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Sleep Problems and Positive Prodromal Symptoms

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Sleep Problems and Positive Prodromal Symptoms

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An abstract of
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Abstract

Sleep Problems and Positive Prodromal Symptoms

By Katrina B. Goines

Sleep dysfunction has long been associated with psychotic disorders. Recent findings on sleep's effect on physical and mental health have spurred interest in whether sleep problems might contribute to psychotic illness. Previous research in the area of sleep and psychotic symptoms was conducted largely on samples with schizophrenia, or in healthy populations. Neither approach is well-suited for testing whether sleep problems contribute to the emergence of psychotic disorders. In addition, previous longitudinal studies of sleep problems and psychotic symptoms have only tested the association across two time points, and in one direction (i.e., tested whether sleep problems predict later psychotic symptoms). No previous studies have attempted to test the reverse relationship (i.e., whether psychotic symptoms predict later sleep problems), or a bidirectional relationship. This dissertation investigated both the cross-sectional and longitudinal relations between sleep problems and positive prodromal symptoms in a large sample of youth at Clinical High Risk (CHR) for psychosis. Study 1 assessed the cross-sectional association of sleep problems and positive prodromal symptoms in an attempt to replicate previous findings and assess whether findings from general population samples and psychotic samples extend to this CHR sample. Results from Study 1 were largely consistent with previous findings and found that sleep problems were significantly associated with positive psychotic symptom severity at baseline. Sleep problems were also found to be associated with only certain specific prodromal symptoms (e.g., suspiciousness, perceptual abnormalities, and disorganized speech). Further, cross-sectional analyses of direct and indirect effects provided some support for depression as a mediator in the association between sleep problems and psychotic symptoms. Study 2 utilized longitudinal data from three time points in an autoregressive panel design. The aims were to characterize the longitudinal relations of sleep problems and positive prodromal symptoms, as well as to test the possibility of a bidirectional association. Results revealed that although sleep problems had no significant effect on later prodromal symptoms, prodromal symptoms significantly predicted sleep problems at later time points. These results run counter to common assumptions of the sleep and psychosis association, and they highlight the benefits of longitudinal designs in understanding the directionality of associations.

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Table of Contents

Sleep Problems and Positive Prodromal Symptoms

The importance of sleep is often stated, and yet the reasons why individuals sleep are not well understood. Sleep is believed to be present and necessary for all but the simplest of animals (Lavie & Berris, 1996). Theories for why sleep is so well conserved throughout evolution tend to focus on the protective role sleep plays against exposing an organism to predators, decreasing its energy demands, and/or optimizing cognitive and other bodily functions. However, a recent line of animal research has indicated that sleep may play a role in the clearance of metabolites of normal neural functioning (Xie et al., 2013). This study also showed that sleep restriction resulted in the accumulation of β-amyloid in brain, which is large quantities makes up the β-amyloid plaques that are believed confer neurotoxic effects in Alzheimer's disease. In fact, sleep dysfunction is commonly found in neurodegenerative diseases, such as Parkinson's, Huntington's, and multiple sclerosis (see Wulff et al., 2010 for review). Sleep dysfunction is also closely associated with various psychiatric disorders including depression, anxiety, bipolar disorder, and alcoholism (see Wulff et al., 2010 for review). A recent increase in research investigating sleep processes in psychiatric disorders has resulted in heightened awareness of the role sleep may play in exacerbating physical and mental health problems (Tkachenko et al., 2014). Thus, optimal functioning of sleep and circadian systems appear to be necessary for an organism's success, and for humans, sleep dysfunction appears to be a risk factor for mental illness.

Sleep Disruption in Psychosis

Sleep disturbance is common in psychotic disorders (for reviews see Cohrs, 2008; Monti & Monti 2005). Even early descriptions of schizophrenia by Kraepelin and Bleuler include mention of sleep disturbances (Manoach & Stickgold, 2009; Bleuler, 1950). More recently, reports show that

between 30-80% of patients with schizophrenia experience significant sleep disturbance (Cohrs, 2008; Waters & Manoach, 2012). Not only is sleep disruption common in schizophrenia, it is also associated with significant levels of subjective distress, and impacts social function, mood, cognitive abilities, and quality of life (Krystal, Thakur & Roth, 2008). Several types of sleep disorders are associated with schizophrenia, including restless-leg syndrome, nightmares, and other parasomnias; however, most research has focused on disorders of sleep duration (e.g., insomnia and hypersomnia) (Reeve, Sheaves & Freeman, 2015). Sleep disruption in schizophrenia is present regardless of medication status, with never medicated, previously medicated, and currently medicated patients all showing disruptions in sleep duration (Chouinard, Poulin, Stip & Godbout, 2004). Additionally, sleep disturbance does not seem to be specific to phase of psychotic illness, and is frequently described in those with both acute, and chronic schizophrenia (Hudson et al., 1993; Lauer, Schreiber, Pollmacher, Holsboer & Krieg, 1997; Tandon et al., 1992), and during the prodromal phase of psychosis (Lunsford-Avery et al., 2013; Yung & McGorry, 1996). Sleep disruption often precedes relapse in chronic schizophrenia (Benson, 2008), and the treatment of sleep problems in those with schizophrenia may result in improvements to some other psychiatric symptoms (Kantrowitz et al., 2010). This all suggests that sleep dysfunction is a common and distressing correlate of psychotic disorders that may be intrinsically related to the pathophysiology of the disorder.

Consistent with this idea, those who go on to develop schizophrenia often present with sleep dysfunction at earlier stages of psychotic illness, including before psychotic symptoms emerge. Retrospective report studies find that even in childhood, those who go on to develop schizophrenia experience more sleep disruption than healthy controls, according to parent interviews and medical record review (Bourgeois & Etchepare, 1986; Massou dit Bourdet & Laffy-Beaufils, 2000; Verdoux et al., 1998). One study even found preliminary evidence that the degree of sleep disruption in childhood may differentiate those who go on to develop psychosis from those who go on to develop non-psychotic internalizing and externalizing disorders, with those going on to develop

schizophrenia presenting with more reports of sleep disturbance (e.g., excessive sleep, nightmares, sleep talking, walking, and screaming) between the ages of 5-16 years (Frazee, 1953). Thus, even at early developmental stages, sleep dysfunction may differentiate those who later develop psychosis from those who do not.

Sleep & Psychotic Experiences in the General Population

Several researchers have examined the relationship between sleep problems and psychotic-like experiences in the general population. A review by Reeve and colleagues (2015) concluded that there is significant evidence of psychotic experiences, particularly paranoid thoughts, co-occurring with insomnia. For example, epidemiological surveys have found that a diagnosis of insomnia is associated with a five times greater risk of paranoid thoughts (e.g., "a group of people are plotting to harm me"), and a four to five times greater likelihood of transient hallucinatory experiences (e.g., "hearing name being called when no-one was around") (Freeman et al., 2012). This effect is seen for cross-sectional analyses, but longitudinal analyses also revealed that insomnia at baseline was associated with new incidences of paranoid thoughts and hallucinatory experiences at a second time point, 18 months later (Sheaves et al., 2016).

Sleep deprivation studies using experimental and observational designs have also found an association between acute sleep loss and psychotic experiences in some people. For example, Hurdiel and colleagues (2014) observed ultra-marathon runners who maintained wakefulness for around 46 hours and found that 4 of the 17 participants experienced hallucinatory experiences during their sleep deprived state. One study that manipulated sleep experimentally found that several otherwise healthy volunteers experienced dissociative symptoms in the context of one night of sleep loss (van Heugten-van der Kloet, 2015). In this case, the dissociative symptoms occurred only during the period of nighttime and dissipated by the daytime even without any period of sleep, suggesting a circadian component to the presence of these unusual experiences. Other experimental studies have found

sleep deprivation to be associated with increased paranoid thoughts (Kahn-Greene et al., 2007) as well as perceptual distortions, cognitive disorganization, and anhedonia (Petrovsky et al., 2014).

It is as yet unclear what these studies can tell us about the determinants of the relationship between psychotic symptoms and sleep dysfunction more generally. Some question whether those experiencing psychotic-like symptoms in the state of sleep deprivation are actually representative of healthy, non-clinical population, or whether they may have a previously undetected vulnerability to psychotic or bipolar disorders, and are thus more representative of a high risk population. Also, in several studies, symptoms of depression were found to partially mediate the relationship (e.g., Freeman et al., 2009). More information about the relationship between sleep and psychotic symptoms in the general population will be forthcoming as there is currently an intervention study underway that is designed to test the impact of insomnia treatment (cognitive behavioral treatment for insomnia) on psychotic-like symptoms in a college-aged population (Freeman et al., 2015). Overall, the current evidence indicates that the link between psychotic experiences and sleep dysfunction is present across a continuum of impairment, from those with schizophrenia to individuals in the general population with no active psychotic illness. Importantly, psychotic-like experiences in the general population are believed to be similar to psychotic disorders in terms of risk factors and pathogenic mechanisms (Linscott & Van Os, 2013), thus the evidence from general populations strengthens the argument that sleep dysfunction may be integrally related to the pathogenic mechanisms resulting in psychosis.

Theories Linking Sleep and Psychosis

Melatonin

Research in psychotic samples has found not only general sleep problems (e.g., insomnia), but also sleep problems more related to circadian functioning such as phase shifts, irregular sleep-

wake cycles, free running rest and activity patterns, to complete day-night reversal (Wirz-Justice et al., 2001, Wulff et al., 2006, 2012; Bromundt et al., 2011). Further, there is evidence of abnormalities in the secretion and response to melatonin (Monti et al., 2013), an endogenous hormone believed to be important for regulating the phase of circadian rhythms in humans (Lewy, 1999). Specifically, it seems that in some individuals with psychosis, melatonin is secreted at lower levels in response to darkness, resulting in a 'blunted' profile (Wulff et al., 2012). Additionally, in schizophrenia samples, a rise in melatonin was found to be less correlated with sleep efficiency in comparison to healthy controls (Afonso, Figueira & Paiva, 2011). This may partly explain the high prevalence of circadian rhythm dysfunction in psychotic samples.

