep disorders and psychotic experiences which shows relatively low numbers of cases where both sleep disorders and psychotic experiences are new onset (1.1%) and where they have both remitted (2.5%). Out of cases where both sleep disorder and psychotic experiences were present at follow up, the vast majority were 'persistent' cases, where both difficulties had been present at baseline (joint persisting group represents 91.5% of joint onset and persistent cases). Table 2 illustrates cross-tabulation of sleep disorders and psychotic experiences.

Focusing specifically on nightmares as per additional exploratory analyses, the prevalence of any nightmares is 19.6% at baseline, decreasing to 15.8% in the follow-up cohort. Interestingly a lower proportion of the nightmares at follow up are 'persisting' (7.6%), versus general sleep disorders (18.5%). The cross-tabulation results are similar in pattern for those of global sleep disorders, although with fewer positive nightmare cases overall.

Table 2: Cross tabulation of sleep disorders and nightmares with distressing psychotic experiences

Cross tabulation 1 (sleep disorders vs distressing psychotic experiences)			
		Psychotic experience onset	
Onset (absent at baseline, present at follow up)		No	Yes
Sleep disorder onset	No	4008 (81.6%)	420 (8.6%)
	Yes	429 (8.7%)	53 (1.1%)
		Psychotic experience persisting	
Persistence (present at baseline and follow up)		No	Yes
Sleep disorder persisting	No	2621 (53.3%)	1379 (28.1%)
	Yes	480 (9.8%)	430 (8.8%)
		Psychotic experience remitting	
Remission (present at baseline, absent at follow up)		No	Yes
Sleep disorder remission	No	3336 (67.9%)	1084 (22.1%)
	Yes	365 (7.4%)	125 (2.5%)
Cross tabulation 2 (nightmares vs distressing psychotic experiences)			
		Psychotic experience onset	
Onset (absent at baseline, present at follow up)		No	Yes
Nightmare onset	No	4059 (82.7%)	445 (9.1%)
	Yes	365 (7.4%)	38 (0.8%)
		Psychotic experience persisting	
Persistence (present at baseline and follow up)		No	Yes
Nightmare persisting	No	3627 (73.9%)	909 (18.5%)
	Yes	252 (5.1%)	120 (2.4%)
		Psychotic experience remitting	
Remission (present at baseline, absent at follow up)		No	Yes
Nightmare remission	No	3387 (69.0%)	931 (19.0%)
	Yes	454 (9.3%)	126 (2.6%)

RQ1: Do sleep disorders and psychotic experiences co-occur?

The regression results associated with this research question can be found in Table 3. They illustrate that sleep disorders and psychotic experiences are significantly and strongly associated within the baseline time point. Reporting sleep disorder symptoms above cut off is associated with an increased likelihood of at least one psychotic experience being present (OR =1.49; 95% CI 1.29-1.71). The OR remains significant but reduces slightly (to 1.39, 95% CI 1.20-1.60) once the confounder variables are added (RQ1f).

RQ2: Do sleep disorders predict later psychotic experiences?

The results of the logistic regression analyses on this research question are shown in Table 4. Sleep disorders at baseline were found to be strongly associated with an increased likelihood of reporting later psychotic experiences (OR=1.64, 95% CI 1.42-1.90) even once sleep disorder symptoms at the follow-up were controlled for (OR = 1.393, 95% CI 1.18-1.64). This association remained stable after confounders were added (OR = 1.33, 95% CI 1.12-1.58).

Table 3: Regression analyses of co-occurrence of sleep disorders and psychotic experiences at baseline

Model (outcome)	Parameters	B	95% CI	p-value	df	AIC
Model 1a (PQ-BC distress total)	**SDSC total T0**	**0.143**	**0.11, 0.18**	**<0.001**	98	36495
Model (outcome)	**Parameters**	**Odds**	**95% CI**	**p-value**	**df**	**AIC**
Model 1b (PQ-BC cut-off T0) [b]	**SDSC total T0**	**1.027**	**1.02, 1.04**	**<0.001**	4904	6508
Model 1c (PQ-BC cut-off T0) [b]	SDSC cut off T0	1.486	1.29, 1.71	<0.001	4904	6520
Model (outcome)	**Parameters**	**B**	**95% CI**	**p-value**	**df**	**AIC**
Model 1d (PQ-BC total T0) [a]	**SDSC total T0**	**0.113**	**0.07, 0.15**	**<0.001**	92	34168
	Gender$_{(RV=Male)}$	-0.336	-0.92, 0.25	0.262		
	Ethnicity$_{(RV=White)}$	0.156	-0.08, 0.40	0.202		
	Socioeconomic status	0.579	0.27, 0.89	<0.001		
	Neighbourhood deprivation	0.034	0.02, 0.05	<0.001		
	IQ	-0.219	-0.32, -0.12	<0.001		
	Family conflict	0.033	-0.13, 0.20	0.692		
	Stimulant medication$_{(RV=Not prescribed)}$	1.667	0.48, 2.85	0.006		
Model (outcome)	**Parameters**	**Odds**	**95% CI**	**p-value**	**df**	**AIC**
Model 1e (PQ-BC cut-off T0) [b]	**SDSC total T0**	1.021	**1.01, 1.03**	**<0.001**	4592	6048
	Gender$_{(RV=Male)}$	1.082	0.95, 1.23	<0.001		
	Ethnicity$_{(RV=White)}$	1.040	0.99, 1.09	0.231		
	Socioeconomic status	1.108	1.03, 1.19	0.138		
	Neighbourhood deprivation	1.006	1.00, 1.01	0.003		
	IQ	0.951	0.93, 0.97	<0.001		
	Family conflict	1.014	0.98, 1.05	0.427		
	Stimulant medication$_{(RV=Not prescribed)}$	1.378	1.06, 1.79	0.016		
Model 1f (PQ-BC cut-off T0) [b]	**SDSC total T0**	**1.385**	**1.20, 1.60**	**<0.001**	4592	6052
	Gender$_{(RV=Male)}$	1.081	0.95, 1.23	0.238		
	Ethnicity$_{(RV=White)}$	1.043	0.99, 1.10	0.113		
	Socioeconomic status	1.115	1.04, 1.19	0.002		
	Neighbourhood deprivation	1.006	1.00, 1.01	<0.001		
	IQ	0.950	0.93, 0.97	<0.001		
	Family conflict	1.019	0.98, 1.05	0.294		
	Stimulant medication$_{(RV=Not prescribed)}$	1.400	1.08, 1.82	0.011		

[a] = linear regression; [b] = logistic regression; [c]reference category = Male

SDSC = Sleep Disorder Scale for Children; PQ-BC = Prodromal Questionnaire – Brief Child version; B = standardised beta; CI = confidence intervals; df = degrees of freedom; AIC = Akaike information criterion; RV = reference value.

Table 4: Regression analyses of sleep disorders at baseline predicting psychotic experiences at 12 months

Model (outcome)	Parameters	Odds	95% CI	p-value	df	AIC
Model 2a (PQ-BC cut off T1)	SDSC cut off T0	1.643	1.42, 1.90	<0.001	4904	5892
Model 2b (PQ-BC cut off T1)	SDSC cut off T0	1.393	1.18, 1.64	<0.001	4903	5880
	SDSC cut off T1	1.384	1.17, 1.63	<0.001		
Model 2c (PQ-BC cut off T1)	SDSC cut off T0	1.523	1.31, 1.77	<0.001	4592	5459
	Gender$_{(RV=Male)}$	1.020	0.89, 1.17	0.772		
	Ethnicity$_{(RV=White)}$	1.038	0.98, 1.10	0.174		
	Socioeconomic status	1.161	1.09, 1.24	<0.001		
	Neighbourhood deprivation	1.007	1.00, 1.01	<0.001		
	IQ	0.964	0.94, 0.99	0.003		
	Family conflict	0.973	0.94, 1.01	0.140		
	Stimulant medication$_{(RV=Not prescribed)}$	1.568	1.20, 2.04	0.001		
Model 2d (PQ-BC cut off T1)	SDSC cut off T0	1.327	1.12, 1.58	0.001	4591	5451
	SDSC cut off T1	1.326	1.12, 1.57	0.001		
	Gender$_{(RV=Male)}$	1.014	0.88, 1.16	0.843		
	Ethnicity$_{(RV=White)}$	1.037	0.98, 1.1	0.185		
	Socioeconomic status	1.154	1.08, 1.24	<0.001		
	Neighbourhood deprivation	1.007	1.00, 1.01	<0.001		
	IQ	0.964	0.94, 0.99	0.003		
	Family conflict	0.970	0.93, 1.01	0.108		
	Stimulant medication$_{(RV=Not prescribed)}$	1.520	1.17, 1.98	0.002		

SDSC = Sleep Disorder Scale for Children; PQ-BC = Prodromal Questionnaire – Brief Child version; CI = confidence intervals; AIC = Akaike information criterion; RV = reference value.

RQ3: Do sleep disorders predict persistence of psychotic experiences?

The results of the logistic regression analyses relating to persistence of psychotic experiences are presented in Table 5. Presence of sleep disorder symptoms at baseline (OR=1.55, 95% CI 1.36-1.76) and persistence of sleep disorder symptoms (OR=1.81, 95% CI 1.51-2.17) significantly predicted increased likelihood of persistence of distressing psychotic experiences across the 12 month study period. Once confounders were added these relationships reduced slightly but remained highly significant (ORs of 1.74 and 1.62 for baseline and persisting sleep disorder symptoms respectively).

Table 5: Regression analyses of sleep disorders at baseline predicting persistence of psychotic experiences over 12 months

Model (outcome)	Parameters	Odds	95% CI	p-value	df	AIC
Model 3a (PQ-BC persist)	**SDSC cut off T0**	**1.550**	**1.36, 1.76**	**<0.001**	**4904**	**5146**
Model 3b (PQ-BC persist)	**SDSC persist**	**1.810**	**1.51, 2.17**	**<0.001**	**4904**	**4869**
Model 3c (PQ-BC persist)	**SDSC cut off T0**	**1.743**	**1.47, 2.07**	**<0.001**	**4592**	**4482**
	Gender$_{(RV=Male)}$	1.102	0.94, 1.29	0.221		
	Ethnicity$_{(RV=White)}$	1.028	0.97, 1.09	0.383		
	Socioeconomic status	1.165	1.08, 1.25	<0.001		
	Neighbourhood deprivation	1.006	1.00, 1.01	0.002		
	IQ	0.945	0.92, 0.97	<0.001		
	Family conflict	0.975	0.93, 1.02	0.239		
	Stimulant medication$_{(RV=Not prescribed)}$	1.711	1.28, 2.28	<0.001		
Model 3d (PQ-BC persist)	**SDSC persist**	**1.624**	**1.34, 1.97**	**<0.001**	**4591**	**4499**
	Gender$_{(RV=Male)}$	1.100	0.94, 1.29	0.226		
	Ethnicity$_{(RV=White)}$	1.027	0.97, 1.09	0.403		
	Socioeconomic status	1.170	1.09, 1.26	<0.001		
	Neighbourhood deprivation	1.006	1.00, 1.01	0.001		
	IQ	0.944	0.92, 0.97	<0.001		
	Family conflict	0.982	0.94, 1.02	0.402		
	Stimulant medication$_{(RV=Not prescribed)}$	1.749	1.31, 2.33	<0.001		

persist = above cut off at T0 and T1; SDSC = Sleep Disorder Scale for Children; PQ-BC = Prodromal Questionnaire – Brief Child version; CI = confidence intervals; AIC = Akaike information criterion; RV = reference value.

RQ4: Do sleep disorders predict remission of psychotic experiences?

Remission of sleep disorder symptoms was not a significant predictor of remission of psychotic experiences (OR=1.06, p=0.408, 95% CI 0.84-1.33, df=4904, AIC 5123) in the uncontrolled model, therefore the analysis with control variables was not carried out.

Differences arising from weighted analysis

The results using the population weighted values are reported in Appendix 6. The pattern of all results remained substantially the same except with respect to the primary sleep predictor variable of interest. The pattern of all results remained substantially the same

except for non-white ethnicity which became a significant predictor of onset of psychotic experiences at 12 months (alongside all other factors).

RQ5 and RQ6: Exploratory analysis of nightmares and psychotic experiences

As can be seen in Table 6 nightmares at baseline were significantly associated with a higher likelihood of distressing psychotic experiences both cross-sectionally (OR=1.44, 95% CI = 1.23-1.69) and at follow up (OR=1.59, 95% CI = 1.35-1.86), when compared to children not reporting nightmares. As with sleep disorders in general, nightmares were particularly predictive of persistence of psychotic experiences (OR = 1.70, 95% CI = 1.42, 2.03) but did not predict remission from distressing psychotic experiences. (OR=0.981, 95% CI 0.82-1.17). When comparing children with nightmares to children with other sleep disorders (models 6a-6d) there was no significant increase in likelihood of distressing psychotic experiences in the nightmare group with ORs reported between 1.0 and 1.2 for all models.

Table 6: Exploratory analysis of relationship between nightmares and psychotic experiences

Model (outcome)	Parameters	B	95% CI	p-value	df	AIC
Model 5a (PQ-BC total T0)[a]	Nightmare frequency T0	1.632	1.03, 2.23	<0.001	4889	36520
		Odds	**95% CI**	**p-value**	**df**	**AIC**
Model 5b (PQ-BC cut-off T0)	Nightmares present T0[b]	1.442	1.23, 1.69	<0.001	4904	6540
Model 5c (PQ-BC cut-off T1)	Nightmares present T0[b]	1.585	1.35, 1.86	<0.001	4904	5907
Model 5d (PQ-BC persist)	Nightmares present T0[b]	1.700	1.42, 2.03	<0.001	4904	4875
Model 5e (PQ-BC remit)	Nightmares present T0[b]	0.981	0.82, 1.17	0.827	4904	5124
Model 6a (PQ-BC cut-off T0)	Nightmares present T0[c]	1.176	0.97, 1.43	0.107	1803	2450
Model 6b (PQ-BC cut-off T1)	Nightmares present T0[c]	1.163	0.95, 1.42	0.146	1803	2343
Model 6c (PQ-BC persist)	Nightmares present T0[c]	1.116	0.89, 1.40	0.339	1803	2051
Model 6d (PQ-BC remit)	Nightmares present T0[c]	1.098	0.87, 1.39	0.432	1803	1852

[a]linear regression [b]comparison group: no nightmares [c]comparison group: other sleep disorders
persist = above cut off at T0 and T1; remit = above cut off at T0 and below at T1; PQ-BC = Prodromal Questionnaire – Brief Child version; CI = confidence intervals; AIC = Akaike information criterion; RV = reference value.

Discussion

The current study finds that sleep disorder symptoms are strong and significant predictors of both the co-occurrence and persistence of psychotic experiences in 9-11 year olds, with associations remaining robust after controlling for confounders such as socioeconomic status, ethnicity, IQ, and stimulant medication. The prediction of persistence of psychotic experiences is especially relevant, given that the persistence of psychotic experiences through adolescence is associated with most severe mental health outcomes (Healy et al., 2018). The remission of sleep disorders did not predict remission of psychotic experiences, and possible reasons for a lack of association are discussed below. Nightmares were found to similarly predict co-occurring, later, and persisting psychotic experience – but not remission – in the cohort. However, a specific relationship of nightmares to psychotic experiences (above other sleep problems) was not supported by the current analysis. Overall the results provide further support for a relationship between sleep problems and psychotic experiences during preadolescence.

Psychotic experiences were common in our study – reported by over 40% of participants at baseline. This is similar to previous studies in this age group (Laurens et al., 2012), and the relatively high rate of remission versus new onset by the one year follow up is also in keeping with existing developmental research of psychotic experiences (de Leede-Smith & Barkus, 2013; Rubio et al., 2012). Sleep disorder symptoms were also relatively common in the study group, with just under a third of the cohort above the cut-off designating significant sleep issues, similar to the 30-40% reported in previous studies (Fricke-Oerkermann et al., 2007).

Guidelines for parents and clinicians on child sleep difficulties tend to advise that many difficulties ameliorate naturally over time, which is contrary to our findings that around two-thirds do not (at least over the one-year observation period reported here) – but previous studies have also found a similar rate of persistence (Fricke-Oerkermann et al., 2007). The results suggest the need for additional screening and support for parents and health services to address sleep difficulties in this age group, particularly given the indications that rates of child and adolescent sleep disorders are increasing over time (Matricciani et al., 2012).

The current study extends the known relationship between sleep and psychotic experiences to early adolescence and addressed potential confounders, yet potential mediating mechanisms of the link between sleep and psychosis itself are not addressed. A particularly relevant mechanism linking sleep and psychotic experiences is negative affect, which is typically found to either partially or totally mediate this relationship in adult studies (Freeman et al., 2012; Reeve, Emsley, et al., 2018; Reeve, Nickless, et al., 2018; Sheaves et al., 2016). This and other potential mediators (such as affect dysregulation) ideally require investigation in ABCD (as further cohorts become available) or other longitudinal study designs, or ideally manipulation studies to appropriately disentangle the direction of influences over time – particularly in reference to predicting persistence of psychotic experiences.

The findings with respect to persistence of psychotic experiences are particularly relevant to clinical outcomes. As discussed above, the persistence of psychotic experiences across adolescence is associated with particularly poor outcomes (Healy et al., 2018, 2019) and is

therefore a more relevant clinical target than complete prevention of these experiences. In addition to potential mediating mechanistic factors (not examined in this study) it seems highly plausible that sleep problems and psychotic experiences could interact and exacerbate each other – for example, distressing psychotic experiences may lead to disturbed sleep, which then lead to higher vulnerability for psychotic experiences the next day, as discussed in relation to nightmares in Part 1 and demonstrated by high-frequency experience sampling studies in adults with psychotic disorders (e.g. Mulligan et al., 2016). This proposed causal model of sleep in contributing to psychotic experiences would support interventions on sleep to prevent persistence of psychotic experiences. These have been piloted in adolescents at-risk of psychosis, with tentative indications that sleep treatment does improve psychotic experiences – but this is awaiting further examination in a follow-up trial currently underway (Bradley et al., 2018; Waite et al., 2020).

However, this current analysis did not support a relationship between the remission of sleep disorders and the remission of psychotic-experiences. As this study was observational, it is not possible to confirm a (lack of) causal relationship although several hypotheses can be generated. The first is that sleep disorders may cause increase and persistence in psychotic symptoms through altering a mediating mechanism that remains when sleep disorders resolve. For example, affective dysregulation has been highlighted as a potential mediating factor (Akram et al., 2020) with some evidence that this may also be apparent in children (Jeppesen et al., 2014), as was also highlighted in Paper 1. Alternatively, sleep disorders may cause sensitisation of the mechanisms that generate psychotic symptoms but more rapidly

than desensitisation occurs when sleep disorders resolve, and although recovery may occur, it may need more than the year interval measured with this data. A 'mechanism' here may be neurocognitive (for example, arousal-based increases in aberrant salience) or social (for example, sleep disorder causing behaviour difficulties, exclusion or victimisation, subsequently impacting on psychotic experiences). Nevertheless, this does raise a question about the potential efficacy of sleep improvement intervention in reducing psychotic symptoms in preadolescent children, given than an association between improved sleep and reduced psychotic experiences would be expected if there were a direct causal association. However, this study only tested remission of sleep disorders as observed in the study, and it may be that a sleep intervention would address some of the shared risk factors for both poor sleep and psychotic experiences leading to an improvement in psychotic experiences not apparent in naturalistic remission.

The exploratory analyses on nightmares found that nightmares were reasonably common, reported by just under 20% of the cohort at baseline and 16% at follow-up, with around of a third of the follow-up cases being persistent from baseline. The analysis confirmed that nightmares as a specific sleep issue were related to concurrent and later psychotic experiences and are associated with the persistence of psychotic experiences – in a similar way to generic sleep disturbances as in the pre-registered analyses. However, the strength of the associations found was similar as for generic sleep difficulties, with no significant association found for nightmares with psychotic experiences above other sleep disorders. These findings are partially in disagreement with previous cohort studies that have found a particularly strong

relationship between nightmares and psychotic experiences, in some cases above other sleep problems (Fisher et al., 2014; Koopman-Verhoeff et al., 2018; Thompson et al., 2015). However, none of these studies have applied as conservative a test as the current study, i.e. removing participants not reporting any sleep difficulties and directly testing the predictive strength of nightmares versus other sleep difficulties. This approach also resulted in a reduced sample size of only 1807 participants, which may have reduced the power of the analyses to detect what would already be expected to be a smaller effect. This interpretation could be supported by the large confidence intervals on the modest odds ratios found. Overall the results support a significant relationship between nightmares and psychotic experiences, but do not support a specific role of nightmares above other sleep problems in this relationship.

Besides our primary focus on the influence of sleep on psychotic experiences, our findings support the association of a wide range of epidemiological factors (male gender, socioeconomic status, neighbourhood deprivation) with psychotic experiences in this age group. Lower socioeconomic status of parents and increased neighbourhood deprivation were consistent predictors in every model as supported by previous research (Solmi, Lewis, Zammit, & Kirkbride, 2020). Non-white ethnicity was not found to be a significant predictor in the unweighted models but was significant in some analyses once the models were weighted (Appendix 6), supporting the longstanding association reported elsewhere (e.g. Jongsma et al., 2020). The results therefore support the importance of broader scale social interventions as preventative of mental health issues, and further investigation of the

mechanisms between, for example, experiences of deprivation or discrimination and the development of psychotic experiences.

Lastly, the strong relationship expressed between stimulant medication and psychotic experiences is in keeping with previous literature e.g. (Shyu et al., 2015). However, the full range of reasons for the extent of this association are not discernible from the data reported here. Given the well-established association between dopamine agonist stimulant medication and psychotic experiences (Tost, Alam, & Meyer-Lindenberg, 2010), it is likely that a proportion of this association can be accounted for as an adverse effect of the medication. However, confounding by indication is likely also to play a role as children who fulfil criteria for prescribing may also have shared risk factors for psychotic experiences that manifest through other causal pathways (Hollis et al., 2019).

Limitations

One limitation of this study is that deviations were made from the pre-registered analysis plan – namely, alteration of the primary logistic regression outcome variable (from at least one psychotic experience to at least one *distressing* psychotic experience) and the addition of weighted analyses. However, in each case these deviations were due to subsequently published guidance or findings, and transparency has been retained about the process of decision making with changes to results both in this manuscript and in the manuscript repository on OSF providing time-stamped changes in documentation and results. It is also worth noting that the findings have not been significantly altered by any changes, partly supporting the robustness of the results and the original analysis plan. Furthermore, incorporating distress

into the psychotic experience measure has significant benefits in improving the validity of the measure as discussed in by Karcher and colleagues (2020). As discussed in Part 1, this is a crucial facet in determining likely impact of psychotic experiences on mental health, and also a useful way of increasing the specificity of the self-report measure used in this age group, and in refining the statistical approach itself make the deviations from the pre-planned analysis justified.

Another issue worth discussing is the use of dichotomous variables for sleep and psychosis, rather than their continuous measures. For both sleep disturbance and psychosis the constructs are known to be dimensional, with spread across a population of each symptom following a positively skewed curve (e.g. see Freeman et al., 2005 for a discussion of this issue as it relates to paranoia and persecutory delusions). The dichotomous (present/absent) approach was taken in part due to the pre-registering (e.g. it was not known whether the data would be transformable from this skew to allow parametric analyses); but also was a choice to aid in interpretability of the results in clinical work. The cost of this dichotomous approach is that a great deal of variation is lost in the data, with concomitant lowering of ability to estimate if, for example, more severe or more numerous psychotic experiences are more strongly associated with sleep problems – these issues therefore require further investigation (perhaps within a clinical participant group).

The observational nature of this study limits the causal conclusions drawn as one cannot rule out that any changes or associations observed are due to unobserved factors. Another limitation of this being an observational study is that the application of planned analyses is

reliant on the data that emerges. This may have limited our ability to reliably test some aspects of the relationship. For example, the particularly low proportion of cases (2.71%) where psychotic experiences and sleep disorders remitted from baseline possibly limited the ability of the remission models to identify any effect (as indicated by the relatively wide confidence intervals for these models) – although it does indicate that any effect would likely be small in magnitude.

The slight demographic shift between baseline and follow-up group is also worth considering as this may have reduced the accuracy of our estimates (even in weighted analysis) due to the initial release follow-up cohort being less representative of the study sample. Confirmation of these findings once the full one-year dataset is released – and with later phases of ABCD data - would be worthwhile.

The current observation is also limited only to one year, which may be considered a short period of time to observe longitudinal associations between exposure and outcome – raising the possibility that the associations reported are merely reflecting the concurrent links at baseline. In response to this one can note the substantial change in sleep disorder and psychotic symptom presentation across time points due to both remission and new onset of cases as indicating change does occur in the study period. Furthermore, statistical controls for contemporaneous sleep problems were introduced to several models either explicitly or by use of derived persistence / remission variables that themselves distinguish specific temporal relationships.

The current study was limited in variables by the measures used in the ABCD study, which have their own benefits and limitations. For example, while self-reported scales for psychotic experiences in adolescence are recommended, false positives are known to occur even with distress accounted for (Kelleher et al., 2011; K.-W. Lee et al., 2016), and therefore psychotic experiences also need to be explored with alternative measures. The sleep measure was parent-reported and parents may vary in their detection of sleep disorders in their offspring, and some sleep disorders may be more detectable by parents than others (e.g. sleep-walking versus insomnia). The nightmare item itself also asks parents to report if their child 'has nightmares which he/she doesn't remember the next day'. However, nightmares are discriminated from night terrors by recollection of content after waking and therefore addition of lack of recollection in the item could have resulted in the exclusion of some genuine nightmares that the child *did* remember during the day.

In conclusion, this study indicates that sleep disorders in preadolescence are common and are associated with increased likelihood of reporting psychotic experiences both at the time and at one year follow up. Sleep disorders were also strongly associated with persistence of psychotic experiences from baseline to one year – this is of particular importance given that persistence of psychotic experiences in this period is associated with raised risk of later psychotic disorder. These associations remained strong even while controlling for a broad range of confounding variables, including ethnicity, neighbourhood deprivation, family conflict, and prescription of stimulant medication. In conclusion, this study suggests further

attention towards sleep disorders in this period both as a plausible contributing factor to later mental health problems, but also as a possible preventative treatment target.

Data statement

Data used in this thesis were obtained from the Adolescent Brain Cognitive Development℠ (ABCD) Study (https://abcdstudy.org), held in the NIMH Data Archive (NDA). This is a multisite, longitudinal study designed to recruit more than 10,000 9-10 year-olds and follow them over 10 years into early adulthood. The ABCD Study® is supported by the National Institutes of Health and additional federal partners under award numbers U01DA041022, U01DA041028, U01DA041048, U01DA041089, U01DA041106, U01DA041117, U01DA041120, U01DA041134, U01DA041148, U01DA041156, U01DA041174, U24DA041123, U24DA041147, U01DA041093, and U01DA041025. A full list of supporters is available at https://abcdstudy.org/federal-partners.html. A listing of participating sites and a complete listing of the study investigators can be found at https://abcdstudy.org/Consortium_Members.pdf. ABCD consortium investigators designed and implemented the study and/or provided data but did not necessarily participate in analysis or writing of this report. This manuscript reflects the views of the authors and may not reflect the opinions or views of the NIH or ABCD consortium investigators. The ABCD data repository grows and changes over time. The ABCD data used in this report came from doi: 10.15154/1521349. DOIs can be found at https://doi.org

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Part 3: Critical Appraisal

Overview

This critical appraisal is composed of two parts. In the first I provide reflections on adopting an open science approach within this thesis, including some of the challenges and opportunities this has brought. In the second part I move on to broader reflections on the state of the field in sleep and mental health, outlining some of the barriers that need to be overcome for the future in our thinking about sleep and causality, and the challenges faced in transferring these findings to clinically benefit patients.

Part 1: Reflections on open science

This thesis was my first introduction to carrying out open science practices in my own research. This required some adjustment not only to initial processes but throughout; however despite this effort the process has been very rewarding and I think improved the overall thesis by enforcing thoughtfulness and transparency.

One particular area of adjustment was the process of pre-registering. Rather than working from the data itself, or planning data collection to fit hypotheses, I had to consult the online data dictionary (available here) in order to assess what data was available, for how many children, and at what time points – and to plan a sensible set of hypotheses and analyses accordingly. This meant that the analysis plan was much more tied to hypotheses from the start, for example given that we had decided to use logistic regressions to predict categorical outcomes in order to aid interpretability of the results (rather than this being based on distribution of the data). This initial process, and uploading the pre-registered document,

took a long time and felt very challenging – but doubtlessly transferred to a benefit when the data was accessed, and the plan was ready to implement.

That plan however then required adjusting in small ways (e.g. packages available in the secure data service not matching those I expected to use), and large (e.g. changing the primary outcome variable). My initial response to this was to feel that it undermined the whole approach of open science – given that I'd then changed from the pre-registered plan regardless. However, on reflection even here I realised that there was a benefit to having our initially stated plan time-stamped and available online – and indeed our initial results from running the analysis with the original outcome variable being available in the draft pre-print. Any reviewers or researchers who might be concerned that about post-hoc adjustment to analysis being due to some lack of findings could relatively easy view the original versions and pre-print to discover that the results were in fact similar. This transparency brings a substantial benefit therefore, even when plans change – and it forces any change to be fully explained rather than hidden from view.

However, some reservations remain. The first is that while my paper cannot be accused of being a 'fishing expedition', it can bias towards carrying out a so-called 'kitchen sink' analysis. It would be possible to pre-register an analysis testing every variable in a dataset and it would still be flawed regardless of the peer review. Therefore there needs to be a defined causal or theoretical basis for the relationships tested in order for the pre-registration to be meaningful. A second issue also results from this 'kitchen sink' problem – in that while it is theoretically possible to check all the past versions of papers or datasets, this approach can produce a huge

quantity of data relating to a single paper. A researcher or clinician *can* check it all, but it is perhaps unlikely that practically this oversight will happen. This could potentially lead to open science being applied towards fraudulent or poor scientific practices whilst still claiming enhanced empirical rigour. My last reservation is the issue that while pre-printing a paper allows it to be accessed and used before being published by a journal (therefore significantly shortening the lead time for results being available to guide other researchers or clinicians), the research is still not peer-reviewed and can yet undergo major changes. For example, the pre-print of my empirical paper that is currently available has been downloaded almost 200 times with >1000 views of the abstract. This version will shortly be updated with the newer analysis approach and various other changes resulting from peer review comments – but the out-of-date version will remain in circulation. In the case of my paper, there are no huge changes to the results or interpretation between versions – but there easily could have been.

Overall it has been worthwhile to explore open science and think about the advantages it brings and where it still needs development. I plan to use open science more in my future research work, and will take a lot of learning forward from this first project.

Part 2: Reflections on sleep and mental health

The topic of this thesis being sleep and psychosis broadly relates to my previous research in this area. This research was inspired from the common clinical observation that sleep problems are very common in patients with psychotic disorders (and indeed, alongside most mental health problems). Put together with the observation that not sleeping tends to result in acutely poor mental health (e.g. anxiety, hallucinations) this led to a programme of research

to establish that sleep problems themselves may have a causal role in psychosis, in parallel with other research programmes examining the same issue for other mental health problems (e.g. depression). Overall this research was successful in establishing that sleep problems contributed to these mental health problems, and that treating the sleep problem not only improved the sleep issues but also had a knock on benefit on the 'primary' mental health issue. This led to further excitement for myself and many other researchers that sleep represented a transdiagnostic treatment target that could be implemented in clinical practice. Given that sleep problems were not currently treated, this potentially represents a huge advance in reducing illness burden across a range of mental and even physical health conditions.

However, as with many things, this has emerged to be a more complex proposal than initially thought. Several substantial barriers exist to this transformation, including the 1) complexity of sleep, 2) complexity of causality in general, and 3) practical barriers in implementation.

Complexity of sleep

When talking about the relationships between sleep and mental health the temptation is to keep the terms broad and generic (e.g. disturbed sleep, sleep problems, sleep disorders). However, this masks the underlying complexity of the actual phenomena involved. As an inexhaustive list, one can have too little sleep; too much sleep; trouble waking up during the night, waking up feeling exhausted, need to sleep too early or too late or at irregular times, nightmares, and a huge range of behavioural issues during sleep (walking, talking, eating etc.

etc.). All of these problems can exist independently, but more frequently they co-occur – for example, it is rare to see a patient who wakes up during the night who is not then sleeping too little as a result, even though these issues do not necessarily entail each other. An equivalent would be to discuss 'mood problems' and expect this to convey the range of grief, depression, bipolar disorder, and beyond without further specification or definitions being provided.

As implied above, this blurring has served to help in making the case for sleep and mental health – very few mental health problems are not accompanied by some kind of sleep disorder – but this can obscure specific relevant relationships such as hypersomnia in depression, insomnia and anxiety, and nightmares in PTSD. This results in both poor clinical practice (where it is common to just ask 'how are you sleeping' and that be the sum of sleep assessment) but also blurs research and our understanding of the shared or reciprocal causal relationships. For example, what can an overlap between hypersomnia and depression tell us about physiological or psychological factors that might subtend both disorders?

An emerging awareness of this issue; and need to go beyond merely 'sleep disorders' to consider specific mechanisms was a specific motivation for part 1 of this thesis, and the secondary analyses in part 2 to focus on nightmares. In the event this only highlighted the problem itself wherein a disorder such as nightmares is indexed only by one relatively poorly worded item even in a specially designed scale for assessing sleep disorders in children. Overall, sleep literacy and understanding has a long way to go.

Complexity of causal networks

When considering causal factors contributing to mental health problems there is a propensity to hold a linear causal view – e.g. this person sleeps poorly, and now they feel anxious. Yet when working clinically, especially in systemic and to an extent in CBT frameworks, we are able to consider circular loops or vicious cycles – e.g. this person sleeps poorly, then feel anxious, and then sleep poorly again – and so on. These 'loops' are hard to investigate, and especially difficult to disentangle from linear causation, and therefore we tend to establish linear causation for all factors and then hypothesise an additional reciprocal role for relevant situations. Mental health research has also begun to increasingly embrace network models for symptoms – which further increase the complexity of causal networks and can be reflected in techniques such as Directed Acyclic Graphs (DAGS). However, even these are built on the fundamental assumption that causality runs in one direction between each node of the network – to my knowledge we do not yet have adequate statistical tools to properly characterise the reciprocal and dynamic interactions that characterise mental health.

This problem is especially acute for sleep as a causative agent in mental health. Sleep is a highly reciprocal as a fundamentally recurring state which reflects waking life, and itself influences waking life. Its influence on each day is small, but cumulatively the impact of a sleep problem will be large – and vice versa with a mental health problem impacting on sleep. Yet in mental health (and science in general) the search is stereotypically for a 'magic bullet' treatment or cause which can provides a complete (or mostly complete) causal story. Increasingly awareness is growing that these do not exist, yet our prioritisation of interesting

findings is still built around ideas of specific causes. Here the very generalism and reciprocal relationship of sleep across all of mental health plays against it. Sleep will never fit this metric for any individual disorder as its contribution will always be small and muddied with interaction. This is especially the case with a backdrop of 'crud theory' – i.e. the theory that everything is at least slightly correlated, therefore small effects can be disregarded as uninformative (Orben & Lakens, 2020). Yet if the small influence that sleep has was added up across each mental and physical health factor it influences then the summative impact is potentially huge.

In this thesis I have attempted to remedy this as much as possible with the tools available to me, for example by utilising risk ratios to increase interpretability and hopefully transferability of the results in to any future meta-analyses or policy – but fundamentally we lack sophistication in causal understanding in relation to mental health in order to make the case for sleep interventions as 'causal enough'.

Practical barriers in implementation

Even despite these barriers there is growing interest in implementing sleep interventions in mental health services. However, despite sleep interventions being relatively straightforward (in comparison to, say, EMDR), there is a lack of staff who are trained in even basic sleep assessment, let alone CBT for insomnia. A survey indicated that UK doctors receive very little training on sleep in medical school (Urquhart et al., 2012); and DClinPsy courses also do not include specific training in CBTi or other sleep interventions. This can be seen in the lack of appropriate sleep assessment or treatment available to patients – in one of my studies I found

that zero patients out of sixty had received a NICE-recommended sleep intervention from their mental health team (Reeve et al., 2019). The most common response reported from mental health teams was to provide a sleep hygiene worksheet – despite the fact that sleep hygiene is not an effective standalone treatment, and furthermore that distribution of worksheets without any follow-up or surrounding intervention is of course unlikely to be effective. Clinicians would be unlikely to take this approach with depression and expect results, yet frustratingly it is the default response for sleep difficulties.

A larger commissioning catch-22 barrier exists – because sleep is not currently treated there is no budget to allow for training or access to CBTi– but it is not currently treated because no services are commissioned or trained to do so. The widespread small impacts of sleep problems are therefore felt across all services, but 'belong' to none. This means that services continue to treat the issue they are commissioned for (depression, anxiety, psychosis) but not address one of the core underlying factors for mental health, despite appropriate treatments existing.

For services to address sleep there would need to be huge training and commissioning shifts – and at this point it becomes worthwhile to consider whether sleep is the best use of such efforts. For example, while I believe that sleep problems are an (often) easily improvable clinical target for a range of issues, I worry about some aspects of its appeal (as a mostly manualised therapy for an individualised problem) meaning that it could be sold as an easy 'fix' in a system that needs to instead invest in large scale changes that we know would have bigger impact in mental health – for example, addressing poverty, racism, or other systemic

injustices. While there is no sign yet of sleep being applied as an 'easy revolution', if this was to occur I think there would need to be sound ethical review of its likely impact versus these more challenging but more wide-ranging alternatives.

Conclusion and implications for future research

For me the state of the field in sleep and mental health demands a response which is not just more general papers showing that sleep problems are moderately correlated with other issues. I would hope that in future we can address these challenges by designing specific intervention studies for a sleep problem (e.g. nightmares), quantifying its summative impact on a range of health factors (from hypertension to hallucinations), and using this to argue for increasing funding and availability of sleep treatments – and then taking the evidence from these 'real world' outcomes and using them to further evaluate the influence between sleep and mental health. Some of these barriers are methodological and some political, but without moving forwards on these it seems likely that the field will lose momentum and others will lose interest in sleep – writing it off as non-specific when its strength is its universality.

References

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Urquhart, D. S., Orme, J. a, & Suresh, S. (2012). Survey of undergraduate sleep medicine teaching in UK medical schools. *Archives of Disease in Childhood*, *97*(1), 90–91. https://doi.org/10.1136/archdischild-2011-301073

Appendices

Contents

Appendix 1: Pre-registration of secondary data analysis

Part 1: Study information

Q1: Provide the working title of your study.

The role of sleep disorders in predicting the onset, persistence, and remission of psychotic experiences in children

Q2: Name the authors of this preregistration.

Sarah Reeve (SR) https://orcid.org/0000-0002-9374-0950

Vaughan Bell (VB) https://orcid.org/0000-0001-8616-4847

Q3: List each research question included in this study.

An increasing amount of evidence supports a causal role for sleep disorders in contributing to psychotic experiences, mediated by negative affect. However, the majority of this research is in adults (from both the clinical and non-clinical population), which limits generalisation to younger age groups. This is especially the case given the known differences in sleep disorders and psychotic experiences at different developmental stages. Therefore, research is needed that establishes if sleep is related to psychotic experiences during childhood – i.e. whether sleep problems are associated with the onset or maintenance of psychotic symptoms. Accordingly, we propose the following research questions:

RQ1 = Do sleep disorders and psychotic experiences co-occur in childhood?
RQ2 = Do sleep disorders predict onset of psychotic experiences?
RQ3 = Do sleep disorders predict persistence of psychotic experiences?
RQ4 = Does remission of sleep disorders predict remission of psychotic experiences?

Q4: For each of the research questions listed in the previous section, provide one or more specific and testable hypotheses, and make it clear whether the hypotheses are directional (e.g., A > B) or non-directional (e.g., A ≠ B). If directional, state the direction.

RQ1: Presence of sleep disorder symptoms at T0 will be positively associated with psychotic symptoms at T0

RQ2: Persistence of sleep disorders (i.e. presence at T0 *and* T1) will be positively associated with new onset of psychotic symptoms at T1 (i.e. presence at T1 *but not previously* at T0)

RQ3: Persistence of sleep disorders (i.e. presence at T0 *and* T1) will be positively associated with persistence of psychotic symptoms (i.e. presence at T0 *and* T1)

RQ4: We will test whether the presence of sleep disorders and psychotic symptoms at T0 followed by absence of sleep disorders at T1 is negatively associated with psychotic symptoms at T1

All analyses will be run with the hypothesised variables as described above as a first round, and shall then be run with the below control variables entered as a block to see if this alters the relationship:

- Sex
- Ethnicity
- Socioeconomic status
- Neighbourhood deprivation
- Child IQ (matrix reasoning scaled score)
- Family conflict
- Stimulant medication prescribed

Part 2: Data description

Q5: Name and briefly describe the dataset(s), and if applicable, the subset(s) of the data you plan to use.