Of particular interest to psychosis research, are the findings from animal studies that melatonin interacts with dopamine and other neurotransmitters implicated in psychosis. Specifically, melatonin has been found to inhibit dopamine release, increase dopamine turnover, and alter dopamine receptor activation (Monti et al., 2013). Since dopamine dysregulation is believed to be a key feature constituting the "final common pathway" to psychosis (Howes & Kapur, 2009), this may be one way in which dysregulated melatonin (and associated circadian rhythm and sleep dysfunction) is related to psychosis.

Neurodevelopment

Sleep dysfunction has generally negative impacts on neurodevelopment (Feinberg, 1982). Based on this general finding, Lunsford-Avery and Mittal (2013) have developed a neurodevelopmental diathesis-stress theory of sleep and psychosis that posits sleep dysfunction may lead to progression of psychotic illness through different avenues. One of the avenues indicated in this model is a direct effect from sleep problems to problems with cognitive functioning. It is now well established that cognitive declines in the premorbid period are predictive of psychotic illness onset (Seidman et al., 2012). Multiple lines of evidence also suggest that sleep has a restorative effect

on neurocognitive functions, both general and specific. Generally, sleep seems to be important for promoting neural plasticity (Durmer & Dinges, 2005) that supports a wide variety of cognitive functions. More specifically, sleep seems to be important for hippocampus-related memory consolidation, which is known to be impaired in those with an established psychotic illness. Thus, it seems likely that in the context of clinical high risk for psychosis, which is characterized by the presence of subclinical or attenuated positive symptoms of psychosis, disrupted circadian rhythms and sleep patterns may lead to exacerbation of cognitive impairments, putting already vulnerable individuals at greater risk for impairment and psychosis onset.

Another avenue posited by Lunsford-Avery and Mittal (2013), is an indirect path from sleep disturbance to psychotic symptom progression through impacts on stress/HPA functioning and subsequent changes to gene expression and typical neuromaturational processes. Stress and sleep dysfunction have a bidirectional relationship whereby increased psychosocial stress results in increased sleep disruption, and suboptimal sleep processes makes one more stress-sensitive and vulnerable to daily stressors (Kahn, Sheppes & Sadeh, 2013). At a biological level, sleep dysfunction not only affects the biological stress response, but is itself heavily influenced by outcomes of the stress response (e.g., cortisol). Thus, sleep dysfunction may start a cycle resulting in a more dysregulated and sensitive hypothalamic-pituitary axis (HPA) stress system, which in turn is believed to modulate the expression of certain genes implicated in neuromaturational processes, such as synaptic pruning and white matter growth, and thus put individuals at greater risk of conversion to psychotic illness (Corcoran et al., 2003; Walker et al., 2008). Additionally, stress-induced increases in cortisol have been found to augment dopamine activity, especially in the striatum (Tsukada et al., 2011; Wand et al., 2007). This is relevant as striatal dopamine hyperactivity is believed to be specifically implicated in positive psychotic symptoms (Howes et al., 2009). These mechanisms may explain the observed relationship between cortisol levels and exacerbation of attenuated psychotic symptoms in those at risk for psychosis (Walker et al., 2014).

Neuroinflammation & Synaptic Homeostasis Theories

Similar to Lunsford-Avery and Mittal's theory that sleep impacts neurodevelopmental processes, there are also theories linking psychosis to sleep problems through abnormalities in specific neural processes, such as neuroinflammation and synaptic potentiation. With regard to the neuroinflammation hypothesis, sleep loss has pro-inflammatory effects generally, including in the brain where there is evidence of neuroinflammatory and microglial changes in response to sleep deprivation (Wisor, Schmidt, Clegen, 2011). Neuroimmune changes are believed to lead to brain changes that may precipitate the onset and progression of schizophrenia (Watkins and Andrews, 2015). In animal studies, sleep disturbance-induced neuroinflammation has also been found to impair several cognitive functions commonly found to be impaired in schizophrenia, including hippocampus dependent-learning and memory (Zhu et al., 2012).

The synaptic homeostasis model posits that the state of wakefulness is associated with synaptic potentiation (the creation of new synapses without any corresponding downscaling of such associations) (Tononi & Cirelli, 2014). The accumulation of sleep pressure eventually results in sleep onset, allowing the brain a chance to downscale connections between neurons, resulting in more efficient informational processing. This process is believed to occur specifically in slow-wave sleep. In the case of chronically disturbed sleep, the mechanisms maintaining synaptic homeostasis are also disrupted. This may result in the occurrence of abnormal cognitive associations, aberrant salience (i.e., errors in assessing the informational value or salience of stimuli), and thus, psychotic experiences (Tononi & Cirelli, 2014). The neuroinflammation and synaptic homeostasis theories of sleep disruption are certainly not mutually exclusive, and may even inform each other. For example, microglia, the phagocytosing cells of the central nervous system, are involved in both synaptic maintenance and neuroinflammatory response, suggesting some areas of overlap between these theories. Additionally, neuroinflammation is believed to be one mechanism connecting stress and

psychosis (Mizrahi, 2016), and thus may also be one neural mechanism through which stress and sleep disruption are associated with psychotic symptoms. Although the proposed study will not examine indicators of neuroinflammation, it is important to note that there is evidence of elevated proinflammatory processes in individuals at clinical high risk for psychosis who later develop a psychotic disorder (Perkins et al., 2014).

Depression and Cognitive Theories

A systematic review of the literature linking sleep dysfunction and psychotic experiences found that depression was the most consistently tested mediator and was frequently found to partially mediate the relationship between sleep dysfunction and psychotic experiences (Reeve, Sheaves & Freeman, 2015). Exactly what this means and how depression or depressive symptoms may be involved in the relationship between sleep problems and psychotic symptoms is still unclear. Reeve and colleagues (2015) suggest that integrating empirical knowledge about depression as a mediator with theoretical cognitive models of paranoid delusions (Freeman et al., 2002) and hallucinatory experiences (Waters et al., 2012) may be helpful. In both models, cognitive biases as well as emotions and beliefs about the self and the world play key roles in the subjective experience of psychotic symptoms. For example, if an individual has a bias towards threat detection (e.g., anxiety) or believes the world to be unsafe and uncaring, they may be more likely to interpret neutral interpersonal experiences as hostile (e.g., paranoia or suspiciousness). In this way, their emotional state and core beliefs mediate their selection of an explanation for an ambiguous situation. Similarly, an individual's emotional state often appears to have significant impacts on the form and content of the hallucination being experienced (e.g., mood congruent hallucinations) (Waters et al., 2012). Although sleep is not directly discussed in these cognitive models of psychotic symptoms, Reeve and colleagues make the point that if sleep problems can precipitate negative affect generally, and depressive symptoms specifically, then perhaps sleep problems are related to psychotic symptoms

indirectly through increases in negative affect/depressive symptoms. These specific relationships have yet to be explored empirically.

Clinical High Risk (CHR) Approach

Retrospective studies of first-episode psychosis reveal that sleep disturbance is a commonly experienced symptom during the prodromal progression towards illness. In fact, as many as 77% and 100% of patients retrospectively reported sleep disturbance during the prodromal phase of illness (Tan & Ang, 2001; Yung & McGorry, 1996). Much of the information about sleep during prodromal periods comes from retrospective studies of those already suffering from a psychotic illness, which has inherent limitations. Studying these groups prospectively is the preferred method for more accurate findings. The difficulty inherent in this approach is that researchers have to prospectively identify which individuals are going to develop a psychotic illness. It is now clear that most individuals who develop a psychotic illness go through a period of a few months to a few years of functional decline and attenuated psychotic symptoms prior to eventually converting to a full psychotic disorder. Thus, researchers interested in understanding the risk factors and mechanisms related to psychotic illness development have begun to work to identify individuals in this "prodromal" phase based on the presence of attenuated psychotic symptoms (i.e., symptoms that are below the threshold of fully psychotic, but are more severe than typically observed in the general population). This is known as the Clinical High Risk (CHR) approach. In this approach, potential participants are enrolled as CHR participants based on the current severity of their positive symptoms. Longitudinal studies of CHR samples, defined by the presence of attenuated psychotic symptoms, have found that up to 36% of the CHR youth develop a psychotic illness within 2 years (Fusar-Poli et al., 2012), indicating that CHR status is a reasonable proxy for 'prodromal status'. Studies of CHR samples have been found to be useful for identifying etiological mechanisms in

psychosis (Addington & Heinssen, 2012), and are ideally suited for answering questions about if and/or how various risk factors (e.g., sleep problems) might impact progression to a psychotic illness.

Sleep disruption and positive prodromal symptoms in CHR samples

Clearly there are many benefits to the CHR approach, and studying sleep and positive prodromal symptoms in this sample is important in order to understand if and/or how sleep may impact progression of psychotic symptoms. To date, there been two recent studies to prospectively explore the relation of psychotic symptoms with either sleep or circadian rhythms in CHR. One study explored sleep in a CHR sample (Poe et al., 2017), and the other specifically examined circadian rhythms in a separate CHR sample (Lunsford-Avery et al., 2017).