The Adolescent Brain and Cognitive Development (ABCD) 2.0 study data will be used in the current analysis. The recruitment process of the study aims to be as inclusive as possible in order to capture a representative sample of US adolescents. All families of children aged 9-10 in geographic catchment area of study sites across the USA were contacted with information about the study via schools. Families that were interested in taking part were then contacted by the research team and screened for inclusion. Participants were purposively recruited to fulfil specific requirements re representativeness to match sociodemographic factors in the US, with targets for each of five major race/ethnicity classifications (White, African-American, Hispanic, Asian All Other).This dataset currently contains cross-sectional data on 11,800 children aged 9-10, with longitudinal follow-up data to be added over subsequent years. Full details are available in the relevant special issue of Developmental Cognitive Neuroscience (Feldstein Ewing & Luciana, 2018).

Q6: Specify whether this data is open or publicly available.

The data is open and available on application to the NIH as described below.

Q7: How can the data be accessed? Provide a persistent identifier or link if the data are available online, or give a description of how you obtained the dataset.

Our request was submitted to https://nda.nih.gov/abcd. Individuals who fulfil the criteria outlined at https://nda.nih.gov/abcd/request-access/access-review.html are able to access the data, following review by the Data Access Committee (https://nda.nih.gov/abcd/request-access/data-access-committee.html).

Q8: Specify the date of download and/or access.

Access to the 2.0 dataset was granted in February 2019 and was downloaded shortly after.

Q9: If the data collection procedure is well documented, provide a link to that information. If the data collection procedure is not well documented, describe, to the best of your ability, how data were collected.

See (Feldstein Ewing & Luciana, 2018) for full details of data collection for the ABCD study.

Q10: Some studies offer codebooks to describe their data. If such a codebook is publicly available, link to it here or upload the document. If not, provide other available documentation. Also provide guidance on what parts of the codebook or other documentation are most relevant.

A codebook for the ABCD data is available at https://nda.nih.gov/data_dictionary.html?source=ABCD%2BRelease%2B2.0&submission=ALL, within which the most relevant subsections for the current analysis are those relating to the variables of this analysis:

- Psychotic symptoms (PQ-BC): pps01_definitions [raw scores], abcd_mhy02 [sum scores]
- Sleep disorder symptoms (SDSC): abcdsds_01_definitions

Control variables are as follows

Control variable	Location in data dictionary ([variable name] from [variable list])	Variable description
Sex	gender from abcdsds_01_definitions	M=Male/F=Female (categorical)
Ethnicity	race_ethnicity from acspsw03	1 = White; 2 = Black; 3 = Hispanic; 4 = Asian; 5 = Other (categorical)

Socioeconomic status	demo_fam_exp1_v2 to demo_fam_exp7_v2 from pdem02	sum to make 0-7 score, higher values indicate lower socioeconomic status (ordinal)
Neighbourhood deprivation	reshist_addr1_adi_perc from abcd_rhds01	Area Deprivation Index: national percentiles, higher means higher value of area deprivation (continuous)
Child IQ (matrix reasoning scaled score)	pea_wiscv_tss from abcd_ps01	WISC-V Matrix Reasoning Total Scaled Score, range 1-19 (continuous)
Family conflict	fam_enviro1_p to fam_enviro9r_p from fes02	sum to 0-9 score, higher values indicate higher levels of family conflict (ordinal)
Stimulant medication prescribed	med1_rxnorm_p up to med15_rxnorm_p from medsy01	These fields searched for stimulant medications (0 = not present in any, 1 = present; categorical).

Part 3: Variables

Q11: If you are going to use any manipulated variables, identify them here. Describe the variables and the levels or treatment arms of each variable (note that this is not applicable for observational studies and meta-analyses). If you are collapsing groups across variables this should be explicitly stated, including the relevant formula.

No manipulated variables are present in this study.

Q12: If you are going to use any measured variables, identify them here. Describe both outcome measures as well as predictors and covariates and label them accordingly. If you are using a scale (a set of items that have an underlying latent construct) or an index (a set of items that directly indicate a value or quantity), state the construct the scale/index represents, which items the scale/index will consist of, how these items will be aggregated, and whether this aggregation is based on a recommendation from the study codebook or validation research. If you are using any categorical variables, state how you will code them in the statistical analyses.

Key outcome variables

Prodromal Questionnaire – Brief Child version (PQ-BC): This is a self reported questionnaire measure assessing presence and distress associated with psychotic like symptoms in children. For each PLE the child is asked if they experience it (yes/no), ad if they do, are asked how much it distresses/bothers them on a pictographic 1 to 5 scale showing a human carton figure in various levels of distress. The questionnaire

was adapted for and validated within the current ABCD dataset (Karcher et al., 2018). This questionnaire yields two outcome variables – the sum of symptoms endorsed (psychosis_total: range 0-21) and the sum of distress reported (psychosis_distress: range 0-126).

For the purposes of the current analysis, the sum of symptoms will be recoded to a categorical 0-1 variable (psychosis_cat), where 1 indicates presence of at least one psychotic symptom (i.e.≥1 on 'psychosis_total') and 0 indicates no psychotic symptoms present (i.e. 0 on 'psychosis_total'). This psychosis_cat variable will used to generate relevant variables for persistence and remission analysis as follows:

psychosis_t0: psychosis_cat value at t0
psychosis_t1: psychosis_cat value at t1
psychosis_persist: categorical variable, value is 1 if psychosis_t0 = 1 and psychosis_t1 = 1, value is 0 otherwise
psychosis_remit: categorical variable, value is 1 psychosis_t0 = 1 and psychosis_t1 = 0= 1 at t0 and 0 at t1, value is 0 otherwise

The variables psychosis _total, psychosis _cat, psychosis_t1, psychosis _persist, and psychosis_remit will be used as dependent variables at different stages of the planned analysis (see Q19).

Key predictor variable

Sleep Disorder Scale for Children (SDSC): The SDSC is a parent-reported questionnaire assessing the presence of a range of sleep disorder symptoms in their children (Bruni et al., 1996). It is composed of 26 likert items assessing the frequency of various disturbances over the past 6 months on a 1 to 5 likert scale (1 = never, 5 = always/daily experiencing a particular issue). All items can be summated for a total measure of sleep disturbance (sleep_total), for which a cut-off point at 39 having sensitivity of 0.89 and specificity of 0.74, correctly identifying 73.4% of a control group and 89.1% of sleep disordered participants.

For the purposes of the current analysis, the sleep_total variable will be transformed to a categorical 0/1 variable (sleep_cat), where 0 indicates an absence of disturbed sleep (i.e. ≤38 total score on SDSC), and 1 indicates presence of sleep disturbance (i.e. ≥39 total score on SDSC).

This sleep_cat variable will used to generate relevant variables for persistence and remission analysis as follows:

sleep_t0: sleep_cat value at t0

sleep_t1: sleep_cat value at t1

sleep_persist: categorical variable, value is 1 if sleep_t0 = 1 and sleep_t1 = 1, value is 0 otherwise

sleep_remit: categorical variable, value is 1 sleep_t0 = 1 and sleep_t1 = 0= 1 at t0 and 0 at t1, value is 0 otherwise

The variables sleep_total, sleep_cat, sleep_t0, sleep_persist, and sleep_remit will be used as independent variables at different stages of the planned analysis (see Q19).

Q13: Which units of analysis (respondents, cases, etc.) will be included or excluded in your study? Taking these inclusion/exclusion criteria into account, indicate the (expected) sample size of the data you'll be using for your statistical analyses (to the best of your knowledge). In the next few questions, you will be asked to refine this sample size estimation based on your judgments about missing data and outliers.

Each analysis will only include participants for whom data from all variables is available. How this breaks down per-variable and by analysis is detailed below:

Variable/Variable collection	Number of T0 cases with complete data	Number of T1 cases with complete data
Sleep disturbance scale (SDSC)	11841	4924
Psychotic experiences – total (PQ-BC)	11860	4941
List-wise total of variables	11830	4922
Total across all time points		4910

Q14: What do you know about missing data in the data set (e.g., overall missingness rate, information about differential dropout)? How will you deal with incomplete or missing data? Based on this information, provide a new expected sample size.

Our analyses will not include any cases for which there is incomplete or missing data.

Q15: How will you define what a statistical outlier is in your data and what will you do when you encounter them? If you plan to remove outliers, provide a new expected

sample size. Note that this will be the definitive expected sample size for your study and you will use this number to do any power analyses.

We will not remove outliers from our dataset.

Q16: Are there sampling weights available with this data set? If so, are you using them and how?

Due to recruitment process the ABCD sample is representative of the population therefore there is no need to apply sampling weights.

Part 4: Knowledge of data

Q17: List the publications, conference presentations (papers, posters), and working papers (in prep, unpublished, preprints) you have worked on that are based on the data set. Describe which variables you have previously analyzed and which information you used in these analyses. Limit yourself to variables that are relevant to the current study. If the dataset is longitudinal, include information about what wave of data was previously analyzed.

Importantly, some of your team members may have used this dataset and others may not have. It is therefore important to specify the relevant work from every co-author separately. If possible, mention other researchers' work with this dataset that is relevant to the current preregistration.

SR has not worked on this data set prior to this current planned analysis. VB has prior experience working with this dataset and with the 1.0 version of this dataset.

Q18: What prior knowledge do you have at the time of preregistration about trends in the data set you will be working with? For example, are you aware of summary statistics or the statistical distribution of variables, or do you know about correlations between variables? Your prior knowledge could stem from working with the data first-hand, from reading previously published research, or from codebooks. Also provide any relevant knowledge of different subsets of the data (e.g., a different wave than you will be using). Finally, provide information about your prior knowledge for every author separately.

SR has no knowledge of the data set prior to working with it. VB has knowledge of the distribution of psychotic-experiences in the dataset and preliminary knowledge of the association between psychotic symptoms and sociodemographic variables due to an in-

progress network analysis being conducted for another study. VB has no knowledge of the distribution or association with sleep variables.

Part 5: Analyses

Q19: For each hypothesis, describe the statistical model you will use to test the hypothesis. Include the type of model (e.g., ANOVA, multiple regression, SEM) and the specification of the model (this includes each variable that will be included as predictor, outcome, or covariate). Specify any interactions and post-hoc analyses and remember that any test not included here must be noted as an exploratory test in the final article.

Comment(s): Think carefully about the variety of statistical methods that are available for testing each of your hypotheses. One of the classic "Questionable Research Practices" is trying multiple methods and only publishing the ones that "work" (i.e., that support your hypothesis). Even methods like multiple-comparison correction have several options that may be more or less suited to the question you are asking (for an overview of multiple-comparison correction methods relevant to secondary data analysis, see Thompson, Wright, Bissett, and Poldrack, 2019). Therefore, it is crucial to specify *a priori* which one you are going to use and how.

If you can, include the code you will use to run your statistical analyses, as this forces you to think about your analysis in detail and improves your preregistration. Ideally, when you have loaded the data in a software program you only have to press one button to run your analyses. If including the code is impossible, describe the analyses such that you could give a positive answer to the question: "Would a colleague who is not involved in this project be able to recreate this statistical analysis?"

We will test the hypotheses and exploratory analysis question using regression analyses. For the test of each hypothesis, we will first examine the association between sleep disorders and psychotic symptoms. If a significant association is found, we will re-run the regression analysis including the control variables listed above to examine whether the association remains significant after adjustment.

RQ1) Do sleep disorders and psychotic experiences co-occur in childhood?

Appendix 1: Pre-registration of secondary data analysis

Model 1a: A linear regression analysis to assess if higher sleep symptoms is positively associated with higher psychotic symptoms - > e.g. lmer(psychosis_total ~ sleep_total)

Model 1b: A binomial logistic regression analysis to assess if higher sleep symptoms is positively associated with presence of psychotic symptoms - > e.g. logitor(psychosis_cat ~ sleep_total)

Model 1c: A binomial logistic regression analysis to assess if presence of sleep symptoms is positively associated with presence of psychotic symptoms -> e.g. logitor(psychosis_cat ~ sleep_cat)

Models 1d-f: for those out of Models1a-1c in which the sleep variable is found to be a significant predictor, the model will re-run with control variables entered as block with aim of testing if the relevant sleep variable remains significantly predictive: e.g. -> **model 1d:** lmer(psychosis_total ~ sleep_total + sex + ethnicity + socioeconomic status + neighbourhood deprivation + child IQ + family conflict + stimulant medication)

RQ2) Do sleep disorders predict onset of psychotic experiences?

Model 2a: A binomial logistic regression analysis to assess if presence of sleep symptoms at t0 is positively predictive of psychotic symptoms at t1 (e.g. logitor(psychosis_t1 ~ sleep_t0))

Model 2b: A binomial logistic regression analysis to assess if presence of sleep symptoms at t0 is positively predictive of psychotic symptoms at t1, controlling for sleep disorder at t1 (e.g. logitor(psychosis_t1 ~ sleep_t0 + sleep_t1))

Model 2c-d: If model 2a or 2b is found to be significantly predictive, it will be re-run with control variables entered as block with aim of testing if sleep variable association remains significant – e.g. -> **model 2c** logitor(psychosis_t1_ cat ~ sleep_t0_ cat + sex + ethnicity + socioeconomic status + neighbourhood deprivation + child IQ + family conflict + stimulant medication)

RQ3) Do sleep disorders predict persistence of psychotic experiences?

Model 3a: A binomial logistic regression analysis to assess if presence of sleep symptoms at t0 is positively predictive of persistence of psychotic symptoms from t0 to t1 (e.g. logitor(psychosis_persist ~ sleep_t0))

Model 3b: A binomial logistic regression analysis to assess if persistence of sleep symptoms from t0 to t1 is positively predictive of persistence of psychotic symptoms from t0 to t1 (e.g. logitor(psychosis_persist ~ sleep_persist))

Model 3c-d: If model 3a or 3b is found to be significantly predictive, it will be re-run with control variables entered as block with aim of testing if sleep variable association remains significant – e.g. **model 3c:** logitor(psychosis_persist ~ sleep_t0+ sex + ethnicity + socioeconomic status + neighbourhood deprivation + child IQ + family conflict + stimulant medication)

RQ4) Does remission of sleep disorders predict remission of psychotic experiences?

Model 4a: A binomial logistic regression analysis to assess if remission of sleep symptoms between t0 and t1 is positively predictive of remission of psychotic symptoms from t0 to t1 (e.g. logitor (psychosis_remit ~ sleep_remit)

Model 4b: If model 4a is found to be significantly predictive, it will be re-run with control variables entered as block with aim of testing if sleep variable association remains significant –> logitor(psychosis_remit ~ sleep_remit + sex + ethnicity + socioeconomic status + neighbourhood deprivation + child IQ + family conflict + stimulant medication)

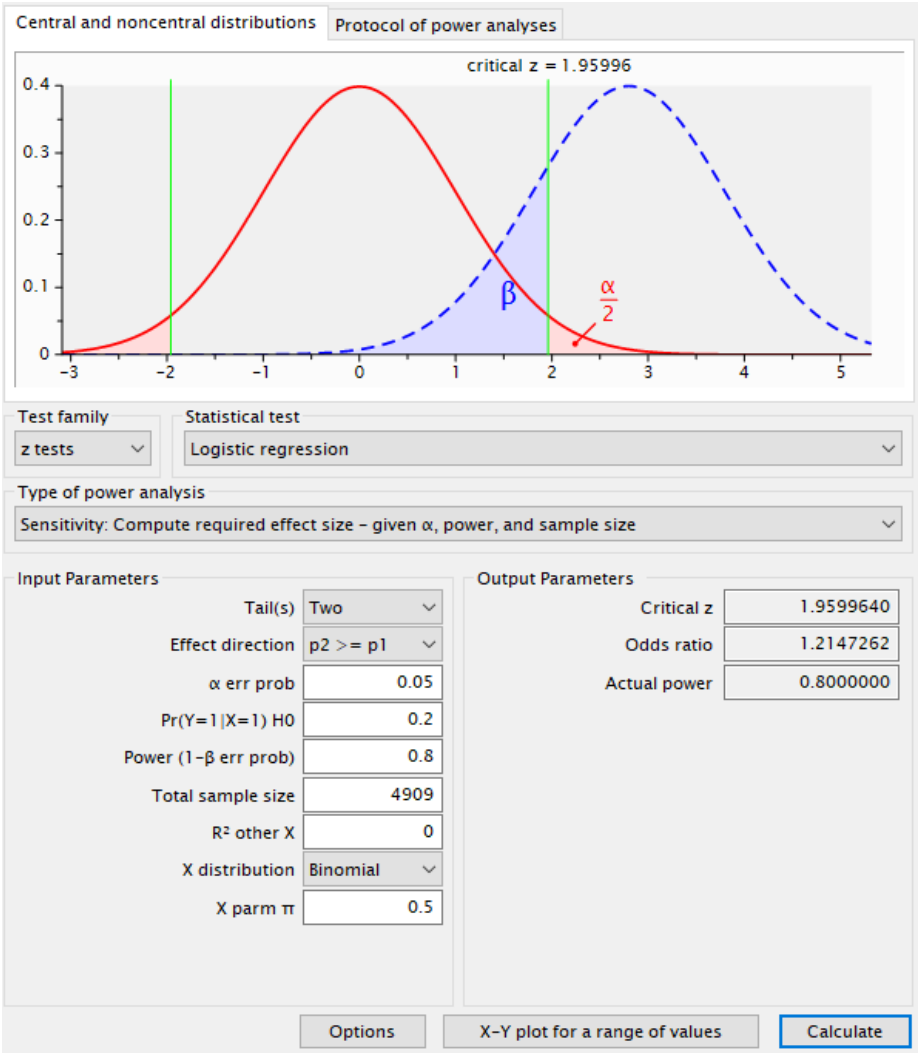
Q20: If applicable, specify a predicted effect size or a minimum effect size of interest for all the effects tested in your statistical analyses.

Any effect meeting statistical significance would be of interest, and reported as supporting key hypotheses in this study, and will be interpreted as meaningful based on the effect size of the association.

Q21: Present the statistical power available to detect the predicted effect size(s) or the smallest effect size(s) of interest. Use the sample size after updating for missing data and outliers.

The full dataset includes data from upwards of 11,800 individuals. We are using the subset of individuals within this dataset for whom both T0 and T1 data is available on all our variables (n=4909). A sensitivity analysis carried out within G*Power indicates the minimum detectable odds-ratio would be 1.21. More data is due to be released in Summer of 2020 and will be included as relevant according to the criteria specified above, which will increase the ability to detect effects in this study.

Appendix 1: Pre-registration of secondary data analysis



Q22: What criteria will you use to make inferences? Describe the information you will use (e.g. specify the p-values, effect sizes, confidence intervals, Bayes factors, specific model fit indices), as well as cut-off criteria, where appropriate. Will you be using one- or two-tailed tests for each of your analyses? If you are comparing multiple conditions or testing multiple hypotheses, will you account for this, and if so, how?

Standard criteria for significance will be applied (p value less than or equal to 0.05) to all analyses. We will not mathematically adjust p values for multiple comparisons but will take this into account during interpretation of the results.

Q23: What will you do should your data violate assumptions, your model not converge, or some other analytic problem arises?

If there is an issue with applying the analytic approach, we will adjust the analysis and report any deviations in the study report.

Q24: Provide a series of decisions about evaluating the strength, reliability, or robustness of your focal hypothesis test. This may include within-study replication attempts, additional covariates, cross-validation efforts (out-of-sample replication, spilt/hold-out sample), applying weights, selectively applying constraints in an SEM context (e.g., comparing model fit statistics), overfitting adjustment techniques used (e.g., regularization approaches such as ridge regression), or some other simulation / sampling / bootstrapping method.

Not applicable for our pre-registration.

Q25: If you plan to explore your data set to look for unexpected differences or relationships, you can describe those tests here, or add them to the final paper under a heading that clearly differentiates this exploratory part of your study from the confirmatory part.

A cross-lagged panel design may be applied to this dataset in order to test pathways of influence over time between sleep and psychosis. This would assist with understanding the direction of influence between sleep and psychotic symptoms in this cohort. This approach would be especially applicable if further cohort time points become available.