Poe and colleagues (2017) focused on sleep as assessed by the Structured Interview for Prodromal Syndromes (SIPS), an examiner-administered interview specific for prodromal symptoms of psychosis, in a sample of 194 CHR youth (13-30 years old), and 66 matched controls. In their cross-sectional analysis, they found that CHR participants experienced significantly more severe sleep disturbance than controls, and that the severity of sleep disturbance was associated with severity of positive and negative symptoms of psychosis, as well as general functioning symptoms (higher severity of sleep disturbance predicted higher severity of positive and negative symptoms, and poorer general functioning). This study replicates and extends previous findings by Lunsford-Avery and colleagues (2013) that sleep disruption is associated with negative symptoms of psychosis. Together, the findings indicate that sleep disturbance and psychotic symptoms are intimately linked in clinical high risk samples. As the study was cross-sectional, questions remain about whether sleep and psychotic symptoms co-vary over time in synchrony, or whether exacerbation of psychotic symptoms predicts exacerbation of sleep disturbance, or vice-versa.

Lunsford-Avery and colleagues (2017) recently explored the relationship of psychotic symptoms with circadian rhythms in a sample of 34 CHR and 32 healthy control participants using actigraphy, a sleep/activity diary, and a clinical interview specific for psychotic syndromes (SIPS). In their cross-sectional analysis, they found that several indicators of circadian rhythm disruption (e.g., fragmented circadian rhythms, reduced daily activity) were associated with positive and negative symptoms of psychosis. Additionally, in longitudinal analyses, certain indicators of circadian rhythm disruption at first interview were predictive of psychotic symptoms one year later (when controlling for severity of psychotic symptoms at time 1). Specifically, more severe 'desynchronization of circadian rhythms with light/dark cycle' and 'fragmented circadian rhythm' was predictive of more severe positive symptoms a year later. Lower daily activity levels at first interview were predictive of increased negative symptoms a year later, and both lower activity levels and less regular circadian rhythms were predictive of poorer overall functioning a year later. These findings provide the first evidence that circadian components of the sleep-wake cycle may have specific impacts on certain psychotic symptoms.

These findings provide evidence that sleep is disrupted in those at CHR for psychosis and suggest that sleep disruption may be associated with worsening prodromal symptoms over time. However, although Lunsford-Avery and colleagues (2017) address this to some degree in their longitudinal analyses, it is still unclear what the direction of the relationship is between sleep and psychotic symptoms in CHR samples. Further, it is also unclear whether sleep problems in CHR samples are associated with all positive prodromal symptoms, or if they show a similar specificity pattern as found in general population studies (e.g., paranoia and hallucinations primarily affected by sleep problems). Finally, no previous CHR studies have attempted to investigate potential mediators of the relationship between sleep problems and positive prodromal symptoms.

Current Studies

In order to better understand the association between sleep problems and psychotic/prodromal symptoms, two studies were conducted to examine their relations within in a large CHR sample. Since the present investigations explore the relationship between psychotic-like symptoms and sleep in a CHR sample, which is comprised of individuals who are experiencing only prodromal level symptoms, the term 'positive prodromal symptoms' is used. The first study explores the associations between sleep disruption and positive prodromal symptoms at the participant's baseline assessment. This cross-sectional study is focused on attempting to replicate previous findings from CHR studies, as well as testing whether findings from general population samples and psychotic samples extend to this CHR sample. The second study utilizes longitudinal data from three time points to explore the associations between sleep problems and positive prodromal symptoms over time. This study is focused on characterizing the longitudinal relationships and testing the directionality of the sleep-positive prodromal symptom relationship (i.e., do sleep problems predict positive prodromal symptoms or vice versa).

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Cross-Sectional Associations Between Sleep Problems and Prodromal Symptoms in a Clinical High Risk Sample

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Cross-Sectional Associations Between Sleep Problems and Prodromal Symptoms in a Clinical High Risk Sample

Sleep problems are common in psychotic disorders with between 30 to 80% of patients with schizophrenia experiencing significant sleep disturbance (Cohrs, 2008). Further, there is evidence from chronic schizophrenia samples, that sleep disruption often precedes relapse (Benson, 2008). Two recent studies have found that sleep disturbance is also more common in those at clinical high risk (CHR) for psychosis compared to control participants (Poe et al., 2017; Lunsford-Avery et al., 2017). Both of these studies found that sleep disturbance was cross-sectionally associated with more severe positive prodromal symptoms (e.g., sub-clinical hallucinations, delusions, grandiosity), and findings from the Lunsford-Avery and colleagues (2017) study suggest that certain aspects of sleep disturbance may be associated with worsening prodromal symptoms over time. These findings all point to a possible role of sleep dysfunction in the pathophysiology of psychosis and highlight the need to better understand this relationship in samples at risk for developing a psychotic illness.

Previous research also suggests that sleep problems may be specifically associated with certain types of psychotic-like symptoms. For example, epidemiological surveys have found that a diagnosis of insomnia is associated with a five times greater risk of paranoid thoughts (e.g., “a group of people are plotting to harm me”), and a four to five times greater likelihood of transient hallucinatory experiences (e.g., “hearing name being called when no-one was around”) (Freeman et al., 2012). In addition, sleep deprivation studies using experimental and observational designs have also found an association between acute sleep loss and certain types of psychotic experiences in some people. For example, Hurdiel and colleagues (2014) observed ultra-marathon runners who maintained wakefulness for around 46 hours and found that 4 of the 17

participants experienced hallucinatory experiences during their sleep deprived state. Other experimental studies have found sleep deprivation to be associated with increased paranoid thoughts (Kahn-Greene et al., 2007) as well as perceptual distortions (Petrovsky et al., 2014). Thus it appears that sleep problems may be specifically associated with suspiciousness/paranoia and perceptual abnormalities/hallucinations, at least in general population studies. It is as yet unclear whether this type of specificity exists in psychotic or CHR samples.

In addition, several studies have attempted to identify mediators of the relationship between psychotic symptoms and sleep problems. A recent systematic review of the literature linking sleep dysfunction and psychotic experiences found that depression was the most consistently tested mediator and was frequently found to partially mediate the relationship between sleep dysfunction and psychotic experiences (Reeve, Sheaves & Freeman, 2015). Negative affect more generally (encompassing symptoms of depression and anxiety) features as an important variable in cognitive model of persecutory delusions (Freeman et al., 2002) and hallucinatory experiences (Waters et al., 2012). The mechanisms by which sleep, negative affect/depression, and psychotic symptoms are related remain unclear despite statistical evidence of their association. Thus, additional research examining this mediation relationship is necessary. Specifically, Lunsford-Avery & Mittal (2013) argue that use of schizophrenia-specific depression measures, such as the Calgary Depression Scale for Schizophrenia (Addington, Addington & Schissel, 1990), will be particularly helpful in understanding the relationship between sleep, depressive symptoms, and psychosis. It is relevant to note that depressive symptoms are common in CHR and psychotic patients with between 40 and 50% of CHR and schizophrenia patients also meeting criteria for a depressive disorder (Buckley, Miller, Lehrer & Castle, 2008). Thus the question of whether depression mediates the relationship between sleep

and psychotic symptoms is important as understanding the links between these variables could highlight the potential utility of targeting both sleep problems and depression in the treatment of CHR patients.

Despite several important findings from the two previously discussed CHR studies, most of the relationships in question with regard to sleep and psychotic symptoms have yet to be tested in a CHR sample. For example, are sleep problems associated with all positive prodromal symptoms, or are they more closely associated with specific types of prodromal psychotic symptoms (e.g., perceptual abnormalities vs. delusional ideas), as previously observed in general population studies? Does depression also mediate the relationship between sleep disturbance and positive prodromal symptoms in CHR samples? And although there is evidence that sleep problems may be associated with symptom worsening in CHR samples (Lunsford-Avery et al., 2017), do sleep problems in CHR samples actually predict higher likelihood of conversion to psychosis or worsening of prodromal symptoms at a later time point? These questions are addressed in the current study by using data from the North American Prodrome Longitudinal Study (NAPLS-II) project, which includes the largest sample of Clinical High Risk (CHR) participants to date.

Current Study

The aims of the current study are 1) to determine whether previous findings from other CHR studies are replicated in the NAPLS CHR sample, 2) to test whether depression acts as mediator between sleep problem and positive prodromal symptoms in this CHR sample, 3) to test whether certain positive prodromal symptoms are more specifically associated with sleep problems than others, and 4) to explore whether sleep disturbance predicts subsequent worsening

of prodromal psychotic symptoms and/or increased likelihood of later conversion to a psychotic illness. Based on previous research in CHR samples (i.e., Poe et al., 2017; Lunsford-Avery et al., 2017), we hypothesize that sleep disturbance will be more severe in the CHR group in comparison to the healthy control (HC) group. Further, based on the same aforementioned studies, we hypothesize that within the CHR group, the severity of sleep disturbance will be positively associated with the severity of positive prodromal symptoms at baseline. With regard to the specificity of sleep disturbance-positive prodromal symptom associations, we hypothesize that sleep disturbance will be more strongly associated with paranoia/suspiciousness and perceptual abnormalities in this CHR sample.

As the current study is cross-sectional in nature, we will assess the direct and indirect effects, rather than true meditational effects, which require longitudinal data. Based on previously discussed findings, we hypothesize that the indirect effect of sleep problems on positive prodromal symptoms through depressive symptoms will be significant in this analysis of a CHR sample. Finally, based on the Lunsford-Avery and colleagues (2017) finding that certain aspects of sleep disturbance predict worsening of psychotic symptoms over time, as well as theories that link sleep problems to worsening neuropsychiatric symptoms, we hypothesize that sleep disruption at the time of the baseline interview will predict later conversion to a psychotic disorder and/or will predict progression of the prodromal syndrome at a later time point. Poe and colleagues (2017) previously tested this hypothesis on a sample of 194 CHR participants and found that sleep disturbance did not predict conversion to psychotic illness at 2.5-year follow-up. However, as described previously, conversion to psychotic illness occurs at a relatively low frequency, even in an enriched CHR sample, thus the Poe and colleagues (2017) sample size of

194 may not have afforded adequate power to detect an association. Testing this hypothesis in the current sample of 740 CHR participants will provide greater power.