References

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Karcher, N. R., Barch, D. M., Avenevoli, S., Savill, M., Huber, R. S., Simon, T. J., … Loewy, R. L. (2018). Assessment of the prodromal questionnaire-brief child version for measurement of self-reported psychoticlike experiences in childhood. *JAMA Psychiatry*, *75*(8), 853–861. https://doi.org/10.1001/jamapsychiatry.2018.1334

Reeve, S., Nickless, A., Sheaves, B., & Freeman, D. (2018). Insomnia, negative affect, and psychotic experiences: Modelling pathways over time in a clinical observational study. *Psychiatry Research*, *269*, 673–680. https://doi.org/10.1016/j.psychres.2018.08.090

Appendix 2: Ethical approval to access ABCD study data

The following page includes the data use certification for access to the ABCD study data from NIH.

Vaughan Bell was the primary holder of ethics, and approval to access the data was maintained throughout the study period.

Appendix 2: Ethical approval to access ABCD study data

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Expiration Date: 11/30/2020

NIMH Data Archive

Data Use Certification

Last updated: December 14, 2017

OMB Control Number: 0925-0667
Expiration Date: 11/30/2020

NIMH Data Archive Data Use Certification

Introduction

The National Institute of Mental Health (NIMH) Data Archive (NDA) is a collaborative resource that contains human subjects research data.

The NIMH Data Archive Data Use Certification (DUC) is used to request access to shared research data in the NIMH Data Archive. Shared data are available with either an Institutional sponsorship or an Individual sponsorship. All data access requests require acceptance of the Data Use Terms and Conditions contained in this DUC. (See the *NIMH Data Archive Recipient Information and Certifications* form in this document for available data and associated sponsorship types.)

- Institutional sponsorship requires Recipients to be affiliated with an NIH recognized institution (foreign or domestic), based upon registration in the NIH's eRA Commons system, with an active Federal Wide Assurance (FWA) issued by the Department of Health and Human Services, Office for Human Research Protections (OHRP). The signature of an Authorized Institutional Business Official is also required on this DUC.
- Individual sponsorship may be requested by a Recipient without the need for sponsorship by or affiliation with an NIH recognized institution and, therefore, the signature of an Authorized Institutional Business Official or an active institutional FWA is not required.

A Data Access Committee(s) (DAC) will objectively review a data access request sponsored by an Institution. Individual sponsorships do not require DAC review. To submit data to the NIMH Data Archive, the NIMH Data Archive Data Submission Agreement (DSA) must be completed, which is a separate document.

The NIMH Data Archive (NDA)

The National Institutes of Health (NIH) and NIMH have developed a repository to store the collection of data from participants in research studies, regardless of the source of funding. The extensive information collected by these studies, and subsequently stored in the National Database for Autism Research (NDAR), the NIH Pediatric MRI Repository (PedsMRI), the National Database for Clinical Trials Related to Mental Illness (NDCT), the Research Domain Criteria Database (RDoCdb), the Adolescent Brain Cognitive Development (ABCD) Study, and the Osteoarthritis Initiative (OAI), provides a rare and valuable scientific resource. The NIH and NIMH seek to encourage the use of these resources to achieve rapid scientific progress. Moreover, NIMH has made data sharing an expectation for all clinical research it funds (see NOT-MH-15-012). In order to take full advantage of such resources and maximize their research value, it is important that data are made **broadly available**, on appropriate terms and conditions, to the largest possible number of qualified investigators in a timely manner.

Data collected by the Submitters have been stripped of all individual identifiers, but the unique and intrinsically personal nature of genomics data, brain imaging, and other derivative data of which are included in these repositories, combined with the recent increase in the accessibility of conducting genotype and other sequence analyses (in terms of technological capacity and cost), has altered the framework through which "identify-ability" can be defined. To protect and assure the confidentiality and privacy of all participants, the Recipient who is granted access to these data is expected to adhere to the specifications of this DUC. Failure to do so could result in denial of further access to data.

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National Database for Autism Research (NDAR)
The National Database for Autism Research (NDAR) is an NIH-funded research data repository that aims to accelerate progress in autism spectrum disorder (ASD) research through data sharing, data harmonization, and the reporting of research results. Raw genomics, clinical, imaging, and neurosignal recording data and results are available.

National Database for Clinical Trials Related to Mental Illness (NDCT)
The NIMH has made data sharing an expectation for all future clinical trials funded by the NIMH (see NOT-MH-14-015). Researchers are expected to submit both positive and negative data and results from NIMH-funded clinical trials to the National Database for Clinical Trials Related to Mental Illness (NDCT). NDCT will provide a system to support the submission, sharing and access of relevant data at all levels of biological and behavioral organization and for all data types. At present, data submitted to NDCT will be the result of grants funded through a series of NIMH funding opportunity announcements (FOAs) as well as other privately funded research projects.

Research Domain Criteria Database (RDoCdb)
The Research Domain Criteria (RDoC) initiative aligns research in neuroscience and behavioral science to develop a precision-medicine approach for classifying mental illnesses. In contrast to current symptom-based diagnostic systems for mental illnesses, precision medicine integrates many levels of information for each patient to define a precise diagnosis. Data submitted to the RDoC Database (RDoCdb) will include the results of grants funded through a series of NIMH FOAs in support of the RDoC project, as well as relevant data submitted by other interested investigators, regardless of funding source. More information on the RDoC project and related FOAs can be found at http://www.nimh.nih.gov/research-priorities/rdoc/index.shtml. Omics data associated with these studies are found in genomics repositories supported by the National Library of Medicine (dbGaP and SRA).

NIH Pediatric MRI Data Repository (PedsMRI)
The goal of the NIH MRI Study of Normal Brain Development and the resulting Pediatric MRI Data Repository (PedsMRI) is to generate data that can help foster a better understanding of normal brain maturation as a basis for understanding atypical brain development associated with a variety of developmental, neurological, and neuropsychiatric disorders affecting children and adults.

Adolescent Brain Cognitive Development Study (ABCD)
The ABCD Study is a long-term study of brain development and child health in the United States. Multiple NIH Institutes and Centers and additional federal partners are supporting this ambitious project. The ABCD Consortium consists of a Coordinating Center, a Data Analysis and Informatics Center, and 21 research sites across the country where investigators will perform regular, comprehensive biological and behavioral assessments on more than 10,000 children beginning at ages 9 or 10 and continuing throughout adolescence into early adulthood. A more complete description of the study is available at https://ABCDStudy.org.

Osteoarthritis Initiative (OAI)
The Osteoarthritis Initiative (OAI) is a multi-center, longitudinal, prospective observational study of knee osteoarthritis (OA). The overall aim of the OAI is to develop a public domain research resource to facilitate the scientific evaluation of biomarkers for osteoarthritis as potential surrogate endpoints for disease onset and progression. The OAI will establish and maintain a natural history database for osteoarthritis that will include clinical evaluation data, radiological (x-ray and magnetic

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resonance) images, and a biospecimen repository from 4796 men and women ages 45-79 enrolled between February 2004 and May 2006. Four 3.0 Tesla MRI scanners, one at each clinical center, are dedicated to imaging the knees of OAI participants annually over four years. The seven-year project will recruit participants who have, and those who are at high risk for developing, symptomatic knee osteoarthritis. Access to biospecimens will be by application to the National Institute of Arthritis, Musculoskeletal and Skin Diseases (NIAMS).

Data Use Terms and Conditions

I request access to shared data from the NIMH Data Archive for the purpose of scientific investigation, scholarship or teaching, or other forms of research and research development as described in the following NIMH Data Archive Data Use Certification (DUC). I, and any Other Recipients listed in this DUC, agree to the following terms:

1. Research Data Use Statement

Generally, these data will be used by the Recipient in connection with the purpose indicated and described in the *Research Data Use Statement* on the DUC. Recipients are encouraged to explore shared data in the NIMH Data Archive for a variety of purposes including secondary analysis, hypothesis generation, and replication regardless of whether said exploration leads to analysis in support of a question beyond the scope of the originally identified purpose described in the *Research Data Use Statement*.

2. Non-transferability of Agreement

This DUC is not transferable. If a Recipient changes institutions and wishes to retain access to the NIMH Data Archive, a new DUC is required.

3. Non-Identification of Subjects

Recipients agree that data will not be used to establish the individual identities of any of the study participants from whom data were obtained (or their relatives) and/or contact the individual study participant, except as permitted by law (e.g., in connection with a separately negotiated collaboration with the original research team or the enrollment of the consented subject in the Recipient's study). Recipients agree to notify the NIH at NDAHelp@mail.nih.gov as soon as possible if, upon use of NIMH Data Archive data, identifying information is discovered.

4. Use of the NIH Global Unique Identifier (GUID)

The Global Unique Identifier (GUID) is a computer-generated alphanumeric code that is unique to each research participant. The GUID allows the NIMH Data Archive to link together all submitted information on a single participant, giving researchers access to information even if the data were collected at different locations or through different studies. If Recipients access data on individuals for whom they, themselves, have previously submitted data to the NIMH Data Archive, Recipients may gain access to more data about an individual participant than they, themselves, collected. Consequently, these research activities may be considered "human subjects research" within the scope of 45 C.F.R. 46. Recipients must comply with the requirements contained in 45 C.F.R. 46, as applicable, which may require Institutional Review Board (IRB) approval of the Research Data Use Statement.

5. Data Disclaimers

Recipients acknowledge that the NIH does not and cannot warrant the results that may be obtained by using any data or data analysis tools included in the NIMH Data Archive. The NIH disclaims all warranties

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as to the accuracy of the data in the NIMH Data Archive or the performance or fitness of the data or data analysis tools for any particular purpose.

6. Data Access for Research

Data and Supporting Documentation in the NIMH Data Archive are eligible for access by qualified researchers, pursuant to the terms set forth in this DUC. Recipients acknowledge that other researchers have access to the data and that downloading and duplication of research is a distinct possibility, thereby decreasing subject data protections. Raw or nearly raw research data files (e.g. fastq, bam, MRI, and EEG recordings) are made available for just in time computation, regardless of where the computational resources may reside. Therefore, data copied shall not be persisted (i.e., stored) beyond the time necessary for computation and shall be expunged once computation has been completed. Recipients are encouraged to utilize the NIMH Data Archive computational capabilities described at https://data-archive.nimh.nih.gov/tools#cloud.

7. Supporting Documentation

Recipients agree to review the supporting information, materials, and documentation ("Supporting Documentation") for the data accessed in the NIMH Data Archive to enable efficient use of the submitted data by Recipients unfamiliar with the data or the research project. Examples of supporting documentation include:

- Research protocol(s)
- Questionnaire(s)
- Study manuals

8. Sharing of an NIMH Data Archive Study/Acknowledgements

Recipients agree to create and share an NIMH Data Archive Study (http://ndar.nih.gov/access_ndar_study.html) for each publication, computational pipeline, or other public disclosure of results from the analysis of data accessed in the NIMH Data Archive, whether reporting positive or negative results, thereby linking it to the underlying data. Recipients agree to create the NIMH Data Archive Study when a manuscript is submitted for review and share the Study when the publication is released. Recipients agree to acknowledge the NIMH Data Archive and the relevant Digital Object Identifier(s) (DOI), which will be created by NIMH Data Archive staff, in any and all oral and written presentations, disclosures, and publications (including abstracts, as space allows) resulting from any and all analyses of data, whether or not the Recipient is collaborating with Submitter(s). The oral or written presentation, disclosure, or publication should include the following acknowledgement, which includes a disclaimer of NIH endorsement, as appropriate:

NDAR Acknowledgement

Data and/or research tools used in the preparation of this manuscript were obtained from the NIH-supported National Database for Autism Research (NDAR). NDAR is a collaborative informatics system created by the National Institutes of Health to provide a national resource to support and accelerate research in autism. Dataset identifier(s): [NIMH Data Archive Collection ID(s) or NIMH Data Archive Digital Object Identifier (DOI)]. This manuscript reflects the views of the authors and may not reflect the opinions or views of the NIH or of the Submitters submitting original data to NDAR.

Pediatric MRI Acknowledgement

Data used in the preparation of this article were obtained from the NIH Pediatric MRI Data Repository created by the NIH MRI Study of Normal Brain Development. This is a multisite,

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longitudinal study of typically developing children from ages newborn through young adulthood conducted by the Brain Development Cooperative Group and supported by the National Institute of Child Health and Human Development, the National Institute on Drug Abuse, the National Institute of Mental Health, and the National Institute of Neurological Disorders and Stroke (Contract #s N01-HD02-3343, N01-MH9-0002, and N01-NS-9-2314, -2315, -2316, -2317, -2319 and -2320). A listing of the participating sites and a complete listing of the study investigators can be found at http://pediatricmri.nih.gov/nihpd/info/participating_centers.html. Dataset identifier(s): [NIMH Data Archive Collection ID(s) or NIMH Data Archive Digital Object Identifier (DOI)].

NDCT Acknowledgement
Data and/or research tools used in the preparation of this manuscript were obtained and analyzed from the controlled access datasets distributed from the NIMH-supported National Database for Clinical Trials (NDCT). NDCT is a collaborative informatics system created by the National Institute of Mental Health to provide a national resource to support and accelerate discovery related to clinical trial research in mental health. Dataset identifier(s): [NIMH Data Archive Collection ID(s) or NIMH Data Archive Digital Object Identifier (DOI)].

RDoCdb Acknowledgement
Data and/or research tools used in the preparation of this manuscript were obtained and analyzed from the controlled access datasets distributed from the NIMH-supported Research Domain Criteria Database (RDoCdb). RDoCdb is a collaborative informatics system created by the National Institute of Mental Health to store and share data resulting from grants funded through the Research Domain Criteria (RDoC) project. Dataset identifier(s): [NIMH Data Archive Collection ID(s) or NIMH Data Archive Digital Object Identifier (DOI)].

ABCD Acknowledgement
Data used in the preparation of this article were obtained from the Adolescent Brain Cognitive Development (ABCD) Study (https://abcdstudy.org), held in the NIMH Data Archive (NDA). This is a multisite, longitudinal study designed to recruit more than 10,000 children age 9-10 and follow them over 10 years into early adulthood. The ABCD Study is supported by the National Institutes of Health and additional federal partners *under award numbers U01DA041022, U01DA041028, U01DA041048, U01DA041089, U01DA041106, U01DA041117, U01DA041120, U01DA041134, U01DA041148, U01DA041156, U01DA041174, U24DA041123, and U24DA041147*. A full list of supporters is available at https://abcdstudy.org/nih-collaborators. A listing of participating sites and a complete listing of the study investigators can be found at https://abcdstudy.org/principal-investigators.html. ABCD consortium investigators designed and implemented the study and/or provided data but did not necessarily participate in analysis or writing of this report. This manuscript reflects the views of the authors and may not reflect the opinions or views of the NIH or ABCD consortium investigators.

(Add the following sentence for a report that uses data from a versioned release)
The ABCD data repository grows and changes over time. The ABCD data used in this report came from [NIMH Data Archive Digital Object Identifier (DOI)]. DOIs can be found at [DOI URL].

(Add the following sentence for a report that uses data from the fast track release)
The ABCD data repository grows and changes over time. The ABCD data used in this report came from the fast track data release. The raw data are available at [NIMH Data Archive Digital Object Identifier (DOI)]. Instructions on how to create a NDA study are available at https://data-archive.nimh.nih.gov/training/modules/study.html).

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Osteoarthritis Initiative (OAI)
Data and/or research tools used in the preparation of this manuscript were obtained and analyzed from the controlled access datasets distributed from the Osteoarthritis Initiative (OAI). OAI is a collaborative informatics system created by the National Institute of Mental Health and the National Institute of Arthritis, Musculoskeletal and Skin Diseases (NIAMS) to provide a worldwide resource to quicken the pace of biomarker identification, scientific investigation and OA drug development. Dataset identifier(s): [NIMH Data Archive Collection ID(s) or NIMH Data Archive Digital Object Identifier (DOI)].

If the Research Project involves collaboration with Submitters or NIH staff (as indicated in the DUC), then Recipient will acknowledge Submitters or NIH staff as co-authors, if appropriate, on any presentation, disclosure, or publication.

9. No Distribution of Data
Recipients agree to retain control over data from the NIMH Data Archive, and further agree not to transfer or sell data, with or without charge, in any form, to any other entity or any individual or to distribute the data to anyone other than the Other Recipients listed on this DUC who also agree to the terms in this DUC. This includes any data derived from the data in the NIMH Data Archive if the associated GUID is distributed with that derived data or if the derived data can aid in the re-identification of a research participant.

10. Non-Governmental Endorsement; Liability
Recipients agree not to claim, infer, or imply endorsement of the research project described in the *Research Data Use Statement*, the entity, or personnel conducting the research project or any resulting commercial product(s) by the United States Government, the Department of Health & Human Services, the National Institutes of Health, or the National Institute of Mental Health. The United States Government assumes no liability except to the extent provided under the Federal Tort Claims Act (28 U.S.C. § 2671-2680).

11. Recipient's Compliance with Institutional Requirements
Recipients with Institutional sponsorship acknowledge that access, if provided, is for research that is approved by the Institution with which they are affiliated, which must be operating under an active Federal Wide Assurance (FWA) issued by the Department of Health & Human Services, Office for Human Research Protections (OHRP). Furthermore, Recipients agree to comply with all applicable rules for the protection of human subjects, which may include Department of Health and Human Services regulations at 45 C.F.R. Part 46, and other federal and state laws for the use of this data. Recipients agree to report promptly to the NIH any unanticipated problems involving risks to subjects or others. This DUC is made in addition to, and does not supersede, any of Recipient's institutional policies or any local, State, and/or Federal laws and regulations that provide additional protections for human subjects.

12. Recipient's Permission to Post Information Publicly
Recipient agrees to permit the NIMH Data Archive to publicly summarize the Recipient's research use of data along with the Recipient's name and organizational/institutional affiliation.

13. Privacy Act Notification
Recipients agree that information collected by the NIH from a Recipient, as part of the DUC, may be made public in part or in whole for tracking and reporting purposes. This Privacy Act Notification is provided pursuant to Public Law 93-579, Privacy Act of 1974, 5 U.S.C. Section 552a. Authority for the

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collection of the information requested below from Recipients comes from the authorities regarding the establishment of the National Institutes of Health, its general authority to conduct and fund research and to provide training assistance, and its general authority to maintain records in connection with these and its other functions (42 U.S.C. 203, 241, 289l-1 and 44 U.S.C. 3101), and Sections 301 and 493 of the Public Health Service Act. These records will be maintained in accordance with the Privacy Act System of Record Notice 09-25-0156 (https://oma.od.nih.gov/forms/Privacy%20Documents/Documents/Privacy%20Act%20Systems%20of%20Records%20Notices%20(SORNs)%205-1-15.pdf) covering "Records of Participants in Programs and Respondents in Surveys Used to Evaluate Programs of the Public Health Service, HHS/PHS/NIH/OD." The primary uses of this information are to document, track, monitor, and evaluate the use of NIMH Data Archive datasets, as well as to notify interested Recipients of updates, corrections or other changes to the database.

The Federal Privacy Act protects the confidentiality of some NIH records. The NIH will use the information collected for the purposes described above. In addition, the Act allows the release of some information in the Recipient's records without the Recipient's permission; for example, if it is requested by members of Congress or other authorized individuals. The information requested in this DUC is voluntary, but necessary for obtaining access to data in the NIMH Data Archive.

14. Security

Recipients acknowledge that the data being made available were made available for researcher use with the expectation that the data will be protected in a manner consistent with security best practices. Such practices include, but are not limited to, the following:

- Accounts and passwords will not be shared.
- Data are protected from anonymous access. Any data transferred or stored outside of the NIMH Data Archive will be protected using standard encryption protocols and/or strong password protection.
- When finished using the data, the data will be expunged, as permitted by law.

15. Annual Update/Research Use Reporting

Recipients will provide to NDAHelp@mail.nih.gov an annual summary of research accomplishments from using the NIMH Data Archive and agree to create and share an NIMH Data Archive Study for each public disclosure of results pursuant to the Sharing of an NIMH Data Archive Study/Acknowledgements term in this DUC. The NIH encourages Recipients who publish manuscripts based on a combination of data from the NIMH Data Archive data, data derived from NDA data, and data collected independent of the NIMH Data Archive to consider submitting the complete analyzed dataset to the NIMH Data Archive.