Methods

Participants

The sample for the present study is drawn from Clinical High Risk (CHR) and control participants, ages 12-30 years old, who met criteria for the NAPLS-II study. NAPLS CHR participants were either referred by health care providers, educators or social service agencies, or by self-referral in response to community announcements (i.e. presentations, postings, websites, and public advertisements). Control participants were recruited through community outreach and advertisements. Potential participants underwent a phone screen to preliminarily exclude anyone outside of the 12-30 year age range, as well as those with psychotic disorders, intellectual disability, or current substance dependence. A later in-person screening assessment was administered including a clinical assessment using the SCID-IV and SIPS measures to determine if potential participants met criteria for a CHR syndrome as well as other psychological disorders. Potential participants were further screened to exclude those with a history of a central nervous system disorder that may contribute to prodromal symptoms, those with a closed head injury that involved multiple signs of concussion, and those who have received treatment with antipsychotic medications for four or more weeks. Exclusion criteria for the HC group were the presence of any CHR syndrome, a family history of psychosis, a neurological disorder, or a serious head injury. All potential CHR participants were discussed on a weekly conference call with investigators from each of the NAPLS sites and only admitted into the study once consensus was reached. The current study utilized data from 740 CHR participants and 280 controls.

Assessments

The *Structured Interview for Prodromal Syndromes* (SIPS) (Miller et al., 1999) is a reliable and valid (Miller et al., 2003) semi-structured interview used to assess prodromal symptoms and determine if individuals meet the Criteria of Prodromal Syndromes. This interview is completed at the screening/baseline interview to determine if a participant meets these criteria and can be considered CHR status for our study. The interview is then repeated at each visit (6 months, 12 months, 18 months, 24 months) to assess the severity of prodromal symptoms at each time point and to determine the current clinical state of that participant. A six-point scale is used to rate individual positive symptoms and reflects severity, frequency, duration, and intensity/degree of conviction. Scores can range from zero to six, with zero to two reflecting what is considered to be normal/sub prodromal symptomatology, three to five indicating a prodromal level of symptomatology/CHR status, and scores of six suggesting the possibility of a psychotic level of severity. The semi-structured interview assesses five positive symptoms, six negative symptoms, four disorganized symptoms, and four general symptoms.

The *Index of Sleep Disturbance* was obtained from the general symptoms section of the SIPS, which contains one item (G1), which is concerned with sleep. The "Sleep Disturbance" item was used in the current study as the measure of sleep problems (see Table 1. for details). The Sleep Disturbance Item is rated from 0-6 based on the severity of the disturbance. The ratings are as follows: 0 – Absent/No sleep disturbance, 1 – Questionably Present (e.g., restless sleep), 2 – Mild (e.g., some difficulty falling asleep), 3 – Moderate (e.g., daytime fatigue due to difficulty sleeping), 4 – Moderately Severe (e.g., sleep pattern interfering with other aspects of functioning), 5 – Severe (e.g., day/night reversal and missing activities due to sleep problems), 6

– Extreme (e.g., unable to sleep for over 48 hours). Only positive prodromal symptom scores are used to determine CHR status and current clinical status, so scores on the sleep variable were not restricted by study design and thus vary across the entire scale.

The *Current Clinical State* of each participant is assessed at each visit after baseline (6 months, 12 months, 18 months, 24 months) using symptom ratings from the SIPS. CHR participants are classified either as 'prodromal stabilization' (i.e., scores between 3 and 5 on the SIPS positive symptoms with no recent changes in severity), 'prodromal progression' (i.e., scores between 3 and 5 on the SIPS positive symptoms with a recent increase in severity) 'converted' (i.e., currently meeting criteria for a psychotic disorder), or 'in remission' (i.e., scores of 2 or less on each of the SIPS positive symptoms). For the purposes of this study, the last available clinical state classification will be used as the outcome measure.

The *Calgary Depression Scale for Schizophrenia* – The CDSS (Addington, Addington & Maticka-Tyndale, 1993) was originally designed to measure depressive symptoms in patients with schizophrenia and shows good reliability and validity for measuring depressive symptoms in those at CHR of psychosis (Addington, Shah, Liu & Addington, 2014). It is administered by an experienced rater in the context of a clinical interview and assesses 9 symptoms of depression that are summed to create a total score indicating severity of depressive symptoms.

A *Medication Log* listing all the medications the participant has ever taken in their life was elicited at the baseline interview. For the purposes of the current study, the medications were classed into the following categories: antipsychotic, antidepressant, mood stabilizer, prescription stimulant, benzodiazepine, other/miscellaneous psychotropics, prescription sleep medications, prescription sleep/wake medications, and 'any psychotropic.' Participants were dummy coded as 1 for each class of medication that

they had ever taken, and 0 if they had never taken a medication from that particular class. Medication classes were allowed to overlap. For example, all antipsychotics and antidepressants were also included in the 'any psychotropic' medication class. In addition, many of the benzodiazepine medications are prescribed specifically for sleep problems. Those benzodiazepines that are considered first-line for sleep problems were therefore included both in the benzodiazepine group, as well as the "sleep medication" group. Only one participant reported taking a prescription sleep/wake medication (i.e., Provigil, which is prescribed for shift work-related sleep disorders and narcolepsy). This participant also reported taking prescription sleep medications and was therefore included in the 'prescription sleep medication' class. Since there was only 1 participant in the 'prescription sleep/wake medication' group, and this individual was already accounted for in the 'prescription sleep medication' group, the sleep/wake prescription medication class was dropped from analyses. The following is the full list of the medications considered to be prescription sleep medications for the purposes of this study: Ambien/Zolpidem, Estazolam/ProSom, Eszopiclone/Lunesta, Halcion/Triazolam, Sonata/Zaleplon, Temazepam/Restoril, Trazodone/Desyrel, Adapin/Doxepin. Only prescription sleep aides were included in the "prescription sleep medication" class and information about the use of non-prescription sleep aides (e.g., Tylenol PM), or over the counter medications often used as sleep aides (e.g., benedryl) was not included in this study. Stimulants were not classed as 'sleep/wake medications,' but were included in analyses as their own class (e.g., 'prescription stimulant medications').

Statistical Analyses

Group Differences and Regression Analyses

All analyses were performed using SPSS version 25. An ANCOVA was used to test for group (CHR versus HC) differences in sleep disturbance differences. All remaining analyses were performed on CHR participants only. Linear regression was used to test the prediction that, at baseline, severity of positive symptoms at baseline would be associated with severity of sleep disturbance. A MANOVA and follow-up ANOVAs were used to test which, if any, of the positive symptoms were significantly associated with sleep disturbance. Finally, an ANOVA was used to test whether any of the 4 outcome groups differed significantly on their baseline sleep disturbance. For this analysis, all participants were coded as belonging to just one of the 4 outcome groups (remission, prodromal stabilization, prodromal progression, and converted) using the last observation carried forward (LOCF) method.

Analyses of Direct and Indirect Effects

To address the question of indirect effects, analyses were performed using the Preacher and Hayes approach. The Hayes' PROCESS macro for SPSS (Hayes, 2013), which uses a nonparametric bootstrapping procedure to determine whether the coefficient of the indirect path is significant, was used in the current analyses. The level of confidence for all confidence intervals in this analysis was 95 and the number of bootstrap samples used to determine confidence intervals was 5000. When the confidence intervals of the indirect effect do not include zero, then the indirect effect is considered significant.

Results

Preliminary Analyses

Chi squared analyses comparing CHR and HC groups revealed significant differences in sex ratio (larger proportion of males in CHR versus control group), but no group differences in race or ethnicity. T-tests revealed significant differences in age between groups (CHR mean =

18.5 years, healthy controls mean = 19.7 years). See Table 2 for a summary of sample characteristics including demographics and mean symptom ratings for the CHR and control groups. Remaining analyses comparing CHR and control groups included age and sex as covariates.

In order to determine if medication status at baseline was related to the sleep variable (in the CHR participants), multiple independent samples T-tests were conducted. Results from the T-tests showed that there was no significant association between sleep disturbance and medication use of any kind, including sleep medications (see Table 3. for breakdown by medication status). Medication status was therefore not included as a covariate in remaining analyses. The lack of association between sleep disturbance and use of sleep medication likely indicates that the use of sleep medication is effective at reducing sleep disturbance.

Group Differences and Regression Analyses

An ANCOVA was performed (with age and sex as covariates) comparing CHR and control groups on the sleep variable (SIPS - G1). Results revealed a significant relationship between sleep disturbance and subject type [$F=339.383$, $p<0.001$], with CHR subjects having significantly more sleep disturbance than controls.

In order to test whether sleep disturbance in the CHR group is associated with more severe positive symptoms, a linear regression was performed with sleep disturbance as the independent variable and total positive symptom severity as the outcome variable. Results (Table 4) show that severity of sleep disturbance is significantly positively associated with total positive symptom severity. An additional MANOVA was performed to investigate whether CHR participants with clinically significant sleep disturbance (i.e., rated as a 3 or above on the SIPS) differed from those without clinically significant sleep disturbance in severity of the five positive

prodromal symptoms. Using Pillai's trace, the MANOVA revealed a significant relation of sleep disturbance with severity of positive prodromal symptoms [$F(5, 733)=5.029$, $p<0.01$]. Univariate analyses, presented in Table 5, revealed significant group differences in severity of suspiciousness/paranoia [$F(1,737)=9.512$, $p=0.002$), perceptual abnormalities/hallucinations [$F(1,737)=9.820$, $p=0.002$], and disorganized communication [$F(1,737)=4.551$, $p=0.033$], such that those with clinically significant sleep disturbance had more severe symptoms than those without significant sleep disturbance. No significant group differences were observed for the symptoms of unusual thought content/delusional ideas or grandiose ideas. An ANOVA comparing the 4 outcome groups (e.g., conversion, prodromal progression, symptomatic, remission) on baseline sleep disturbance revealed no significant differences by group [$F(1,6)=0.895$, $p=0.49$], indicating that sleep disturbance at baseline is not significantly associated with any outcome group (e.g., sleep disturbance at baseline is not significantly associated with later conversion to psychotic disorder).

Analyses of Direct and Indirect Effects

For each positive prodromal symptom that was significantly associated with sleep disturbance (e.g., suspiciousness, perceptual abnormalities, disorganized communication, and total positive symptoms), we tested whether the indirect effect through depression, as measured by the CDSS, was also significant. The indirect effect through depression was found to be a significant in only 1 of the 4 analyses. Specifically, the indirect effect through depression was only significant in the relationship between sleep disturbance and suspiciousness/persecutory ideas, but the indirect effect was not significant in the relationship of sleep disturbance with general positive symptoms, perceptual abnormalities/hallucinations, or disorganized

communication. As Figure 3. illustrates, for suspiciousness/persecutory ideas, the standardized regression coefficient between sleep disturbance and depression was significant, as was the regression coefficient between depression and suspiciousness/persecutory ideas. The standardized indirect effect was (.291)(.199) = .058. The significance of the indirect effect was tested using bootstrapping procedures in the PROCESS macro. The bootstrapped unstandardized indirect effect was .0558 and the 95% confidence interval ranged from .0332 to .0818, indicating that the indirect effect was statistically significant. For the remaining three indirect effect analyses (see Figures 4, 5, and 6), the regression coefficients between the proposed 'mediator' (i.e., depression) and the outcome variables (i.e., general positive symptoms, perceptual abnormalities, and disorganized communication) were not statistically significant. In addition, significance testing with bootstrapping procedures revealed 95% confidence intervals that included 0, indicating that the indirect effects for these remaining 3 models were not statistically significant.

Discussion

This study replicates previous cross-sectional findings indicating that clinical high-risk participants experience significantly more sleep disturbance than healthy controls, and that the severity of sleep disturbance is positively associated with concurrent severity of positive symptoms. Further, this is the first CHR study to test specifically which types of positive symptoms are significantly related to sleep disturbance. The results indicate that, in this CHR sample, sleep disturbance is only associated with increases in suspiciousness (precursor of paranoia), perceptual abnormalities (precursor of hallucinations), and disorganized speech (indicator/precursor of thought disorder). This is consistent with the prediction based largely on studies of sleep disturbance and psychotic-like symptoms in general/healthy populations.

Although we did not originally hypothesize that disorganized speech would be specifically associated with sleep disturbance, one experimental study on healthy participants conducted by Petrovsky and colleagues (2014) found that both perceptual distortions and cognitive disorganization were elicited by sleep deprivation. This finding is consistent with our current finding that sleep disturbance is associated with disorganized speech (an indicator/precursor of thought disorder). Thus, it appears that the same pattern of association between sleep disturbance and psychotic-like symptom is observed in both CHR individuals and healthy participants under conditions of sleep deprivation.

Another noteworthy finding from the current study was that depression, or depressive symptoms, did not significantly 'mediate' the cross-sectional relationship between sleep disturbance and general positive symptom severity. This result was counter to our original hypothesis and appeared to contradict some previous findings. For example, a systematic review of the literature linking sleep dysfunction and psychotic experiences found that depression was the most consistently tested mediator and was frequently found to partially mediate the relationship between sleep dysfunction and psychotic experiences (Reeve, Sheaves & Freeman, 2015). However, in the current study, when analyses of indirect effects were performed on the subtypes of positive psychotic-like symptoms, it became apparent that the indirect effect through depression/depressive symptoms was only significant in the relationship between sleep disturbance and suspiciousness, but it was not significant in the relationships between sleep disturbance and other psychotic symptoms (i.e., perceptual abnormalities, disorganized speech). This finding fits with the cognitive model of persecutory delusions, which posits that certain cognitive biases, often present in those with depression and anxiety, may predispose someone to select a threatening/suspicious explanation for neutral experiences (Freeman et al., 2002). Thus,

if sleep disturbance increases depressive/anxious cognitive biases (as suggested in various studies including Gobin, Banks, Fins & Tartar, 2015 and Alfano, Zakem, Costa, Taylor & Weems, 2009), then suspiciousness/paranoid symptoms will also increase in severity. An increase in suspiciousness would, in turn, be expected to result in a state of hypervigilance which would be expected to interfere with sleep. The specifics of this particular mediation model require further empirical testing with longitudinal data.

Our final hypothesis that worse sleep disturbance at baseline would predict later worsening of prodromal syndrome and/or conversion to psychotic disorder was not supported by results from this study. In fact, none of the outcome groups (i.e., conversion, prodromal progression, symptomatic, remission) differed in severity of baseline sleep disturbance. It is possible that this finding is due to the temporal lag between the baseline assessment of sleep and the subsequent designation of clinical outcome, which can have a duration of up to two years. The adverse effects of sleep disturbance on clinical status may be more proximal. Thus, it may be that sleep problems are related to psychotic symptom severity only contemporaneously, but are not predictive of continued worsening of symptoms over time. There are examples in the experimental sleep literature showing that acute sleep deprivation may be associated with transient psychotic symptoms in a state-dependent way, such that psychotic-like symptoms are only present during the night of deprived sleep and dissipate during the day, or when recovery sleep is allowed (van Heugten-van der Kloet, Giesbrecht, & Merckelbach, 2015). The chronicity of sleep problems may also be an important factor to explore. For example, the neurological impact of a few bouts of insomnia over a lifetime may be negligible in comparison to long-term chronic insomnia. Chronicity of sleep problems was not assessed in this study, but may be an important factor to consider when investigating the potential role of sleep problems in psychotic

symptom exacerbation over time. Additional longitudinal analyses of sleep and psychotic symptoms over time will be important to more fully understand the role of sleep problems in the development of psychotic disorders and the directionality of the sleep problem-psychotic symptom relationship over time.

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Appendix A: Manuscript 1 Tables & Figures

Table 1. G1 SIPS Sleep Disturbance Symptom, based on the SIPS (Miller et al., 1999)

Symptom Scale	*Descriptive Anchors**
0 (Absent)	
1 (Questionably Present)	Restless sleep.
2 (Mild)	Some mild difficulty falling asleep or getting back to sleep.
3 (Moderate)	Daytime fatigue resulting from difficulty falling asleep at night or early awakening. Sleeping more than considered average.
4 (Moderately Severe)	Sleep pattern significantly disrupted and has intruded on other aspects of functioning (e.g. trouble getting up for school or work). Difficult to awaken for appointments. Spending a large part of the day asleep.
5 (Severe)	Significant difficult falling asleep or awakening early on most nights. May have day/night reversal. Usually not getting to scheduled activities at all.
6 (Extreme)	Unable to sleep at all for over 48 hours.

*Anchors in each scale are intended to provide guidelines and examples of signs for every symptom observed. It is not necessary to meet every criterion in any one anchor to assign a particular rating. Basis for ratings includes both interviewer observations and patient reports.

Table 2. Sample Characteristics

	CHR	Control
N	740	280
*Age, years (mean ± SD)***	18.5 (± 4.26)	19.7 (± 4.67)
*Sex, n (%)**		
Males	424 (57.3%)	141 (50.4%)
Females	316 (42.7%)	139 (49.6%)
Race, n (%)		
White	426 (57.6%)	152 (54.3%)
Black	111 (15%)	49 (17.5%)
Interracial	94 (12.7%)	29 (10.4%)
Central/South American	32 (4.3%)	13 (4.6%)
East Asian	19 (2.6%)	15 (5.4%)
South Asian	20 (2.7%)	8 (2.9%)
Southeast Asian	15 (2.0%)	7 (2.5%)
First Nations	13 (1.8%)	4 (1.4%)
West/Central Asia and Middle East	6 (0.8%)	2 (0.7%)
Native Hawaiian or Pacific Islander	3 (0.4%)	1 (0.4%)
Ethnicity (Hispanic/Lantinx), n (%)	136 (18.4%)	50 (17.9%)
*Positive Symptoms, mean (SD)***	11.86 (3.832)	1.07 (1.67)
*Negative Symptoms, mean (SD)***	11.89 (6.067)	1.46 (2.23)
*Sleep Disturbance, mean (SD)***	2.31 (1.568)	0.48 (.904)

Percentages add up to > 100% because one participant can score multiple items.
* $p < .05$ ** $p < .01$

Table 3. Results of T-tests comparing sleep disturbance rating in CHR participants with and without medication use reported at baseline

Type of Medication	Mean Sleep Disturbance Rating		*t-value*	*df*	*p-value*
	Medication Use	No medication use			
Sleep Medication	2.63	2.29	-1.359	738	.174
Antipsychotic	2.20	2.36	1.239	738	.216
Antidepressant	2.39	2.25	-1.192	738	.234
Mood Stabilizer	2.26	2.32	.302	738	.763
Stimulant	2.20	2.34	1.015	738	.311
Benzodiazepine	2.58	2.27	-1.778	738	.076
Any Psychotropic	2.32	2.29	-.287	738	.774