16. Amendments

Amendments to this DUC must be in writing and signed by authorized representatives of all parties.

17. Termination

Either party may terminate this DUC, without cause, provided 30 days' advanced written notice to the other party. Recipients agree to immediately report violations of this agreement to the appropriate NIMH Data Archive Data Access Committee. Additionally, the NIH may terminate this agreement with 5 days' advanced written notice if the NIH determines, in its sole discretion, that a Recipient has committed a material breach of this DUC. The NIH may, in its sole discretion, provide a Recipient with 30 days' advanced written notice to remedy a breach before termination.

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18. Term and Access Period
Recipients are granted permission to access requested and approved data from the NIMH Data Archive for a period of one year and this DUC will automatically terminate at that time. Data access may be renewed upon certification of a new DUC.

19. Accurate Representations
Recipients expressly certify that the contents of any statements made or reflected in this document are truthful and accurate.

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Burden Disclosure Statement

Public reporting burden for this collection of information is estimated to vary from 15 min to 1.5 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. **An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.** Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to: NIH, Project Clearance Branch, 6705 Rockledge Drive, MSC 7974, Bethesda, MD 20892-7974, ATTN: PRA (0925-0667). Do not return the completed form to this address.

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NIMH Data Archive Recipient Information and Certifications 04/29/19

1. Access Request:

Application Type		Data Requested	Recipient Sponsor*
NEW ☐	RENEWAL ☐	National Database for Autism Research (NDAR)	Institutional
NEW ☐	RENEWAL ☐	Pediatric MRI Data Repository (PedsMRI)	Institutional
NEW ☐	RENEWAL ☐	National Database for Clinical Trials (NDCT)	Institutional
NEW ☐	RENEWAL ☐	Research Domain Criteria Database (RDoCdb)	Institutional
NEW ☐	RENEWAL ☑	Adolescent Brain Cognitive Development Study (ABCD)	Institutional
NEW ☐	RENEWAL ☐	Osteoarthritis Initiative (OAI)	Individual

**Institutional sponsorship requires the signature of an Authorized Institutional Business Official and an active Federal Wide Assurance (FWA) number in the Signatures section below. See the "Introduction" section on page 1 for more information.*

2. Lead Recipient:

First Name: Vaughan Last Name: Bell Degree: PhD

Institution: University College London

City: London State/Province: Country: UNITED KINGDOM

Phone: [redacted] E-mail Address: [redacted]

3. Research Data Use Statement:

Describe the purpose of the scientific investigation, scholarship or teaching, or other form of research and research development for which you are requesting access to the NIMH Data Archive.

Psychosis typically occurs in late adolescence and early adulthood but psychosis-like experiences are common in earlier life and have been shown to be associated with a range of risk factors. We intend to use network analysis to examine this in the ABCD dataset to understand the pathways and interactions between cognitive, neural and environmental risk factors, and their relation to specific psychotic symptoms. We intend to include symptoms from the prodromal psychosis scale, measures of family function and neighbourhood risk, cognitive function, volumetric measures of key brain areas altered by chronic stress, depression, anxiety, social support, substance use and pubertal development. Network analysis will help show which of these factors are the most central and important in supporting psychotic symptoms and we will complete pathway analysis to understand which are the key bridging factors between psychosis-like experience and environmental stresses.

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4. Renewal Applicants Only:

Has a publication, computational pipeline, or other public disclosure of results from the analysis of data accessed in the NIMH Data Archive resulted from a Recipient's previous access period? ☐ Yes ☒ No

If Yes, has an NDA Study been created? ☐ Yes List the NDA Study number(s): _____
☐ No* List the PubMed ID(s) or citation(s): _____

_____

_____

_____

** See 8. Sharing of an NIMH Data Archive Study/Acknowledgements above. Contact the NDA Help Desk (NDAHelp@mail.nih.gov) to create an NDA Study.*

5. Other Recipient(s): List all individuals who will access, use, or analyze the data regardless of position title or data use role. Use additional sheets as needed.

[redacted]

First Name: Sarah Last Name: Reeve Degree: PhD
Institution: University College London
City: London State/Province: Country: UNITED KINGDOM
Phon[redacted] E-mail Address: [redacted]

First Name: _____ Last Name: _____ Degree: _____
Institution: _____
City: _____ State/Province: _____ Country: _____
Phone: _____ E-mail Address: _____

First Name: _____ Last Name: _____ Degree: _____
Institution: _____
City: _____ State/Province: _____ Country: _____
Phone: _____ E-mail Address: _____

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6. **Authorized Institutional Business Official**: Requests to access data requiring an Institutional sponsorship must list an individual with an "SO" role as defined in the NIH eRA Commons - https://commons.era.nih.gov/commons

Name: Research Services Email Address: researchadministration@ucl.ac.uk

7. **Signatures:** By signing and dating this DUC to request access to data in the NIMH Data Archive, I and my Institutional Official *(if required)* certify that we will abide by the Data Use Terms and Conditions defined in this DUC. I further acknowledge that I have shared this document with any Other Recipients who will participate in the use of data from the NIMH Data Archive. My Institutional Business Official *(if required)* also acknowledges that they have shared this document with appropriate institutional organizations.

[redacted] 7th June 2019

Lead Recipient Signature Date

[redacted] 3 JULY 2019

Authorized Institutional Business Official Signature *(If required)* Date

Inquiries and requests to access data in the NIMH Data Archive should be sent to:
Office of Technology Development and Coordination (OTDC), Program Director
National Institute of Mental Health | National Institutes of Health
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Appendix 3: Primary study measures (PQBC and SDSC)

The following pages include copies of the primary study measures (PQBC and SDSC) as printed in (Karcher et al., 2018) and (Bruni et al., 1996).

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Appendix 4: R packages used in analysis

Package	Version	Citation
dplyr	1.0.2	(Wickham, François, Henry, & Müller, 2020)
readr	1.3.1	(Wickham, Hester, & Francois, 2018)
tidyr	1.1.1	(Wickham, 2020)
psych	1.9.12.31	(Revelle, 2020)
knitr	1.29	(Xie, 2020)
survey	3.37	(Lumley, 2020)
lme4	1.1.21	(Bates, Maechler, Bolke, & Walker, 2019)
lmertest	3.1.1	(Kuznetsova, Brockhoff, & Christensen, 2019)
memisc	0.99.22	(Elff, 2020)
mfx	1.2.2	(Fernihough, 2019)
MASS	7.3.51.5	(Ripley, 2019)
parameters	0.8.2	(Lüdecke, Waggoner, & Makowski, 2019)

Bates, D., Maechler, M., Bolke, B., & Walker, S. (2019). Linear Mixed-Effects Models using "Eigen" and S4 [R package lme4 version 1.1.21]. Comprehensive R Archive Network (CRAN).

Elff, M. (2020). Management of Survey Data and Presentation of Analysis Results [R package memisc version 0.99.22]. Comprehensive R Archive Network (CRAN).

Fernihough, A. (2019). Marginal Effects, Odds Ratios and Incidence Rate Ratios for GLMs [R package mfx version 1.2-2]. Comprehensive R Archive Network (CRAN).

Kuznetsova, A., Brockhoff, P., & Christensen, R. (2019). Tests in Linear Mixed Effects Models [R package lmerTest version 3.1.1]. Comprehensive R Archive Network (CRAN).

Lüdecke, D., Waggoner, P., & Makowski, D. (2019). A Unified Interface to Access Information from Model Objects in R [R package parameters version 0.8.2]. Journal of Open Source Software, 4(38), 1412. https://doi.org/10.21105/joss.01412

Lumley, T. (2020). survey: analysis of complex survey samples [R package survey version 3.37]. Comprehensive R Archive Network (CRAN).

Revelle, W. (2020). Procedures for Psychological, Psychometric, and Personality Research [R package psych version 1.9.12.31]. Comprehensive R Archive Network (CRAN).

Ripley, B. (2019). Support Functions and Datasets for Venables and Ripley's MASS [R package MASS version 7.3.51.5]. Comprehensive R Archive Network (CRAN).

Wickham, H. (2020). Tidy Messy Data [R package tidyr version 1.1.1]. Comprehensive R Archive Network (CRAN).

Wickham, H., François, R., Henry, L., & Müller, K. (2020). A Grammar of Data Manipulation [R package dplyr version 1.0.2]. Comprehensive R Archive Network (CRAN).

Wickham, H., Hester, J., & Francois, R. (2018). Read Rectangular Text Data [R package readr version 1.3.1]. Comprehensive R Archive Network (CRAN).

Xie, Y. (2020). A General-Purpose Package for Dynamic Report Generation in R [R package knitr version 1.29]. Comprehensive R Archive Network (CRAN).

Appendix 5: R code used in analysis

```
# Load libraries
library(dplyr)
library(readr)
library(tidyr)
library(psych)
library(knitr)

# Set data and output directories
data_dir <-
output_dir <-

# Note ABCD files needed and create full pathnames
sds01_filename <- "abcd_sds01.txt"
sds01_filename <- paste(data_dir, sds01_filename, sep="/")

mhy02_filename <- "abcd_mhy02.txt"
mhy02_filename <- paste(data_dir, mhy02_filename, sep="/")

pps01_filename<-"pps01.txt"
pps01_filename <- paste(data_dir, pps01_filename, sep="/")

acspsw03_filename <- "acspsw03.txt"
acspsw03_filename <- paste(data_dir, acspsw03_filename, sep="/")

pdem02_filename <- "pdem02.txt"
pdem02_filename <- paste(data_dir, pdem02_filename, sep="/")

rhds01_filename <- "abcd_rhds01.txt"
rhds01_filename <- paste(data_dir, rhds01_filename, sep="/")

ps01_filename <- "abcd_ps01.txt"
ps01_filename <- paste(data_dir, ps01_filename, sep="/")

fes02_filename <- "fes02.txt"
fes02_filename <- paste(data_dir, fes02_filename, sep="/")

medsy01_filename <- "medsy01.txt"
medsy01_filename <- paste(data_dir, medsy01_filename, sep="/")

lt01_filename <- "abcd_lt01.txt"
lt01_filename <- paste(data_dir, lt01_filename, sep="/")
```

Appendix 5: R code used in analysis

```
# The following function reads in an ABCD datafile using readr to get around some formatting issues,
namely that the file is tab delimited and the first row is the variable description name which tends
# set the variable type wrongly. This code reads in the column names, then reads in the datafile
# skipping the first two rows, then uses column names already read in. This means read_delim
# correctly identifies the data type when it reads in the data

read_abcd_file <- function(abcd_filename) {
  col_names <- names(read_delim(abcd_filename, delim="\t", n_max = 0))
  abcd_df <- read_delim(abcd_filename, delim="\t", na = "", col_names = col_names, skip = 3)
  return(abcd_df)
}

# Read sleep file, remove collection_title variable
sleep <- read_abcd_file(sds01_filename)
sleep$collection_title <- NULL

# From sleep dataframe, calculate subtotals, removing missing
sleep <-
  sleep %>%
  mutate(dims = sleepdisturb1_p + sleepdisturb2_p + sleepdisturb3_p + sleepdisturb4_p+
sleepdisturb5_p+ sleepdisturb10_p+ sleepdisturb11_p) %>% #disorder sleep maintenance
  mutate(swtd = sleepdisturb6_p + sleepdisturb7_p + sleepdisturb8_p + sleepdisturb12_p +
sleepdisturb18_p + sleepdisturb19_p) %>% #sleep wake timing disturbance
  mutate(sbd = sleepdisturb13_p + sleepdisturb14_p + sleepdisturb15_p)%>% #sleep behaviour
disorder
  mutate(da = sleepdisturb17_p + sleepdisturb20_p + sleepdisturb21_p)%>% #disorders of arousal
  mutate(does = sleepdisturb22_p + sleepdisturb23_p+ sleepdisturb24_p + sleepdisturb25_p +
sleepdisturb26_p) %>% #disorders excessive sleepiness
  mutate(shy = sleepdisturb9_p + sleepdisturb16_p) %>% #sleep hydrosis
  mutate(sleepdisturbtotal = da+dims+does+sbd+shy+swtd) %>% #sleep disorder total
  mutate(nmare=sleepdisturb21_p) %>% # Nnmare continuous
  mutate(nmarecat=ifelse(nmare>1, 1, 0)) %>% #nmares >2 = >1 per week, move to >1 for 'occasional'
(see nmare analysis below)
  mutate(sex = ifelse(sex== "F", 2, ifelse(sex=="M",1, 99))) %>%
  drop_na() #removing na(n=61)

# Calculate categorical sleep variables (38 score cut off for sleep disorders)
sleep <-   mutate(sleep, sleepdisturbcat = ifelse(sleepdisturbtotal>=39, 1, 0))

# Slim down sleep database to key variables
sleep <- select(sleep, subjectkey, eventname, interview_age, sex, dims, swtd, sbd, da, does, shy,
sleepdisturbtotal, sleepdisturbcat, nmare, nmarecat)

# Take baseline data
sleepdisturbb <- filter(sleep, sleep$eventname=="baseline_year_1_arm_1")
sleepdisturb1y <- filter(sleep, sleep$eventname=="1_year_follow_up_y_arm_1")
```

Appendix 5: R code used in analysis

```
# Import psychosis data
psy <- read_abcd_file(mhy02_filename)

# Remove missing data etc
psy <-
 psy %>%     #importing psychosis data
 select(subjectkey,
       eventname,
       28:40) %>%                    #retaining useful variables (identifier, timepoint, and pps variables)
 filter(!is.na(pps_y_ss_number))        #removing NA to number of psychotic symptoms endorsed
(n=25)
#drop_na()                            #if apply over whole dataframe is n=7250 removed aka anyone not
reporting any PE)

# Rename variables to make more straightforward identification
psy <-
 rename(psy, psychosis_total=pps_y_ss_number)%>%
 rename(psychosis_distress=pps_y_ss_severity_score) %>%
 rename(psychosis_distress_sum=pps_y_ss_bother_sum)%>%
 rename(psychosis_mean=pps_ss_mean_severity)

# Make categorical psychosis variable
psy <-
 mutate(psy, psychosis_cat = ifelse(psy$psychosis_total>=1, 1, 0)) %>% #at least one psychosis
symptom
 mutate(psy, psychosisdis_cat = ifelse(psy$psychosis_distress_sum>=1, 1, 0)) #at least one psychosis
symptom that bothered them
psy$psychosisdis_cat[is.na(psy$psychosisdis_cat)] <-0 # convert NA values to 0

# Slim down psychosis dataframe
psy <-
 select(psy, subjectkey, eventname, psychosis_total, psychosis_distress, psychosis_distress_sum,
psychosis_mean, psychosis_cat, psychosisdis_cat)

# Separate baseline and 1 year follow up data
psy_b <- filter(psy, psy$eventname=="baseline_year_1_arm_1")
psy_1y <- filter(psy, psy$eventname=="1_year_follow_up_y_arm_1")

# Import control variables (sex - already in sleep, ethnicity, socioeconomic status, neighbourhood
deprivation, child IQ, family conflict, stimulant medication)
# to fit each to sleepdisturbb dataset in preparation for join below

# Import ethnicity data
ethnicity <- read_abcd_file(acspsw03_filename)

# Code for white/non-white (binary coding is unplanned addition)
ethnicity <-
```

```
  ethnicity %>%
  rename(ethnicity=race_ethnicity) %>%
  filter(eventname=="baseline_year_1_arm_1")%>%
  select(subjectkey,
         ethnicity)%>%
  mutate(eth_cat=ifelse(ethnicity=="1", 1, 2)) %>%
  drop_na()

# Join to sleepdisturbb
sleepdisturbb <- left_join(sleepdisturbb, ethnicity, by="subjectkey")

# Import socioeconomic staus data
ses <- read_abcd_file(pdem02_filename)

# Filter
ses <-
  ses %>%
  mutate(ses=
           demo_fam_exp1_v2+
           demo_fam_exp2_v2+
           demo_fam_exp3_v2+
           demo_fam_exp4_v2+
           demo_fam_exp5_v2+
           demo_fam_exp6_v2+
           demo_fam_exp7_v2) %>%
  filter(eventname=="baseline_year_1_arm_1")%>%
  mutate(ses=ifelse(ses>8, NA, ses)) %>%
  select(subjectkey,
         ses) %>%
  drop_na()

# Join to sleepdisturbb
sleepdisturbb <- left_join(sleepdisturbb, ses, by="subjectkey")

# Read Neighbourhood deprivation file
ndep <- read_abcd_file(rhds01_filename)

# Neighbourhood deprivation
ndep <-
  ndep %>%
  rename(ndep=reshist_addr1_adi_perc)%>%
  filter(eventname=="baseline_year_1_arm_1") %>%
  select(subjectkey,
         ndep)%>%
  drop_na()

# Join to sleepdisturbb
```

Appendix 5: R code used in analysis

```
sleepdisturbb <- left_join(sleepdisturbb, ndep, by="subjectkey")

# Read child IQ data
IQ <- read_abcd_file(ps01_filename)

# Child IQ
IQ <-
 IQ %>%
 rename(IQ=pea_wiscv_tss)%>%
 filter(eventname=="baseline_year_1_arm_1") %>%
 select(subjectkey,
       IQ)%>%
 drop_na()

# Join to sleepdisturbb
sleepdisturbb <- left_join(sleepdisturbb, IQ, by="subjectkey")

# Read family conflict data
fconflict_import <- read_abcd_file(fes02_filename)

# Family conflict
fconflict_import <-
 fconflict_import %>%
 mutate(fconflict =
         fam_enviro1_p +
         fam_enviro2r_p +
         fam_enviro3_p +
         fam_enviro4r_p +
         fam_enviro5_p +
         fam_enviro6_p +
         fam_enviro7r_p +
         fam_enviro8_p +
         fam_enviro9r_p) %>%
 filter(eventname=="baseline_year_1_arm_1")%>%
 mutate(fconflict_import=ifelse(fconflict>10, NA, fconflict)) %>%
 select(subjectkey,
       fconflict) %>%
 drop_na()

# Join to sleepdisturbb
sleepdisturbb <- left_join(sleepdisturbb, fconflict_import, by="subjectkey")

# Read medication file
stim_import <- read_abcd_file(medsy01_filename)

# Get meds data from baseline
library(stringr)
```

Appendix 5: R code used in analysis

```
stim_import <-
  stim_import %>%
  filter(eventname=="baseline_year_1_arm_1")%>%
  select(subjectkey,
         eventname,
         med1_rxnorm_p,
         med2_rxnorm_p,
         med3_rxnorm_p,
         med4_rxnorm_p,
         med5_rxnorm_p,
         med6_rxnorm_p,
         med7_rxnorm_p,
         med8_rxnorm_p,
         med9_rxnorm_p,
         med10_rxnorm_p,
         med11_rxnorm_p,
         med12_rxnorm_p,
         med13_rxnorm_p,
         med14_rxnorm_p,
         med15_rxnorm_p,)

# Define search function for stimulant medications
regexsearchfunction <- function(column) {
  (str_detect(column, regex("Methylphenidate", ignore_case=TRUE))
   | str_detect(column, regex("Relexxi", ignore_case=TRUE))
   | str_detect(column, regex("Ritalin", ignore_case=TRUE))
   | str_detect(column, regex("Adhansia", ignore_case=TRUE))
   | str_detect(column, regex("Quillivant", ignore_case=TRUE))
   | str_detect(column, regex("Aptensio", ignore_case=TRUE))
   | str_detect(column, regex("Methylin", ignore_case=TRUE))
   | str_detect(column, regex("Quillichew", ignore_case=TRUE))
   | str_detect(column, regex("Concerta", ignore_case=TRUE))
   | str_detect(column, regex("Metadate", ignore_case=TRUE))
   | str_detect(column, regex("Jornay", ignore_case=TRUE))
   | str_detect(column, regex("Focalin", ignore_case=TRUE))
   | str_detect(column, regex("Dexmethylphenidate", ignore_case=TRUE))
   | str_detect(column, regex("Dextroamphetamine", ignore_case=TRUE))
   | str_detect(column, regex("Zenzedi", ignore_case=TRUE))
   | str_detect(column, regex("ProCentra", ignore_case=TRUE))
   | str_detect(column, regex("Dexedrine", ignore_case=TRUE))
   | str_detect(column, regex("Mydayis", ignore_case=TRUE))
   | str_detect(column, regex("Adderall", ignore_case=TRUE)))
}

# Create med1 to med15 columns and include a 1 where any stimulant medication from above is listed
stim_import<-
  mutate(stim_import, med1=as.numeric(regexsearchfunction(med1_rxnorm_p)))%>%
```

```
  mutate(med2=as.numeric(regexsearchfunction(med2_rxnorm_p))) %>%
  mutate(med3=as.numeric(regexsearchfunction(med3_rxnorm_p))) %>%
  mutate(med4=as.numeric(regexsearchfunction(med4_rxnorm_p))) %>%
  mutate(med5=as.numeric(regexsearchfunction(med5_rxnorm_p))) %>%
  mutate(med6=as.numeric(regexsearchfunction(med6_rxnorm_p))) %>%
  mutate(med7=as.numeric(regexsearchfunction(med7_rxnorm_p))) %>%
  mutate(med8=as.numeric(regexsearchfunction(med8_rxnorm_p))) %>%
  mutate(med9=as.numeric(regexsearchfunction(med9_rxnorm_p))) %>%
  mutate(med10=as.numeric(regexsearchfunction(med10_rxnorm_p))) %>%
  mutate(med11=as.numeric(regexsearchfunction(med11_rxnorm_p))) %>%
  mutate(med12=as.numeric(regexsearchfunction(med12_rxnorm_p))) %>%
  mutate(med13=as.numeric(regexsearchfunction(med13_rxnorm_p))) %>%
  mutate(med14=as.numeric(regexsearchfunction(med14_rxnorm_p))) %>%
  mutate(med15=as.numeric(regexsearchfunction(med15_rxnorm_p)))

# Create number of stimulants column and stimulants yes / no column, taking account of missing
variables
stim_import <-
  stim_import %>%
  mutate(stimsum=rowSums(across(med1:med15), na.rm = TRUE)) %>%
  mutate(stimYN=ifelse(stimsum>0, 1, 0))

# Check on numbers
table(stim_import$stimsum)
table(stim_import$stimYN)

# Remove unnecessary variables, link in with baseline database
stim_import <- select(stim_import, subjectkey, stimYN)
sleepdisturbb <- left_join(sleepdisturbb, stim_import, by="subjectkey")

# Family variable for clustering NB right join to ensure all have family ID (unplanned addition)
family <- read_abcd_file(acspsw03_filename)
family <-
  family %>%
  rename(fam=rel_family_id) %>%
  select(subjectkey,fam)

sleepdisturbb <- right_join(sleepdisturbb, family, by="subjectkey")

# Site variable for clustering NB right join to make sure all have site value (unplanned addition)
site_import <- read_abcd_file(lt01_filename)

site_import <-
  site_import %>%
  filter(eventname=="baseline_year_1_arm_1") %>%
  rename(site=site_id_l) %>%
  select(subjectkey, site)
```

Appendix 5: R code used in analysis

```
sleepdisturbb <- right_join(sleepdisturbb, site_import, by="subjectkey")

# Weights variable, NB right join to ensure all have weights /onset (unplanned addition)
weights <- read_abcd_file(acspsw03_filename)

weights <-
  weights %>%
  rename(weight=acs_raked_propensity_score) %>%
  select(subjectkey, weight)%>%
  drop_na()

sleepdisturbb <- right_join(sleepdisturbb, weights, by="subjectkey")

# Joining sleep and psy baselines in to one data set by subject key, retaining only rows with matches in
both
sleeppsy_b <- inner_join(sleepdisturbb, psy_b) %>%
  mutate(time=1)
sleeppsy_1y <- inner_join(sleepdisturb1y, psy_1y) %>%
  mutate(time=2)

#matching dataframes by those which have follow up data
s1 <- semi_join(sleeppsy_b, sleeppsy_1y, by = "subjectkey")
s2 <- semi_join(sleeppsy_1y, sleeppsy_b, by = "subjectkey")

#long format (time =1 is baseline, time=2 is follow up)
sp_lf <- bind_rows(s1, s2)
#short format
#sp_wf<-bind_cols(s1,s2)
sp_wf <- inner_join(sleeppsy_b, sleeppsy_1y, by = "subjectkey")

colnames(sp_wf)
sp_wf <-
  rename(sp_wf, sleepdisturbt0=sleepdisturbcat.x) %>%
  rename(sleepdisturbt1=sleepdisturbcat.y)%>%
  rename(sleepdisturbtotal_t0=sleepdisturbtotal.x)%>%
  rename(sleepdisturbtotal_t1=sleepdisturbtotal.y)%>%
  rename(sex=sex.x) %>%
  rename(psychosis_t0=psychosis_cat.x) %>%
  rename(psychosis_t1=psychosis_cat.y) %>%
  rename(psychosis_total_t0=psychosis_total.x)%>%
  rename(psychosis_total_t1=psychosis_total.y)%>%
  rename(psychosis_distress_t0=psychosis_distress.x)%>%
  rename(psychosis_distress_t1=psychosis_distress.y)%>%
  rename(psychosisdis_t0=psychosisdis_cat.x) %>%
  rename(psychosisdis_t1=psychosisdis_cat.y) %>%
  rename(psychosis_mean_t0=psychosis_mean.x)%>%
```

```
 rename(psychosis_mean_t1=psychosis_mean.y) %>%
 rename(nmare_t0=nmare.x) %>%
 rename(nmare_t1=nmare.y) %>%
 rename(nmarecat_t0=nmarecat.x) %>%
 rename(nmarecat_t1=nmarecat.y)

#calculating derived variables for sleep persistent/remitting/onset
sp_wf <- mutate(sp_wf,
sleepdisturbpersist=ifelse(sp_wf$sleepdisturbt0==1&sp_wf$sleepdisturbt1==1, 1, 0))
sp_wf <- mutate(sp_wf, sleepdisturbremit=ifelse(sp_wf$sleepdisturbt0==1&sp_wf$sleepdisturbt1==0,
1, 0))
sp_wf <- mutate(sp_wf, sleepdisturbonset=ifelse(sp_wf$sleepdisturbt0==0&sp_wf$sleepdisturbt1==1,
1, 0))
table(sp_wf$sleepdisturbpersist)
table(sp_wf$sleepdisturbremit)
table(sp_wf$sleepdisturbonset)

#calculating derived variables for  psychosis persistent/remitting/onset

sp_wf <- mutate(sp_wf, psychosis_persist=ifelse(sp_wf$psychosis_t0==1&sp_wf$psychosis_t1==1, 1,
0))
sp_wf <- mutate(sp_wf, psychosis_remit=ifelse(sp_wf$psychosis_t0==1&sp_wf$psychosis_t1==0, 1,
0))
sp_wf <- mutate(sp_wf, psychosis_onset=ifelse(sp_wf$psychosis_t0==0&sp_wf$psychosis_t1==1, 1,
0))
table(sp_wf$psychosis_persist)
table(sp_wf$psychosis_remit)
table(sp_wf$psychosis_onset)

#calculating derived variables for distressing psychosis persistent/remitting/onset

sp_wf <- mutate(sp_wf,
psychosisdis_persist=ifelse(sp_wf$psychosisdis_t0==1&sp_wf$psychosisdis_t1==1, 1, 0))
sp_wf <- mutate(sp_wf,
psychosisdis_remit=ifelse(sp_wf$psychosisdis_t0==1&sp_wf$psychosisdis_t1==0, 1, 0))
sp_wf <- mutate(sp_wf,
psychosisdis_onset=ifelse(sp_wf$psychosisdis_t0==0&sp_wf$psychosisdis_t1==1, 1, 0))

table(sleeppsy_b$psychosisdis_cat)
table(sp_wf$psychosisdis_t1)
table(sp_wf$psychosisdis_persist)
table(sp_wf$psychosisdis_remit)
table(sp_wf$psychosisdis_onset)


#Analysis begins
```

Appendix 5: R code used in analysis

```
#descriptives (unweighted)

#age
describe(sp_wf$interview_age.x)
describe(sp_wf$interview_age.y)

#gender
table(sleeppsy_b$sex)
table(sleeppsy_1y$sex)

#ethnicity
table(sleeppsy_b$ethnicity)
table(sp_wf$ethnicity)

#ses
describe(sleeppsy_b$ses)
describe(sp_wf$ses)

#childIQ
describe(sleeppsy_b$IQ)
describe(sp_wf$IQ)

#neighbourhood deprivation
describe(sleeppsy_b$ndep)
describe(sp_wf$ndep)

#family conflict
describe(sleeppsy_b$fconflict)
describe(sp_wf$fconflict)

#stimulant medication
table(sleeppsy_b$stimYN)
table(sp_wf$stimYN)

#PQ-BC
describe(sleeppsy_b$psychosis_total)
describe(sp_wf$psychosis_total_t1)
describe(sleeppsy_b$psychosis_distress)
describe(sp_wf$psychosis_distress_t1)

#SDSC
describe(sleeppsy_b$sleepdisturbtotal)
describe(sp_wf$sleepdisturbtotal_t1)


#logistic regression package
library(lme4)
```

Appendix 5: R code used in analysis

```
library(lmerTest)
library(memisc)
library(mfx)
library(MASS)
library(parameters)
library(epitools)

sp_wf <- rescale_weights(data=sp_wf, "site", "weight")

#RQ1 = are sleep problems assoc with psychosis (at t0 or across all time points?)

##RQ1a: linear regression between sleep and psychosis (baseline)
RQ1a <- lmer(psychosis_distress_t0 ~
          sleepdisturbtotal_t0 +
          (1|site) + (1|fam),
          data = sp_wf, REML=TRUE,
          control = lmerControl(optimizer = "bobyqa", optCtrl = list(maxfun = 2e5))
         )
summary(RQ1a)
summary(RQ1a)$coefficients
write.csv(summary(RQ1a)$coefficients, paste(output_dir, "RQ1a.csv", sep="/"))
RQ1aCI <- confint(RQ1a, method="Wald")
write.csv(RQ1aCI, paste(output_dir, "RQ1aCI.csv", sep="/"))
AIC(RQ1a)

##RQ1b: logistic regression - prediction of presence of psychotic symptoms by amount of sleep
disturbance
RQ1b <- glmer(psychosisdis_t0 ~
           sleepdisturbtotal_t0 +
           (1|site) + (1|fam),
           data = sp_wf,
           family = binomial(link = "logit"),
           control = glmerControl(optimizer="bobyqa", optCtrl = list(maxfun = 2e5))
          )
summary(RQ1b)
RQ1bCI <- confint(RQ1b, parm="beta_", method="Wald")
RQ1bCItab <- cbind(est=fixef(RQ1b),RQ1bCI)
RQ1bOR <- exp(RQ1bCItab)
#risk ratio approximation
RQ1b_baselinerisk<-(sum(sp_wf$psychosisdis_t0==1 &
sp_wf$sleepdisturbtotal_t0==0))/count(sp_wf)
RQ1bRR<-RQ1bOR[2,1]/(1-RQ1b_baselinerisk + (RQ1b_baselinerisk*RQ1bOR[2,1]))

RQ1bORCI <- cbind(RQ1bOR, RQ1bCI,RQ1bRR)
write.csv(getSummary.merMod(RQ1b)$coef, paste(output_dir, "RQ1b.csv", sep="/"))
write.csv(RQ1bORCI, paste(output_dir, "RQ1bORCI.csv", sep="/"))
AIC(RQ1b)
```

Appendix 5: R code used in analysis

```
##RQ1c: logistic regression - presence of psychotic symptoms assoc w presence of sleep symptoms
RQ1c <- glmer(psychosisdis_t0 ~
              sleepdisturbt0 +
              (1|site) + (1|fam),
              data = sp_wf,
              family = binomial(link = "logit"),
              control = glmerControl(optimizer = "bobyqa", optCtrl = list(maxfun = 2e5))
             )
summary(RQ1c)
RQ1cCI <- confint(RQ1c, parm="beta_", method="Wald")
RQ1cCItab <- cbind(est=fixef(RQ1c),RQ1cCI)
RQ1cOR <- exp(RQ1cCItab)
#risk ratio approximation
RQ1c_baselinerisk<-(sum(sp_wf$psychosisdis_t0==1 & sp_wf$sleepdisturbt0==0))/count(sp_wf)
RQ1cRR<-RQ1cOR[2,1]/(1-RQ1c_baselinerisk + (RQ1c_baselinerisk*RQ1cOR[2,1]))

RQ1cORCI <- cbind(RQ1cOR, RQ1cCI,RQ1cRR)
write.csv(getSummary.merMod(RQ1c)$coef, paste(output_dir, "RQ1c.csv", sep="/"))
write.csv(RQ1cORCI, paste(output_dir, "RQ1cORCI.csv", sep="/"))

table(sp_wf$psychosisdis_t0, sp_wf$sleepdisturbt0)
AIC(RQ1c)

#RQ1d: repeat of RQ1a with control variables
RQ1d <- lmer(psychosis_distress_t0 ~
             sleepdisturbtotal_t0 +
             sex +
             ethnicity +
             ses +
             ndep +
             IQ +
             fconflict +
             stimYN +
             (1|site) + (1|fam),
             data=sp_wf,
             control = lmerControl(optimizer = "bobyqa", optCtrl = list(maxfun = 2e5))
            )
summary(RQ1d)
summary(RQ1d)$coefficients
write.csv(summary(RQ1d)$coefficients, paste(output_dir, "RQ1d.csv", sep="/"))
RQ1dCI <- confint(RQ1d, method="Wald")
write.csv(RQ1dCI, paste(output_dir, "RQ1dCI.csv", sep="/"))
AIC(RQ1d)

#RQ1e: repeat of RQ1b with control variables
```

Appendix 5: R code used in analysis

```
RQ1e <- glmer(psychosisdis_t0 ~
            sleepdisturbtotal_t0 +
            sex +
            ethnicity +
            ses +
            ndep +
            IQ +
            fconflict +
            stimYN +
            (1|site) + (1|fam),
            data = sp_wf,
            family = binomial(link="logit"),
            control = glmerControl(optimizer="bobyqa", optCtrl = list(maxfun = 2e5))
          )
summary(RQ1e)
RQ1eCI <- confint(RQ1e, parm="beta_", method="Wald")
RQ1eCItab <- cbind(est=fixef(RQ1e),RQ1eCI)
RQ1eOR <- exp(RQ1eCItab)
#risk ratio approximation
RQ1e_baselinerisk<-(sum(sp_wf$psychosisdis_t0==1 &
sp_wf$sleepdisturbtotal_t0==0))/count(sp_wf)
RQ1eRR<-RQ1eOR[2,1]/(1-RQ1e_baselinerisk + (RQ1e_baselinerisk*RQ1eOR[2,1]))

RQ1eORCI <- cbind(RQ1eOR, RQ1eCI, RQ1eRR)
write.csv(getSummary.merMod(RQ1e)$coef, paste(output_dir, "RQ1e.csv", sep="/"))
write.csv(RQ1eORCI, paste(output_dir, "RQ1eORCI.csv", sep="/"))
AIC(RQ1e)

#RQ1f: repeat of RQ1c with control variables
RQ1f <- glmer(psychosisdis_t0 ~
            sleepdisturbt0 +
            sex +
            ethnicity +
            ses +
            ndep +
            IQ +
            fconflict +
            stimYN +
            (1|site)+(1|fam),
            data = sp_wf, family=binomial(link="logit"),
            control = glmerControl(optimizer = "bobyqa", optCtrl = list(maxfun=2e5))
          )
summary(RQ1f)
RQ1fCI <- confint(RQ1f, parm="beta_", method="Wald")
RQ1fCItab <- cbind(est=fixef(RQ1f),RQ1fCI)
RQ1fOR <- exp(RQ1fCItab)
#risk ratio approximation
```

Appendix 5: R code used in analysis

```
RQ1f_baselinerisk<-(sum(sp_wf$psychosisdis_t0==1 & sp_wf$sleepdisturbt0==0))/count(sp_wf)
RQ1fRR<-RQ1fOR[2,1]/(1-RQ1f_baselinerisk + (RQ1f_baselinerisk*RQ1fOR[2,1]))

RQ1fORCI <- cbind(RQ1fOR, RQ1fCI, RQ1fRR)
write.csv(getSummary.merMod(RQ1f)$coef, paste(output_dir, "RQ1f.csv", sep="/"))
write.csv(RQ1fORCI, paste(output_dir, "RQ1fORCI.csv", sep="/"))
AIC(RQ1f)

#RQ2 onset

##RQ2a is psychosis at t1 predicted by sleep problems at t0
RQ2a <- glmer(psychosisdis_t1 ~
            sleepdisturbt0 +
            (1|site) + (1|fam),
            data = sp_wf,
            family = binomial(link = "logit"),
            control = glmerControl(optimizer = "bobyqa", optCtrl = list(maxfun = 2e5))
          )
summary(RQ2a)
RQ2aCI <- confint(RQ2a, parm="beta_", method="Wald")
RQ2aCItab <- cbind(est=fixef(RQ2a),RQ2aCI)
RQ2aOR <- exp(RQ2aCItab)
#risk ratio approximation
 RQ2a_baselinerisk<-(sum(sp_wf$psychosisdis_t1==1 & sp_wf$sleepdisturbt0==0))/count(sp_wf)
 RQ2aRR<-RQ2aOR[2,1]/(1-RQ2a_baselinerisk + (RQ2a_baselinerisk*RQ2aOR[2,1]))

RQ2aORCI <- cbind(RQ2aOR, RQ2aCI,RQ2aRR)
write.csv(getSummary.merMod(RQ2a)$coef, paste(output_dir, "RQ2a.csv", sep="/"))
write.csv(RQ2aORCI, paste(output_dir, "RQ2aORCI.csv", sep="/"))
AIC(RQ2a)

##RQ2b: does this assoc continue even accounting for sleep problems at t1
RQ2b <- glmer(psychosisdis_t1 ~
            sleepdisturbt0 +
            sleepdisturbt1 +
            (1|site) + (1|fam),
            data = sp_wf,
            family = binomial(link = "logit"),
            control = glmerControl(optimizer = "bobyqa", optCtrl = list(maxfun = 2e5))
          )
summary(RQ2b)
RQ2bCI <- confint(RQ2b, parm="beta_", method="Wald")
RQ2bCItab <- cbind(est=fixef(RQ2b),RQ2bCI)
RQ2bOR <- exp(RQ2bCItab)
#risk ratio approximation
 RQ2b_baselinerisk<-(sum(sp_wf$psychosisdis_t1==1 & sp_wf$sleepdisturbt0==0))/count(sp_wf)
 RQ2bRR<-RQ2bOR[2,1]/(1-RQ2b_baselinerisk + (RQ2b_baselinerisk*RQ2bOR[2,1]))
```