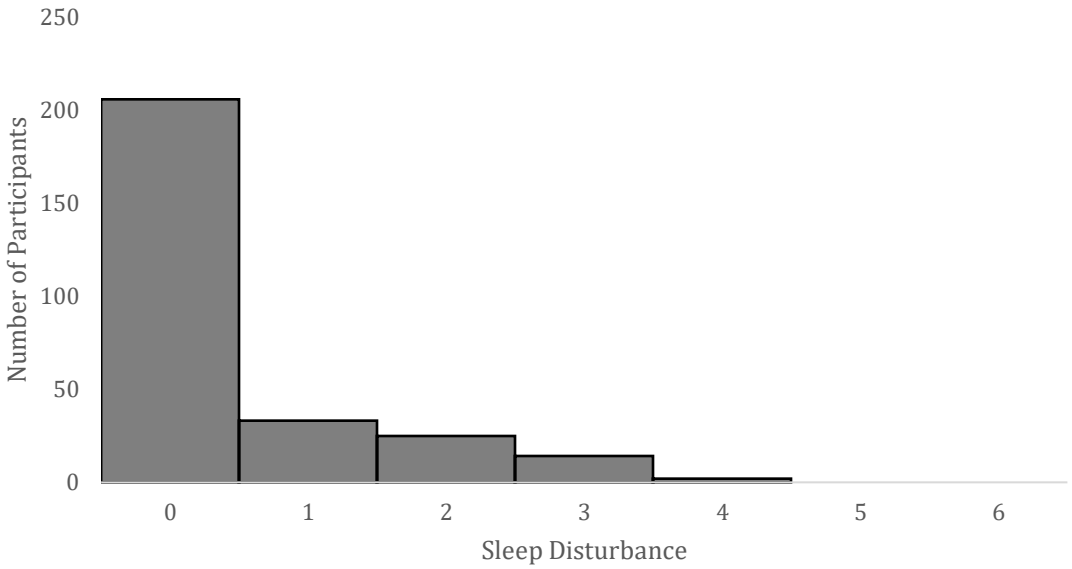

Figure 1. Count data showing the distribution of healthy control participants across each level of sleep disturbance (0 = no sleep disturbance, 6 = extreme sleep disturbance)

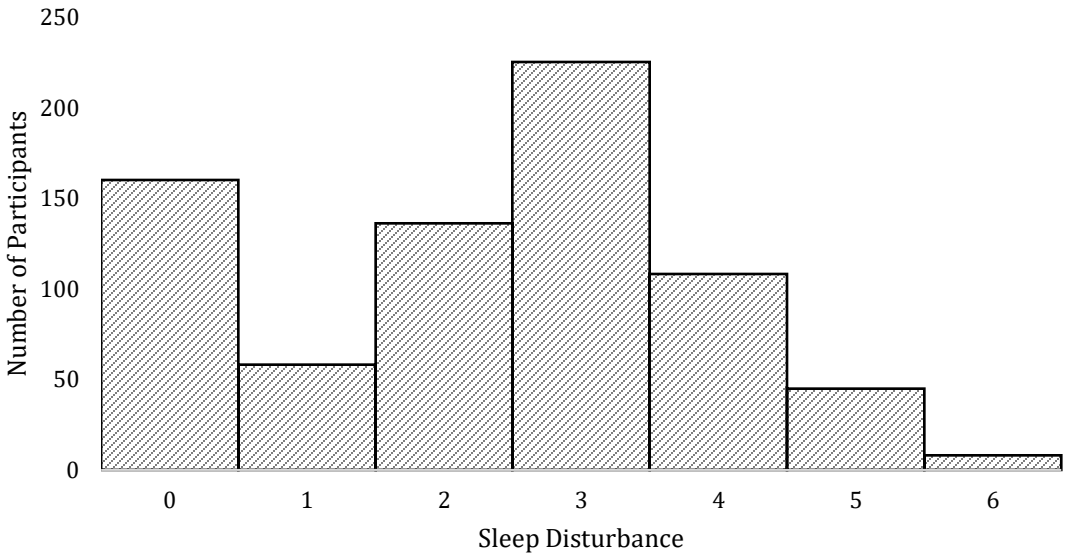

Figure 2. Count data showing the distribution of Clinical High Risk participants across each level of sleep disturbance (0 = no sleep disturbance, 6 = extreme sleep disturbance

Table 4. Summary of Linear Regression Analysis for Overall Positive Symptom Severity

Variable	B	SE (B)	Beta	R^2	t	p-value
Sleep disturbance	0.409	0.089	0.167	0.028	4.601	0.000005

Table 5. Summary of Univariate Analyses for Positive Prodromal Symptoms

Symptom	*df*	Mean Square	*F*	p-value	Group Mean (Sleep Disturbance)	Group Mean (No Sleep Disturbance)
Unusual Thought Content/Delusional Ideas	1,737	4.349	2.469	.117	3.41	3.25
Suspiciousness/Persecutory Ideas	1,737	21.396	9.512	.002	2.92	2.58
Grandiose Ideas	1,737	1.345	.798	.372	.94	1.03
Perceptual Abnormalities/Hallucinations	1,737	22.147	9.820	.002	3.24	2.89
Disorganized Communication	1,737	9.711	4.551	.033	1.83	1.60

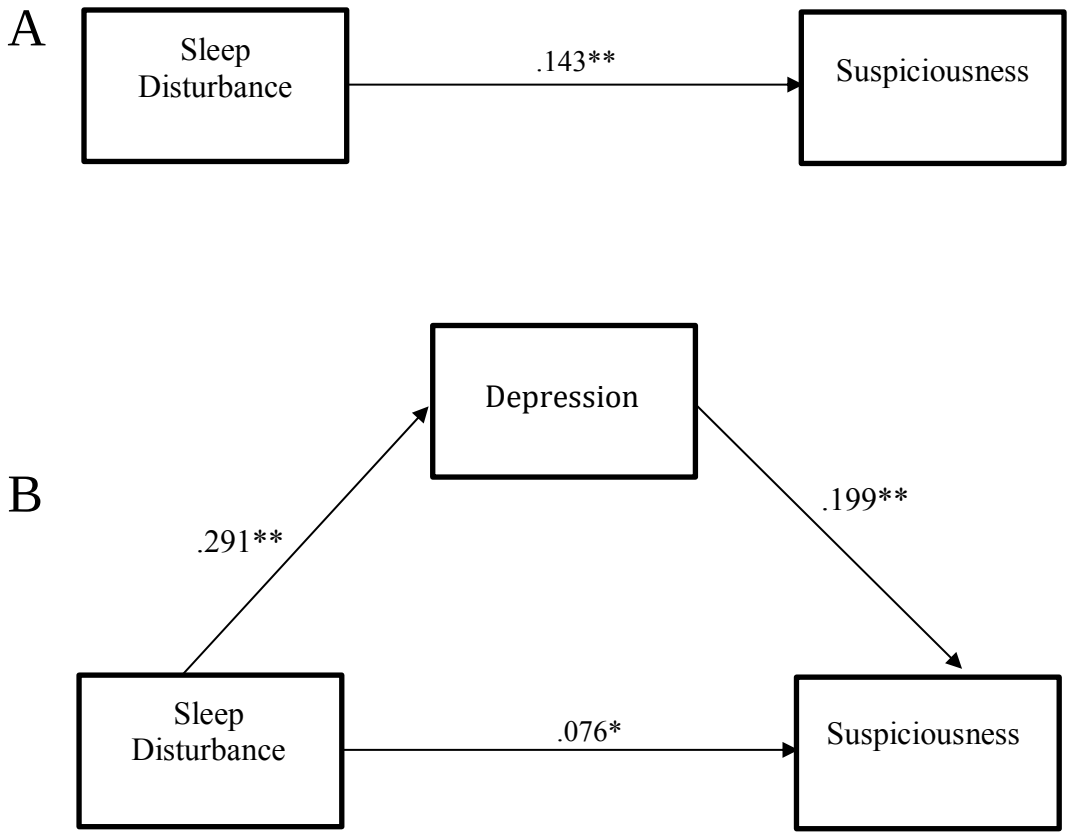

Figure 3. Standardized regression coefficients for the direct effect between sleep disturbance and suspiciousness without depression (A) and indirect effect between sleep disturbance and suspiciousness through depression (B). The indirect effect was statistically significant (Unstandardized indirect effect: b = .0558, 95% CI [.0332, .0818]). *p<.05, **p<.01

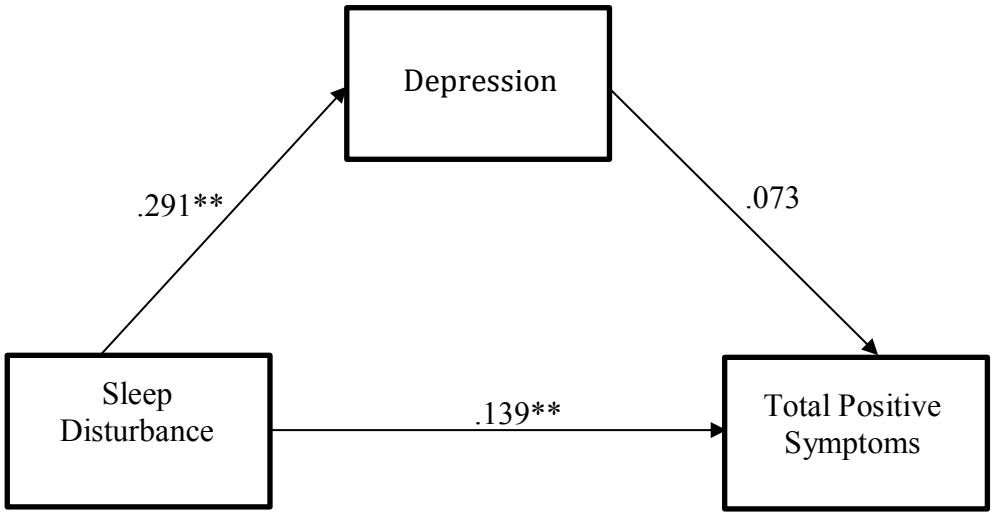

Figure 4. Standardized regression coefficients for the relationship between sleep disturbance and total positive symptoms. The indirect effect through depression was not significant (Unstandardized indirect effect: b = .05, 95% CI [-.0019, .1092]). *p< .05, **p<.01