Appendix 5: R code used in analysis

```
RQ2bORCI <- cbind(RQ2bOR, RQ2bCI,RQ2bRR)
write.csv(getSummary.merMod(RQ2b)$coef,paste(output_dir, "RQ2b.csv", sep="/"))
write.csv(RQ2bORCI, paste(output_dir, "RQ2bORCI.csv", sep="/"))
AIC(RQ2b)
##RQ2c controls added to RQ2b
RQ2c <- glmer(psychosisdis_t1 ~
            sleepdisturbt0 +
            sex +
            ethnicity +
            ses +
            ndep +
            IQ +
            fconflict +
            stimYN +
            (1|site) + (1|fam),
            data = sp_wf,
            family = binomial(link = "logit"),
            control = glmerControl(optimizer = "bobyqa", optCtrl = list(maxfun = 2e5))
          )
summary(RQ2c)
RQ2cCI <- confint(RQ2c, parm="beta_", method="Wald")
RQ2cCItab <- cbind(est=fixef(RQ2c),RQ2cCI)
RQ2cOR <- exp(RQ2cCItab)
#risk ratio approximation
 RQ2c_baselinerisk<-(sum(sp_wf$psychosisdis_t1==1 & sp_wf$sleepdisturbt0==0))/count(sp_wf)
 RQ2cRR<-RQ2cOR[2,1]/(1-RQ2c_baselinerisk + (RQ2c_baselinerisk*RQ2cOR[2,1]))

RQ2cORCI <- cbind(RQ2cOR, RQ2cCI, RQ2cRR)
write.csv(getSummary.merMod(RQ2c)$coef,paste(output_dir, "RQ2c.csv", sep="/"))
write.csv(RQ2cORCI, paste(output_dir, "RQ2cORCI.csv", sep="/"))
AIC(RQ2c)

##RQ2d controls added to RQ2b
RQ2d <- glmer(psychosisdis_t1 ~
            sleepdisturbt0 +
            sleepdisturbt1 +
            sex +
            ethnicity +
            ses +
            ndep +
            IQ +
            fconflict +
            stimYN +
            (1|site) + (1|fam),
            data = sp_wf,
            family = binomial(link = "logit"),
```

```
            control = glmerControl(optimizer = "bobyqa", optCtrl = list(maxfun = 2e5))
          )
summary(RQ2d)
RQ2dCI <- confint(RQ2d, parm="beta_", method="Wald")
RQ2dCItab <- cbind(est=fixef(RQ2d),RQ2dCI)
RQ2dOR <- exp(RQ2dCItab)
#risk ratio approximation
   RQ2d_baselinerisk<-(sum(sp_wf$psychosisdis_t1==1 & sp_wf$sleepdisturbt0==0))/count(sp_wf)
   RQ2dRR<-RQ2dOR[2,1]/(1-RQ2d_baselinerisk + (RQ2d_baselinerisk*RQ2dOR[2,1]))

RQ2dORCI <- cbind(RQ2dOR, RQ2dCI, RQ2dRR)
write.csv(getSummary.merMod(RQ2d)$coef,paste(output_dir, "RQ2d.csv", sep="/"))
write.csv(RQ2dORCI, paste(output_dir, "RQ2dORCI.csv", sep="/"))
AIC(RQ2d)



#risk ratio approximation
RQ2d_baselinerisk<-(sum(sp_wf$psychosisdis_t1==1 & sp_wf$sleepdisturbt0==0))/count(sp_wf)
RQ2dRR<-RQ2dOR[2,1]/(1-RQ2d_baselinerisk + (RQ2d_baselinerisk*RQ2dOR[2,1]))

#RQ3 = persistence

##RQ3a: is persistence of psychosis predicted by sleep problems at t0
RQ3a <- glmer(psychosisdis_persist ~
            sleepdisturbt0 +
            (1|site) + (1|fam),
            data = sp_wf,
            family = poisson(link = "log"),
            control = glmerControl(optimizer = "bobyqa", optCtrl = list(maxfun = 2e5))
          )
summary(RQ3a)
RQ3aCI <- confint(RQ3a, parm="beta_", method="Wald")
RQ3aCItab <- cbind(est=fixef(RQ3a),RQ3aCI)
RQ3aOR <- exp(RQ3aCItab)
#risk ratio approximation
 RQ3a_baselinerisk<-(sum(sp_wf$psychosisdis_persist==1 &
sp_wf$sleepdisturbt0==0))/count(sp_wf)
 RQ3aRR<-RQ3aOR[2,1]/(1-RQ3a_baselinerisk + (RQ3a_baselinerisk*RQ3aOR[2,1]))

RQ3aORCI <- cbind(RQ3aOR, RQ3aCI, RQ3aRR)
write.csv(getSummary.merMod(RQ3a)$coef,paste(output_dir, "RQ3a.csv", sep="/"))
write.csv(RQ3aORCI, paste(output_dir, "RQ3aORCI.csv", sep="/"))
AIC(RQ3a)

##RQ3b: is persistence of psychosis predicted by persistence of sleep problems
RQ3b <- glmer(psychosisdis_persist ~
            sleepdisturbpersist +
```

```
            (1|site) + (1|fam),
            data=sp_wf,
            family = binomial(link = "logit"),
            control = glmerControl(optimizer = "bobyqa", optCtrl = list(maxfun = 2e5))
           )
summary(RQ3b)
RQ3bCI <- confint(RQ3b, parm="beta_", method="Wald")
RQ3bCItab <- cbind(est=fixef(RQ3b),RQ3bCI)
RQ3bOR <- exp(RQ3bCItab)
#risk ratio approximation
 RQ3b_baselinerisk<-(sum(sp_wf$psychosisdis_persist==1 &
sp_wf$sleepdisturbpersist==0))/count(sp_wf)
 RQ3bRR<-RQ3bOR[2,1]/(1-RQ3b_baselinerisk + (RQ3b_baselinerisk*RQ3bOR[2,1]))
RQ3bORCI <- cbind(RQ3bOR, RQ3bCI,RQ3bRR)
write.csv(getSummary.merMod(RQ3b)$coef,paste(output_dir, "RQ3b.csv", sep="/"))
write.csv(RQ3bORCI, paste(output_dir, "RQ3bORCI.csv", sep="/"))
AIC(RQ3b)

##RQ3c: controls on RQ3a
RQ3c <- glmer(psychosisdis_persist ~
            sleepdisturbt0 +
            sex +
            ethnicity +
            ses +
            ndep +
            IQ +
            fconflict +
            stimYN +
            (1|site) + (1|fam),
            data = sp_wf,
            family = binomial(link = "logit"),
            control = glmerControl(optimizer = "bobyqa", optCtrl = list(maxfun = 2e5))
           )
summary(RQ3c)
RQ3cCI <- confint(RQ3c, parm="beta_", method="Wald")
RQ3cCItab <- cbind(est=fixef(RQ3c),RQ3cCI)
RQ3cOR <- exp(RQ3cCItab)
#risk ratio approximation
 RQ3c_baselinerisk<-(sum(sp_wf$psychosisdis_persist==1 &
sp_wf$sleepdisturbt0==0))/count(sp_wf)
 RQ3cRR<-RQ3cOR[2,1]/(1-RQ3c_baselinerisk + (RQ3c_baselinerisk*RQ3cOR[2,1]))

RQ3cORCI <- cbind(RQ3cOR, RQ3cCI,RQ3cRR)
write.csv(getSummary.merMod(RQ3c)$coef,paste(output_dir, "RQ3c.csv", sep="/"))
write.csv(RQ3cORCI, paste(output_dir, "RQ3cORCI.csv", sep="/"))
AIC(RQ3c)
```

Appendix 5: R code used in analysis

```
##RQ3d: controls on RQ3b
RQ3d <- glmer(psychosisdis_persist ~
            sleepdisturbpersist +
            sex +
            ethnicity +
            ses +
            ndep +
            IQ +
            fconflict +
            stimYN +
            (1|site) + (1|fam),
            data = sp_wf,
            family = binomial(link = "logit"),
            control = glmerControl(optimizer = "bobyqa", optCtrl = list(maxfun = 2e5))
          )
summary(RQ3d)
RQ3dCI <- confint(RQ3d, parm="beta_", method="Wald")
RQ3dCItab <- cbind(est=fixef(RQ3d),RQ3dCI)
RQ3dOR <- exp(RQ3dCItab)
#risk ratio approximation
 RQ3d_baselinerisk<-(sum(sp_wf$psychosisdis_persist==1 &
sp_wf$sleepdisturbpersist==0))/count(sp_wf)
 RQ3dRR<-RQ3dOR[2,1]/(1-RQ3d_baselinerisk + (RQ3d_baselinerisk*RQ3dOR[2,1]))

RQ3dORCI <- cbind(RQ3dOR, RQ3dCI,RQ3dRR)
write.csv(getSummary.merMod(RQ3d)$coef,paste(output_dir, "RQ3d.csv", sep="/"))
write.csv(RQ3dORCI, paste(output_dir, "RQ3dORCI.csv", sep="/"))
AIC(RQ3d)

#RQ4
##RQ4a= remission: are remitting sleep problems (t0Y + t1N) assoc w remittance of psychotic
symptoms (t0Y+t1N)
RQ4a <- glmer(psychosisdis_remit ~
            sleepdisturb_t0 +
            (1|site) + (1|fam),
            data=sp_wf,
            family=binomial(link = "logit"),
            control = glmerControl(optimizer = "bobyqa", optCtrl = list(maxfun = 2e5))
          )
summary(RQ4a)
RQ4aCI <- confint(RQ4a, parm="beta_", method="Wald")
RQ4aCItab <- cbind(est=fixef(RQ4a),RQ4aCI)
RQ4aOR <- exp(RQ4aCItab)
#risk ratio approximation
 RQ4a_baselinerisk<-(sum(sp_wf$psychosisdis_remit==1 &
sp_wf$sleepdisturbremit==0))/count(sp_wf)
 RQ4aRR<-RQ4aOR[2,1]/(1-RQ4a_baselinerisk + (RQ4a_baselinerisk*RQ4aOR[2,1]))
```

Appendix 5: R code used in analysis

```
RQ4aORCI <- cbind(RQ4aOR, RQ4aCI,RQ4aRR)
write.csv(getSummary.merMod(RQ4a)$coef,paste(output_dir, "RQ4a.csv", sep="/"))
write.csv(RQ4aORCI, paste(output_dir, "RQ4aORCI.csv", sep="/"))
AIC(RQ4a)

##RQ4b: not calculated as sleepdisturb_t0 not significant in RQ4a

#NIGHTMARES ANALYSIS

#descriptives
describe(sleeppsy_b$nmare)
describe(sp_wf$nmare_t1)
table(sleeppsy_b$nmare)
table(sp_wf$nmare_t1)
table(sleeppsy_b$nmarecat)
table(sp_wf$nmarecat_t1)

#calculating derived variables for nightmare persistent/remitting/onset
sp_wf <- mutate(sp_wf, nmarecat_persist=ifelse(sp_wf$nmarecat_t0==1&sp_wf$nmarecat_t1==1, 1,
0))
sp_wf <- mutate(sp_wf, nmarecat_remit=ifelse(sp_wf$nmarecat_t0==1&sp_wf$nmarecat_t1==0, 1,
0))
sp_wf <- mutate(sp_wf, nmarecat_onset=ifelse(sp_wf$nmarecat_t0==0&sp_wf$nmarecat_t1==1, 1,
0))
table(sp_wf$nmarecat_persist)
table(sp_wf$nmarecat_remit)
table(sp_wf$nmarecat_onset)

#crosstabs
table(sp_wf$nmarecat_onset, sp_wf$psychosisdis_onset)
table(sp_wf$nmarecat_persist, sp_wf$psychosisdis_persist)
table(sp_wf$nmarecat_remit, sp_wf$psychosisdis_remit)

#RQ5 = are nightmares assoc with psychosis (at t0 or across all time points?)

##RQ5a: linear regression between nmares and psychosis (baseline)
RQ5a <- lmer(psychosis_distress_t0 ~
               nmare_t0 +
               (1|site) + (1|fam),
             data = sp_wf, REML=TRUE,
             control = lmerControl(optimizer = "bobyqa", optCtrl = list(maxfun = 2e5))
)
summary(RQ5a)
summary(RQ5a)$coefficients
write.csv(summary(RQ5a)$coefficients, paste(output_dir, "RQ5a.csv", sep="/"))
RQ5aCI <- confint(RQ5a, method="Wald")
write.csv(RQ5aCI, paste(output_dir, "RQ5aCI.csv", sep="/"))
```

Appendix 5: R code used in analysis

```
AIC(RQ5a)

##RQ5b: logistic regression - prediction of presence of psychotic symptoms by presence of nmare
symptoms
RQ5b <- glmer(psychosisdis_t0 ~
              nmarecat_t0 +
              (1|site) + (1|fam),
            data = sp_wf,
            family = binomial(link = "logit"),
            control = glmerControl(optimizer="bobyqa", optCtrl = list(maxfun = 2e5))
)
summary(RQ5b)
RQ5bCI <- confint(RQ5b, parm="beta_", method="Wald")
RQ5bCItab <- cbind(est=fixef(RQ5b),RQ5bCI)
RQ5bOR <- exp(RQ5bCItab)
#risk ratio approximation
 RQ5b_baselinerisk<-(sum(sp_wf$psychosisdis_t0==1 & sp_wf$nmarecat_t0==0))/count(sp_wf)
 RQ5bRR<-RQ5bOR[2,1]/(1-RQ5b_baselinerisk + (RQ5b_baselinerisk*RQ5bOR[2,1]))

RQ5bORCI <- cbind(RQ5bOR, RQ5bCI,RQ5bRR)
write.csv(getSummary.merMod(RQ5b)$coef, paste(output_dir, "RQ5b.csv", sep="/"))
write.csv(RQ5bORCI, paste(output_dir, "RQ5bORCI.csv", sep="/"))
AIC(RQ5b)

##RQ5c: logistic regression - presence of nmares at baseline predictive of psychotic symptoms at
followup
RQ5c <- glmer(psychosisdis_t1 ~
              nmarecat_t0 +
              (1|site) + (1|fam),
            data = sp_wf,
            family = binomial(link = "logit"),
            control = glmerControl(optimizer = "bobyqa", optCtrl = list(maxfun = 2e5))
)
summary(RQ5c)
RQ5cCI <- confint(RQ5c, parm="beta_", method="Wald")
RQ5cCItab <- cbind(est=fixef(RQ5c),RQ5cCI)
RQ5cOR <- exp(RQ5cCItab)
#risk ratio approximation
 RQ5c_baselinerisk<-(sum(sp_wf$psychosisdis_t0==1 & sp_wf$nmarecat_t0==0))/count(sp_wf)
 RQ5cRR<-RQ5cOR[2,1]/(1-RQ5c_baselinerisk + (RQ5c_baselinerisk*RQ5cOR[2,1]))

RQ5cORCI <- cbind(RQ5cOR, RQ5cCI,RQ5cRR)
write.csv(getSummary.merMod(RQ5c)$coef, paste(output_dir, "RQ5c.csv", sep="/"))
write.csv(RQ5cORCI, paste(output_dir, "RQ5cORCI.csv", sep="/"))
AIC(RQ5c)
```

Appendix 5: R code used in analysis

```
##RQ5d - logistic regression - presence of nmares at baseline predictive of persistence of psychotic experiences
RQ5d<-glmer(psychosisdis_persist ~
             nmarecat_t0 +
             (1|site) + (1|fam),
           data = sp_wf,
           family = binomial(link = "logit"),
           control = glmerControl(optimizer = "bobyqa", optCtrl = list(maxfun = 2e5))
)
summary(RQ5d)
RQ5dCI <- confint(RQ5d, parm="beta_", method="Wald")
RQ5dCItab <- cbind(est=fixef(RQ5d),RQ5dCI)
RQ5dOR <- exp(RQ5dCItab)
RQ5cOR <- exp(RQ5cCItab)
#risk ratio approximation
 RQ5d_baselinerisk<-(sum(sp_wf$psychosisdis_persist==1 &
sp_wf$nmarecat_t0==0))/count(sp_wf)
 RQ5dRR<-RQ5dOR[2,1]/(1-RQ5d_baselinerisk + (RQ5d_baselinerisk*RQ5dOR[2,1]))

RQ5dORCI <- cbind(RQ5dOR, RQ5dCI,RQ5dRR)
write.csv(getSummary.merMod(RQ5d)$coef, paste(output_dir, "RQ5d.csv", sep="/"))
write.csv(RQ5dORCI, paste(output_dir, "RQ5dORCI.csv", sep="/"))
AIC(RQ5d)

##RQ5e - logistic regression - prediction of remission by nmares at baseline
RQ5e<-glmer(psychosisdis_remit ~
             nmarecat_t0 +
             (1|site) + (1|fam),
           data = sp_wf,
           family = binomial(link = "logit"),
           control = glmerControl(optimizer = "bobyqa", optCtrl = list(maxfun = 2e5))
)
summary(RQ5e)
RQ5eCI <- confint(RQ5e, parm="beta_", method="Wald")
RQ5eCItab <- cbind(est=fixef(RQ5e),RQ5eCI)
RQ5eOR <- exp(RQ5eCItab)
#risk ratio approximation
 RQ5e_baselinerisk<-(sum(sp_wf$psychosisdis_remit==1 & sp_wf$nmarecat_t0==0))/count(sp_wf)
 RQ5eRR<-RQ5eOR[2,1]/(1-RQ5e_baselinerisk + (RQ5e_baselinerisk*RQ5eOR[2,1]))

RQ5eORCI <- cbind(RQ5eOR, RQ5eCI,RQ5eRR)
write.csv(getSummary.merMod(RQ5e)$coef, paste(output_dir, "RQ5e.csv", sep="/"))
write.csv(RQ5eORCI, paste(output_dir, "RQ5eORCI.csv", sep="/"))
AIC(RQ5e)

#RQ6 - to generate stronger/more conservative comparison (are nightmares associated even more than generic sleep disorder?
```

Appendix 5: R code used in analysis

```
#(0 for other sleep disorders, 1 for nightmares, remove ppts with no sleep disorders to facilitate
comparison

nmaretest<-
 sp_wf %>%
 mutate(ntest = ifelse(nmarecat_t0==1,1,ifelse(sleepdisturbt0==1, 0, -99))) %>%
 filter(ntest>=0)
table(nmaretest$ntest)

#replicate logstic regression tests with this variable  -logistic withn baseline
RQ6a <- glmer(psychosisdis_t0 ~
              ntest +
              (1|site) + (1|fam),
            data = nmaretest,
            family = binomial(link = "logit"),
            control = glmerControl(optimizer = "bobyqa", optCtrl = list(maxfun = 2e5))
)
summary(RQ6a)
RQ6aCI <- confint(RQ6a, parm="beta_", method="Wald")
RQ6aCItab <- cbind(est=fixef(RQ6a),RQ6aCI)
RQ6aOR <- exp(RQ6aCItab)
#risk ratio approximation
RQ6a_baselinerisk<-(sum(nmaretest$psychosisdis_t0==1 & nmaretest$ntest==0))/count(nmaretest)
RQ6aRR<-RQ6aOR[2,1]/(1-RQ6a_baselinerisk + (RQ6a_baselinerisk*RQ6aOR[2,1]))

RQ6aORCI <- cbind(RQ6aOR, RQ6aCI,RQ6aRR)
write.csv(getSummary.merMod(RQ6a)$coef, paste(output_dir, "RQ6a.csv", sep="/"))
write.csv(RQ6aORCI, paste(output_dir, "RQ6aORCI.csv", sep="/"))
AIC(RQ6a)

#logistic regression of category relationship at follow up

RQ6b <- glmer(psychosisdis_t1 ~
              ntest +
              (1|site) + (1|fam),
            data = nmaretest,
            family = binomial(link = "logit"),
            control = glmerControl(optimizer = "bobyqa", optCtrl = list(maxfun = 2e5))
)
summary(RQ6b)
RQ6bCI <- confint(RQ6b, parm="beta_", method="Wald")
RQ6bCItab <- cbind(est=fixef(RQ6b),RQ6bCI)
RQ6bOR <- exp(RQ6bCItab)
#risk ratio approximation
 RQ6b_baselinerisk<-(sum(nmaretest$psychosisdis_t1==1 & nmaretest$ntest==0))/count(nmaretest)
 RQ6bRR<-RQ6bOR[2,1]/(1-RQ6b_baselinerisk + (RQ6b_baselinerisk*RQ6bOR[2,1]))
```

Appendix 5: R code used in analysis

```
RQ6bORCI <- cbind(RQ6bOR, RQ6bCI,RQ6bRR)
write.csv(getSummary.merMod(RQ6b)$coef, paste(output_dir, "RQ6b.csv", sep="/"))
write.csv(RQ6bORCI, paste(output_dir, "RQ6bORCI.csv", sep="/"))
AIC(RQ6b)

#logistic regression of persistence of PE predicted by nmare vs other sleep disorders

RQ6c <- glmer(psychosisdis_persist ~
            ntest +
            (1|site) + (1|fam),
          data = nmaretest,
          family = binomial(link = "logit"),
          control = glmerControl(optimizer = "bobyqa", optCtrl = list(maxfun = 2e5))
)
summary(RQ6c)
RQ6cCI <- confint(RQ6c, parm="beta_", method="Wald")
RQ6cCItab <- cbind(est=fixef(RQ6c),RQ6cCI)
RQ6cOR <- exp(RQ6cCItab)
#risk ratio approximation
 RQ6c_baselinerisk<-(sum(nmaretest$psychosisdis_persist==1 &
nmaretest$ntest==0))/count(nmaretest)
 RQ6cRR<-RQ6cOR[2,1]/(1-RQ6c_baselinerisk + (RQ6c_baselinerisk*RQ6cOR[2,1]))


RQ6cORCI <- cbind(RQ6cOR, RQ6cCI,RQ6cRR)
write.csv(getSummary.merMod(RQ6c)$coef, paste(output_dir, "RQ6c.csv", sep="/"))
write.csv(RQ6cORCI, paste(output_dir, "RQ6cORCI.csv", sep="/"))
AIC(RQ6c)

#logistic regression of remission of PE predicted by nmare vs other sleep disorders

RQ6d <- glmer(psychosisdis_remit ~
            ntest +
            (1|site) + (1|fam),
          data = nmaretest,
          family = binomial(link = "logit"),
          control = glmerControl(optimizer = "bobyqa", optCtrl = list(maxfun = 2e5))
)
summary(RQ6d)
RQ6dCI <- confint(RQ6d, parm="beta_", method="Wald")
RQ6dCItab <- cbind(est=fixef(RQ6d),RQ6dCI)
RQ6dOR <- exp(RQ6dCItab)
#risk ratio approximation
RQ6d_baselinerisk<-(sum(nmaretest$psychosisdis_remit==1 &
nmaretest$ntest==0))/count(nmaretest)
RQ6dRR<-RQ6dOR[2,1]/(1-RQ6d_baselinerisk + (RQ6d_baselinerisk*RQ6dOR[2,1]))
```