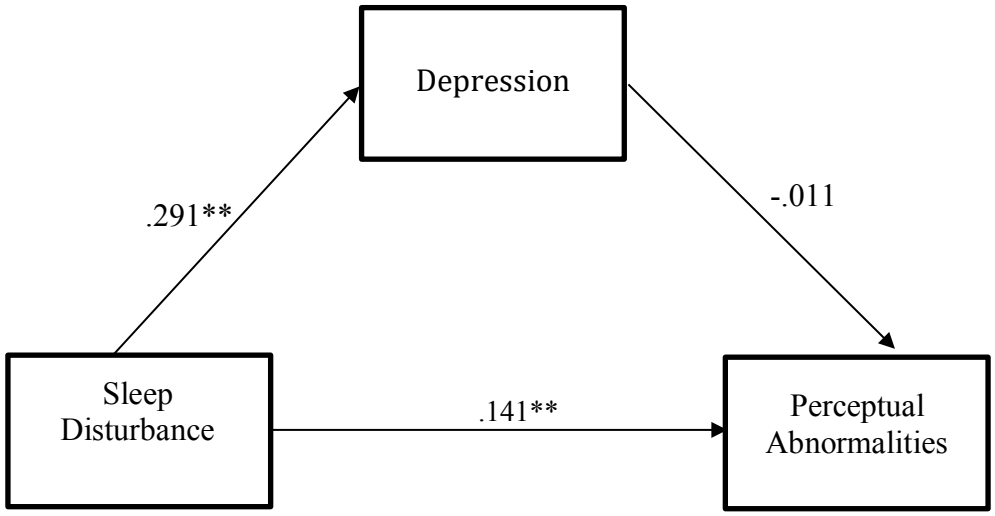

Figure 5. Standardized regression coefficients for the relationship between sleep disturbance and perceptual abnormalities. The indirect effect through depression was not significant (Unstandardized indirect effect: b = -.0031, 95% CI [-.0267, .0196]). *p< .05, **p<.01

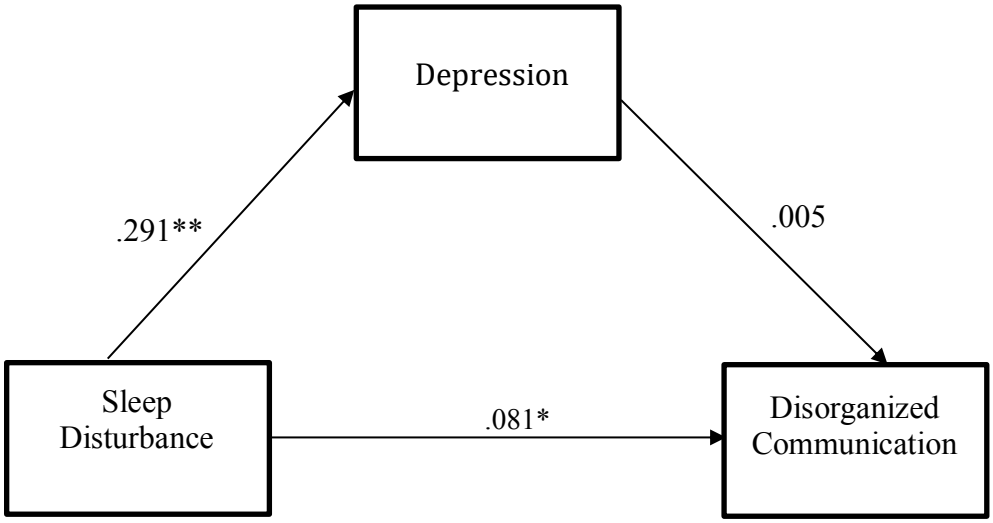

Figure 6. Standardized regression coefficients for the relationship between sleep disturbance and disorganized communication. The indirect effect through depression was not significant (Unstandardized indirect effect: b = .0013, 95% CI [-.0195, .0228]). *p< .05, **p<.01

Longitudinal Associations Between Sleep Problems and Prodromal Symptoms in a Clinical High Risk Sample

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Longitudinal Relationships Between Sleep Problems and Prodromal Symptoms in a Clinical High Risk Sample

Sleep problems are common in individuals with psychotic disorders (for reviews see Cohrs, 2008; Monti & Monti, 2005) as well as those at clinical high risk (CHR) of developing psychotic disorders (Lunsford-Avery et al., 2017; Poe et al., 2017). In line with a recent focus on sleep dysfunction as a potentially modifiable risk factor for various physical and mental health issues, researchers have begun to question whether sleep problems may contribute to the development or worsening of psychotic symptoms over time. In fact, Lunsford-Avery & Mittal (2013) have developed a neurodevelopmental diathesis-stress conception of sleep dysfunction in which they posit that, in the context of constitutional vulnerability to psychosis, sleep dysfunction will interact with various other risk factors (e.g., biological and psychosocial stress, cognitive dysfunction) to increase the risk of developing a psychotic disorder. Much of the evidence cited in support of this causal relationship actually comes from cross-sectional studies, which repeatedly show associations between sleep and psychotic symptoms in various populations (e.g., psychotic samples, high risk samples, and general population samples) (see Reeve, Sheaves, & Freeman 2015 for a review of this literature).

Although limited, there are also some examples of longitudinal investigations of the relationship between sleep problems and psychotic symptoms. Most of these come from studies of the general (non-clinical) population. For example, Freeman and colleagues (2012) found that insomnia in the general population predicted new paranoid thinking at 18-month follow-up. A separate study by Freeman and colleagues (2013) also found that insomnia was a significant predictor of paranoid thoughts 6 months later. Another general population study by Sheaves and colleagues (2016) found that insomnia was associated with new hallucinatory experiences at 18-

month follow-up. These findings support Lunsford-Avery & Mittal's general theory that sleep problems may have a causal impact on later worsening of psychotic symptoms.

However, there are several limitations to the previous longitudinal studies of sleep and psychotic symptoms that are important to discuss. Firstly, no studies to date have used data from more than two time points. As a result, the process of longitudinal change cannot be explored. Secondly, the previously discussed studies have assumed a unidirectional relationship, and only tested sleep as a predictor of current or future psychotic symptoms. None have tested psychotic symptoms as a predictor of subsequent sleep problems, or the potential of a bidirectional relationship between sleep and psychotic symptoms. Reeve and colleagues (2015) point this out as weakness of the longitudinal investigations to date and mention that these studies lacked the statistical power to test the reverse association.

The most compelling evidence for a causal association between sleep problems and psychotic symptoms comes from a few experimental studies of sleep deprivation in healthy participants. Kahn-Greene and colleagues (2007) found that acute sleep deprivation was associated with an increase in paranoia, while other studies found that sleep deprivation was associated with an increase in perceptual abnormalities/hallucinatory experiences (Petrovsky et al., 2014, Hurdiel et al., 2014). Overall, these studies strongly suggest a causal relationship between sleep problems and later development of psychotic symptoms. However, because these experimental studies were conducted on small samples of healthy samples, statistical power was limited, and it has not been shown that the findings generalize to those with psychotic disorders or at increased risk for psychotic disorders. Further, the "psychotic-like" symptoms measured in these studies were mild and assumed to be transient; there were no reports of individuals experiencing persistent psychotic-like symptoms, or developing a psychotic illness, as a result of the sleep deprivation.

Thus, while these studies point to a causal effect of sleep problems on emergence of transient, psychotic-like symptoms, they do not provide information about whether sleep problems contribute to the emergence of a prodromal state or psychotic illness.

The Current Study

The current study characterizes the longitudinal association of sleep dysfunction and positive prodromal symptoms in a large CHR sample. Studying this association in a CHR sample, which is enriched for individuals in the prodromal period preceding psychosis, will allow a better understanding of how sleep problems may contribute to worsening prodromal symptoms and/or psychotic illness. Further, utilizing data from three time points allows the opportunity to explore nuances of the longitudinal change process. Finally, the uniquely large sample size of this study also allows for more statistical power to test for bidirectional relationships between sleep and positive prodromal symptoms over time. As noted above, this has not been examined to date, and the present study will apply a rigorous test of the directionality of the relationships across time. Based on past findings, as well as theories of the adverse effects of sleep disturbance, it is predicted that problems with sleep will contribute to an increase in positive symptom severity.

Methods

Sample

The sample for the present study is drawn from Clinical High Risk (CHR) and control participants, ages 12-30 years old, who met criteria for the NAPLS-II study. NAPLS CHR participants were either referred by health care providers, educators or social service agencies, or by self-referral in response to community announcements (i.e. presentations, postings, websites, and public advertisements). Potential participants underwent a phone screen to preliminarily

exclude anyone outside of the 12-30 year age range, as well as those with psychotic disorders, intellectual disability, or current substance dependence. A later in-person screening assessment was administered including a clinical assessment using the SCID-IV and SIPS measures to determine if potential participants met criteria for a CHR syndrome as well as other psychological disorders. Potential participants were further screened to exclude those with a history of a central nervous system disorder that may contribute to prodromal symptoms, those with a closed head injury that involved multiple signs of concussion, and those who have received treatment with antipsychotic medications for four or more weeks. All potential CHR participants were discussed on a weekly conference call with investigators from each of the NAPLS sites and only admitted into the study once consensus was reached. Data for prodromal symptoms was available for 763 participants at baseline (Time 1), 511 participants at 6-month follow-up (Time 2), and 413 participants at 12-month follow-up (Time 3). A previous NAPLS investigation found that CHR individuals who dropped out of the study prior to completion did not differ from those who completed the study in terms of any clinical (e.g., positive symptom severity), functional, or demographic factors (Stowkowy et al., 2018).