Appendix 5: R code used in analysis

```
RQ6dORCI <- cbind(RQ6dOR, RQ6dCI,RQ6dRR)
write.csv(getSummary.merMod(RQ6d)$coef, paste(output_dir, "RQ6d.csv", sep="/"))
write.csv(RQ6dORCI, paste(output_dir, "RQ6dORCI.csv", sep="/"))

AIC(RQ6d)
```

Appendix 6: Weighted analysis tables

Appendix 6 Table 1: Sample demographics and descriptive variables (weighted)

Descriptive statistics	Baseline n = 11830	12-month follow-up n = 4910
Age (months) – mean (SE)	119.2 (0.3)	132.2 (0.5)
Gender – male % (SE)	51.13 (0.1)	51.04 (0.9)
Ethnicity % (SE)		
White	52.34 (5.6)	59.48 (6.3)
Black	13.31 (2.5)	7.61 (1.6)
Hispanic	23.83 (6.2)	22.50 (6.7)
Asian	3.61 (0.9)	4.02 (0.9)
Other	6.89 (1.0)	6.40 (1.3)
Socioeconomic status scale – mean (SE)	0.56 (0.1)	0.47 (0.1)
Child IQ – mean (SE)	9.74 (0.1)	10.03 (0.1)
Neighbourhood deprivation percentile – mean (SE)	43.49 (3.8)	40.5 (3.9)
Family conflict scale – mean (SE)	2.52 (0.1)	2.45 (0.06)
Stimulant medication prescribed – % (SE)	6.41 (<0.1)	7.00 (<0.1)
PQ-BC total – mean (SE)	2.74 (0.3)	1.82 (0.2)
PQ-BC distress – mean (SE)	6.67 (0.6)	4.32 (0.4)
SDSC total– mean (SE)	36.78 (0.3)	36.59 (0.3)
Nightmares (SDSC item 21) – mean (SE)	1.23 (<0.1)	1.18 (<0.1)
Derived variable counts		
Sleep disorders present (≥39 cut off on SDSC) – % (SE)	31.71 (1.5)	29.15 (1.6)
Sleep disorders new onset (absent at baseline, present at follow up) – % (SE)		9.56 (0.1)
Sleep disorders persisting (present at both baseline and follow up) – % (SE)		19.50 (1.6)
Sleep disorders remitting (present at baseline, absent at follow up) – % (SE)		10.48 (0.8)
Psychotic experiences present (≥1 on PQ-BC total) – % (SE)	44.68 (2.4)	32.58 (2.4)
Psychotic experiences new onset – % (SE)		9.9 (0.8)
Psychotic experiences persisting – % (SE)		22.67 (2.2)
Psychotic experiences remitting – % (SE)		21.92 (1.2)
Nightmares present (at least 'Occasionally') – % (SE)	20.49 (0.6)	16.08 (0.9)
Nightmares new onset - % (SE)		7.97 (0.7)
Nightmares persisting - % (SE)		9.11 (0.6)
Nightmares remitting - % (SE)		12.15 (0.7)

SDSC = Sleep Disorder Scale for Children; PQBC = Prodromal Questionnaire – Brief Child version; SE = standard error;

Appendix 6 Table 2: Cross-tabulation of sleep disorders, nightmares, and psychotic experiences (weighted)

Cross tabulation (sleep disorders vs psychotic experiences, % prevalence)			
		Psychotic experience onset	
Onset (absent at baseline, present at follow up)		No	Yes
Sleep disorder onset	No	82.10	8.34
	Yes	8.66	0.90
		Psychotic experience persisting	
Persistence (present at baseline and follow up)		No	Yes
Sleep disorder persisting	No	51.17	29.33
	Yes	9.84	9.66
		Psychotic experience remitting	
Remission (present at baseline, absent at follow up)		No	Yes
Sleep disorder remission	No	67.70	21.81
	Yes	7.77	2.71
Cross tabulation (nightmares vs psychotic experiences, % prevalence)			
		Psychotic experience onset	
Onset (absent at baseline, present at follow up)		No	Yes
Nightmares onset	No	83.52	8.51
	Yes	7.22	0.74
		Psychotic experience persisting	
Persistence (present at baseline and follow up)		No	Yes
Nightmares persisting	No	57.16	34.73
	Yes	3.89	4.22
		Psychotic experience remitting	
Remission (present at baseline, absent at follow up)		No	Yes
Nightmares remission	No	66.12	21.72
	Yes	9.36	2.79

Appendix 6 Table 2a: Regression analyses of co-occurrence of sleep disorders and psychotic experiences at baseline (T0) – weighting method A

Model (outcome)	Parameters	B	95% CI	p-value	AIC
Model 1a (PQBC total T0) [a]	SDSC total T0	0.154	0.12, 0.19	<0.001	26047
Model (outcome)	Parameters	Odds	95% CI	p-value	AIC
Model 1b (PQBC cut-off T0) [b]	SDSC total T0	1.032	1.02, 1.04	<0.001	6053
Model 1c (PQBC cut-off T0) [b]	SDSC cut off T0	1.573	1.34, 1.84	<0.001	6067
Model (outcome)	Parameters	B	95% CI	p-value	AIC
Model 1d (PQBC total T0) [a]	SDSC total T0	0.123	0.09, 0.16	<0.001	24325
	Gender	-0.248	-0.84, 0.35	0.412	
	Ethnicity	0.221	-0.04, 0.48	0.099	
	Socioeconomic status	0.171	0.551	0.24, 0.86	0.001
	Neighbourhood deprivation	0.011	0.034	0.02, 0.05	<0.001
	IQ	-0.190	-0.29, -0.09	<0.001	
	Family conflict	0.063	-0.1, 0.23	0.456	
	Stimulant medication	0.581	1.643	0.45, 2.83	0.007
Model (outcome)	Parameters	Odds	95% CI	p-value	AIC
Model 1e (PQBC cut-off T0) [b]	SDSC total T0	1.025	1.01, 1.04	<0.001	5641
	Gender	1.175	1.01, 1.37	0.035	
	Ethnicity	1.062	0.99, 1.14	0.101	
	Socioeconomic status	1.127	1.04, 1.22	0.002	
	Neighbourhood deprivation	1.006	1, 1.01	0.002	
	IQ	0.954	0.93, 0.98	0.001	
	Family conflict	1.027	0.99, 1.07	0.204	
	Stimulant medication	1.461	1.08, 1.98	0.014	
Model 1f (PQBC cut off T0) [b]	SDSC cut off T0	1.428	1.21, 1.69	<0.001	5647
	Gender	1.174	1.01, 1.36	0.036	
	Ethnicity	1.064	0.99, 1.14	0.089	
	Socioeconomic status	1.139	1.06, 1.23	0.001	
	Neighbourhood deprivation	1.006	1, 1.01	0.002	
	IQ	0.954	0.93, 0.98	0.001	
	Family conflict	1.033	0.99, 1.08	0.116	
	Stimulant medication	1.502	1.11, 2.03	0.008	

[a] = linear regression; [b] = logistic regression; SDSC = Sleep Disorder Scale for Children; PQBC = Prodromal Questionnaire – Brief Child version; B = standardised beta; CI = confidence intervals; AIC = Akaike information criterion.

Appendix 6 Table 2b: Regression analyses of co-occurrence of sleep disorders and psychotic experiences at baseline (T0) – weighting method B

Model (outcome)	Parameters	B	95% CI	p-value	AIC
Model 1a (PQBC total T0) [a]	SDSC total T0	0.154	0.12, 0.19	<0.001	26054
Model (outcome)	Parameters	Odds	95% CI	p-value	AIC
Model 1b (PQBC cut-off T0) [b]	SDSC total T0	1.027	1.02, 1.04	<0.001	5027
Model 1c (PQBC cut-off T0) [b]	SDSC cut off T0	1.452	1.25, 1.68	<0.001	5039
Model (outcome)	Parameters	B	95% CI	p-value	AIC
Model 1d (PQBC total T0) [a]	SDSC total T0	0.123	0.09, 0.16	<0.001	24333
	Gender	-0.246	-0.84, 0.35	0.417	
	Ethnicity	0.225	-0.04, 0.49	0.096	
	Socioeconomic status	0.547	0.23, 0.86	0.001	
	Neighbourhood deprivation	0.034	0.02, 0.05	<0.001	
	IQ	-0.188	-0.29, -0.09	<0.001	
	Family conflict	0.063	-0.1, 0.23	0.459	
	Stimulant medication	1.641	0.45, 2.83	0.007	
Model (outcome)	Parameters	Odds	95% CI	p-value	AIC
Model 1e (PQBC cut-off T0) [b]	SDSC total T0	1.021	1.01, 1.03	<0.001	4687
	Gender	1.161	1.01, 1.33	0.035	
	Ethnicity	1.059	0.99, 1.13	0.089	
	Socioeconomic status	1.147	1.120	1.05, 1.2	0.001
	Neighbourhood deprivation	1.008	1.005	1, 1.01	0.003
	IQ	0.963	0.94, 0.99	0.003	
	Family conflict	1.024	0.99, 1.06	0.216	
	Stimulant medication	1.311	0.99, 1.73	0.057	
Model 1f (PQBC cut off T0) [b]	SDSC cut off T0	1.332	1.14, 1.56	<0.001	4693
	Gender	1.160	1.01, 1.33	0.035	
	Ethnicity	1.061	0.99, 1.13	0.079	
	Socioeconomic status	1.130	1.05, 1.21	0.001	
	Neighbourhood deprivation	1.005	1, 1.01	0.003	
	IQ	0.964	0.94, 0.99	0.004	
	Family conflict	1.030	0.99, 1.07	0.125	
	Stimulant medication	1.347	1.02, 1.78	0.035	

[a] = linear regression; [b] = logistic regression; SDSC = Sleep Disorder Scale for Children; PQBC = Prodromal Questionnaire – Brief Child version; B = standardised beta; CI = confidence intervals; AIC = Akaike information criterion.

Appendix 6 Table 3a: Regression analyses of whether sleep disorders at baseline predict onset of psychotic experiences at 12 months – weighting method A

Model (outcome)	Parameters	Odds	95% CI	p-value	AIC
Model 2a (PQBC cut off T1)	SDSC cut off T0	0.550	0.71, 1.73	0.387	6303
Model 2b (PQBC cut off T1)	SDSC cut off T0	1.468	1.22, 1.77	<0.001	6294
	SDSC cut off T1	1.396	1.16, 1.69	0.001	
Model 2c (PQBC cut off T1)	SDSC cut off T0	1.554	1.3, 1.85	<0.001	5826
	Gender	1.087	0.93, 1.27	0.300	
	Ethnicity	1.057	0.98, 1.14	0.150	
	Socioeconomic status	1.232	1.14, 1.33	<0.001	
	Neighbourhood deprivation	1.008	1, 1.01	<0.001	
	IQ	0.976	0.95, 1	0.097	
	Family conflict	0.983	0.94, 1.03	0.452	
	Stimulant medication	1.566	1.15, 2.14	0.005	
Model 2d (PQBC cut off T1)	SDSC cut off T0	1.340	1.34, 1.34	<0.001	5819
	SDSC cut off T1	1.325	1.32, 1.33	<0.001	
	Gender	1.064	1.06, 1.06	<0.001	
	Ethnicity	1.047	1.05, 1.05	<0.001	
	Socioeconomic status	1.218	1.22, 1.22	<0.001	
	Neighbourhood deprivation	1.008	1.01, 1.01	<0.001	
	IQ	0.973	0.97, 0.97	<0.001	
	Family conflict	0.979	0.98, 0.98	<0.001	
	Stimulant medication	1.515	1.51, 1.52	<0.001	

SDSC = Sleep Disorder Scale for Children; PQBC = Prodromal Questionnaire – Brief Child version; CI = confidence intervals; AIC = Akaike information criterion

Appendix 6 Table 3b: Regression analyses of whether sleep disorders at baseline predict onset of psychotic experiences at 12 months – weighting method B

Model (outcome)	Parameters	Odds	95% CI	p-value	AIC
Model 2a (PQBC cut off T1)	SDSC cut off T0	1.572	1.35, 1.83	<0.001	5226
Model 2b (PQBC cut off T1)	SDSC cut off T0	1.369	1.15, 1.63	<0.001	5220
	SDSC cut off T1	1.314	1.1, 1.57	0.003	
Model 2c (PQBC cut off T1)	SDSC cut off T0	1.423	1.21, 1.67	<0.001	4836
	Gender	1.111	0.96, 1.29	0.161	
	Ethnicity	1.066	0.99, 1.14	0.072	
	Socioeconomic status	1.200	1.12, 1.29	<0.001	
	Neighbourhood deprivation	1.007	1, 1.01	<0.001	
	IQ	0.979	0.95, 1	0.109	
	Family conflict	0.995	0.96, 1.04	0.814	
	Stimulant medication	1.350	1.02, 1.79	0.039	
Model 2d (PQBC cut off T1)	SDSC cut off T0	1.270	1.05, 1.53	0.012	4832
	SDSC cut off T1	1.269	1.05, 1.53	0.012	
	Gender	1.105	0.95, 1.28	0.183	
	Ethnicity	1.065	0.99, 1.14	0.077	
	Socioeconomic status	1.191	1.11, 1.28	<0.001	
	Neighbourhood deprivation	1.007	1, 1.01	<0.001	
	IQ	0.978	0.95, 1	0.104	
	Family conflict	0.993	0.95, 1.03	0.712	
	Stimulant medication	1.314	0.99, 1.75	0.061	

SDSC = Sleep Disorder Scale for Children; PQBC = Prodromal Questionnaire – Brief Child version; CI = confidence intervals; AIC = Akaike information criterion

Appendix 6 Table 4a: Regression analyses of whether sleep disorders at baseline predict persistence of psychotic experiences at 12 months – weighting method A

Model (outcome)	Parameters	Odds	95% CI	p-value	AIC
Model 3a (PQBC persist)	SDSC cut off T0	1.531	1.35, 1.73	<0.001	5996
Model 3b (PQBC persist)	SDSC persist	1.923	1.54, 2.41	<0.001	5994
Model 3c (PQBC persist)	SDSC cut off T0	1.835	1.49, 2.26	<0.001	5537
	Gender	1.256	1.04, 1.52	0.018	
	Ethnicity	1.056	0.97, 1.15	0.223	
	Socioeconomic status	1.237	1.13, 1.35	<0.001	
	Neighbourhood deprivation	1.007	1, 1.01	0.003	
	IQ	0.955	0.92, 0.99	0.006	
	Family conflict	0.986	0.94, 1.04	0.597	
	Stimulant medication	1.742	1.22, 2.49	0.002	
Model 3d (PQBC persist)	SDSC persist	1.651	1.31, 2.09	<0.001	5532
	Gender	1.255	1.04, 1.52	0.018	
	Ethnicity	1.058	0.97, 1.16	0.205	
	Socioeconomic status	1.243	1.14, 1.36	<0.001	
	Neighbourhood deprivation	1.007	1, 1.01	0.002	
	IQ	0.954	0.92, 0.99	0.005	
	Family conflict	0.994	0.94, 1.05	0.809	
	Stimulant medication	1.808	1.27, 2.58	0.001	

persist = above cut off at T0 and T1; SDSC = Sleep Disorder Scale for Children; PQBC = Prodromal Questionnaire – Brief Child version; CI = confidence intervals; AIC = Akaike information criterion.

Appendix 6 Table 4b: Regression analyses of whether sleep disorders at baseline predict persistence of psychotic experiences at 12 months – weighting method B

Model (outcome)	Parameters	Odds	95% CI	p-value	AIC
Model 3a (PQBC persist)	SDSC cut off T0	1.527	1.33, 1.75	<0.001	4989
Model 3b (PQBC persist)	SDSC persist	1.687	1.39, 2.05	<0.001	4987
Model 3c (PQBC persist)	SDSC cut off T0	1.628	1.36, 1.96	<0.001	4609
	Gender	1.255	1.06, 1.49	0.008	
	Ethnicity	1.07	0.99, 1.16	0.09	
	Socioeconomic status	1.203	1.12, 1.3	<0.001	
	Neighbourhood deprivation	1.006	1, 1.01	0.006	
	IQ	0.962	0.93, 0.99	0.012	
	Family conflict	1.001	0.96, 1.05	0.956	
	Stimulant medication	1.411	1.03, 1.94	0.033	
Model 3d (PQBC persist)	SDSC persist	1.479	1.2, 1.82	<0.001	4321
	Gender	1.255	1.06, 1.49	0.008	
	Ethnicity	1.071	0.99, 1.16	0.089	
	Socioeconomic status	1.209	1.12, 1.3	<0.001	
	Neighbourhood deprivation	1.006	1, 1.01	0.003	
	IQ	0.961	0.93, 0.99	0.011	
	Family conflict	1.007	0.96, 1.05	0.752	
	Stimulant medication	1.463	1.07, 2.01	0.018	

persist = above cut off at T0 and T1; SDSC = Sleep Disorder Scale for Children; PQBC = Prodromal Questionnaire – Brief Child version; CI = confidence intervals; AIC = Akaike information criterion.

Appendix 6: Weighted analysis tables

RQ4a: Regression analysis of whether remission of sleep problems predicts remission of psychotic experiences (weighted method A):

Remission of sleep disorder symptoms was not a significant predictor of remission of psychotic experiences (OR=1.056, p=0.643, 95% CI 0.84, 1.34, AIC=5241) in the uncontrolled model.

RQ4a: Regression analysis of whether remission of sleep problems predicts remission of psychotic experiences (weighted method B):

Remission of sleep disorder symptoms was not a significant predictor of remission of psychotic experiences (OR=1.011, p=0.588, 95% CI 0.79, 1.29, AIC = 5241) in the uncontrolled model, therefore the analysis with control variables was not carried out.

Appendix 7: Table of estimated risk ratios

Model	Primary predictor variable	Primary outcome variable	Risk ratio
RQ1a	SDSC total score T0	PQBC total T0	*n/a (linear outcome)*
RQ1b	SDSC total score T0	PQBC cut-off T0	1.03*
RQ1c	SDSC cut off T0	PQBC cut-off T0	1.30*
RQ1d	SDSC total score T0	PQBC total T0	*n/a (linear outcome)*
RQ1e	SDSC total score T0	PQBC cut-off T0	1.02*
RQ1f	SDSC cut off T0	PQBC cut-off T0	1.25*
RQ2a	SDSC cut off T0	PQBC cut-off T1	1.45*
RQ2b	SDSC cut off T0	PQBC cut-off T1	1.29*
RQ2c	SDSC cut off T0	PQBC cut-off T1	1.38*
RQ2d	SDSC cut off T0	PQBC cut-off T1	1.25*
RQ3a	SDSC cut off T0	PQBC persist	1.45*
RQ3b	SDSC persist	PQBC persist	1.61*
RQ3c	SDSC cut off T0	PQBC persist	1.59*
RQ3d	SDSC persist	PQBC persist	1.48*
RQ4a	SDSC remit	PQBC remit	1.04
RQ5a	SDSC nightmare frequency	PQBC total	*n/a (linear outcome)*
RQ5b	SDSC nightmares present	PQBC cut-off T0	1.26*
RQ5c	SDSC nightmares present	PQBC cut-off T1	1.33*
RQ5d	SDSC nightmares present	PQBC persist	1.53*
RQ5e	SDSC nightmares present	PQBC remit	0.98
RQ6a	SDSC nightmares present[a]	PQBC cut-off T0	1.13
RQ6b	SDSC nightmares present[a]	PQBC cut-off T1	1.13
RQ6c	SDSC nightmares present[a]	PQBC persist	1.10
RQ6d	SDSC nightmares present[a]	PQBC remit	1.09

*predictor was statistically significant in main model

[a]comparison group was children without nightmares but with other sleep disorders

persist = above cut off at both T0 and T1; remit = above cut off at T0, below at T1