Assessments

The *Structured Interview for Prodromal Syndromes* (SIPS) (Miller et al., 1999) is a reliable and valid (Miller et al., 2003) semi-structured interview used to assess prodromal symptoms and determine if individuals meet the Criteria of Prodromal Syndromes. This interview is completed at the screening/baseline interview to determine if a participant meets these criteria and can be considered CHR status for our study. The interview is also completed at other follow-up appointments. A six-point scale is used to rate individual positive symptoms and reflects severity, frequency, duration, and intensity/degree of conviction. Scores can range from

zero to six, with zero to two reflecting what is considered to be normal/sub prodromal symptomatology, three to five indicating a prodromal level of symptomatology/CHR status, and scores of six suggesting the possibility of a psychotic level of severity. The semi-structured interview assesses five positive symptoms, six negative symptoms, four disorganized symptoms, and four general symptoms. The five positive prodromal symptoms assessed in the SIPS are: Unusual Thought Content/Delusional Ideas (P1), Suspiciousness/Paranoia (P2), Grandiose Ideas (P3), Perceptual Abnormalities/Hallucinations (P4), and Disorganized Speech (P5). For the purpose of the current analyses, the 5 positive prodromal symptoms were combined into a 5-symptom composite (PosTotal), as well as a 2-symptom composite of just Suspiciousness/Paranoia (P2) and Perceptual Abnormalities/Hallucinations (P4), weighted equally. This second Paranoia/Hallucinations (Par/Hal) composite made of only P2 and P4 was created due to previous findings that sleep problems were specifically associated with the psychotic-like symptoms of paranoia and hallucinations in general populations (Reeve, Sheaves & Freeman, 2015) as well as in this CHR sample (Goines et al., Unpublished Manuscript). Since this knowledge comes only from cross-sectional studies, it is unclear if the specificity applies to longitudinal associations as well, so both composites were used separately in all analyses in the current study.

The *Index of Sleep Disturbance* was obtained from the general symptoms section of the SIPS, which contains one item (G1), which is concerned with sleep. The "Sleep Disturbance" item was used in the current study as the measure of sleep problems. As with all SIPS symptoms, the Sleep Disturbance Item is rated from 0-6 based on the severity of the disturbance. The ratings are as follows: 0 – Absent/No sleep disturbance, 1 – Questionably Present (e.g., restless sleep), 2 – Mild (e.g., some difficulty falling asleep), 3 – Moderate (e.g., daytime fatigue due to difficulty

sleeping), 4 – Moderately Severe (e.g., sleep pattern interfering with other aspects of functioning), 5 – Severe (e.g., day/night reversal and missing activities due to sleep problems), 6 – Extreme (e.g., unable to sleep for over 48 hours). The full SIPS is administered at baseline, 6 months follow-up, 12 months follow-up, 18 months follow-up, and 24 months follow-up. For the current study, data was used from three different time points Baseline (Time 1), 6 months follow-up (Time 2), and 12 months follow-up (Time 3).

A *Medication Log* listing all the medications the participant has ever taken in their life was elicited at the baseline interview. For the purposes of the current study, the medications were classed into the following categories: antipsychotic, antidepressant, mood stabilizer, prescription stimulant, benzodiazepine, other/miscellaneous psychotropics, prescription sleep medications, prescription sleep/wake medications, and 'any psychotropic.' Participants were dummy coded as 1 for each class of medication that they had ever taken, and 0 if they had never taken a medication from that particular class. Medication classes were allowed to overlap. For example, all antipsychotics and antidepressants were also included in the 'any psychotropic' medication class. In addition, many of the benzodiazepine medications are prescribed specifically for sleep problems. Those benzodiazepines that are considered first-line for sleep problems were therefore included both in the benzodiazepine group, as well as the "sleep medication" group. Only one participant reported taking a prescription sleep/wake medication (i.e., Provigil, which is prescribed for shift work-related sleep disorders and narcolepsy). This participant also reported taking prescription sleep medications and was therefore included in the 'prescription sleep medication' class. Since there was only 1 participant in the 'prescription sleep/wake medication' group, and this individual was already accounted for in the

'prescription sleep medication' group, the sleep/wake prescription medication class was dropped from analyses. The following is the full list of the medications considered to be prescription sleep medications for the purposes of this study: Ambien/Zolpidem, Estazolam/ProSom, Eszopiclone/Lunesta, Halcion/Triazolam, Sonata/Zaleplon, Temazepam/Restoril, Trazodone/Desyrel, Adapin/Doxepin. Only prescription sleep aides were included in the "prescription sleep medication" class and information about the use of non-prescription sleep aides (e.g., Tylenol PM), or over the counter medications often used as sleep aides (e.g., benedryl) was not included in this study. Stimulants were not classed as 'sleep/wake medications,' but were included in analyses as their own class (e.g., 'prescription stimulant medications').

Analyses

An autoregressive panel model and a latent growth model were both fit to the data using Structural Equation Modeling (SEM) and the Mplus statistical software package. Full Information Maximum Likelihood (FIML) treatment was used for missing data for both models. This is a missing data estimation approach for structural equation modeling which has been shown to produce unbiased parameter estimates and standard errors by estimating a likelihood function for each case based on the available data so that all cases are included. An autoregressive panel model (see Figure 1 in appendix) allows for estimation of the impact of one variable (e.g., sleep at time 1) on another variable (psychotic symptoms at time 2), while controlling for the prior level of the construct being predicted (i.e., controlling for psychotic symptoms at time 1). The addition of the autoregressive effect (AR1) in the model allows one to rule-out the possibility that any cross-lagged effect (CL) is simply due to the fact that the two variables were correlated at time 1. This results in more conservative estimations of the potential

cross-lagged effect that minimizes bias (Cole & Maxwell, 2003). Other paths can also be added to the model including a second-order autoregressive effect (AR2). In Figure 1, the curved arrow between both variables at Time 1 represents a correlation (Corr.). At later time points, the curved arrows represent residual correlations (Res. Corr.), which accounts for the residual variance after the effects of prior time points are estimated.

Although there are many advantages to using an autoregressive panel model to investigate longitudinal relationships between variables, there are also limitations to this type of model, such as the assumption of linear change, lack of focus on intra-individual variability, and its lack of theory and ability to show how change occurs (Selig & Little, 2012). Latent growth models have been suggested as alternatives that benefit from taking these issues into account (Rogosa, 1987). Since there is a lack of longitudinal research in this area and therefore no strong theories of longitudinal change process, either model could be appropriate. Thus, both models were used and then evaluated for fit. See Figure 2 in appendix for the full growth curve model used in these analyses.

Order of Analyses

First, both the full autoregressive panel model and the growth curve model were evaluated for fit using the absolute fit index, Root Mean Square Error of Approximation (RMSEA) (Steiger, 1990). Although the growth curve model and the autoregressive panel model contained the same variables, the relationships estimated between the variables were different. The growth curve and autoregressive panel model could therefore not be directly compared to each other. Each individual model was evaluated for how well it fits the data using the suggested RMSEA fit criteria such that RMSEA values lower than .08 indicated acceptable fit, and values below .05 indicated good/close fit (Browne & Cudeck 1992, 1993; Little, 2013). Confidence

intervals (90%) around the RMSEA were also evaluated. We evaluated models using the overall 5-P symptom composite (PosTotal) before evaluating models using the composite of symptoms more theoretically related to sleep (Par/Hal).

After the best fitting full model was selected to represent the longitudinal relationships, post-hoc modifications (e.g., dropping non-significant paths) were applied to the full models resulting in nested models. Nested models were then compared using the -2log likelihood estimates, distributed as a χ^2 square with degrees of freedom. Changes in comparative fit indices of the Akaike Information Criterion (AIC) (Akaike, 1987) and the Sample Size Adjusted Bayesian Information Criterion (SABIC) (Enders & Tofighi, 2008) (where lower AIC and SABIC indicate more parsimonious/better fitting models), as well as the comparative fit index (CFI) (Bentler, 1990) and the Tucker-Lewis index (TLI) [where CFI and TLI values above 0.90 to 0.95 indicate a good fit to the data (Hooper, Coughlan, & Mullen, 2008)] were also used to compare the fit of nested models.

Finally, the effects of potential covariates, age, sex, and psychotropic medication use were explored. Previous literature indicates that both age and sex may have specific impacts on both psychotic symptoms (e.g., younger CHR participants show more severe prodromal symptoms than older ones, females and males typically report differences in type of prodromal symptoms experienced) and sleep problems (e.g., sleep changes over normatively over development, females in the general population report more sleep disturbance than males). Thus, rather than control for age, sex, and medication use by including them as covariates in the models, which may result in "over control" that obscures meaningful associations between variables of interest, the decision was made to dichotomize each possible covariate and run the best fitting model separately for each group. Thus, the model was run separately by sex (males

and females), by each age group (i.e., 18 yrs. old and above, under 18 yrs.), and by psychotropic medication use at baseline (medication use and no use). The dichotomization of age groups at 18 years of age is based on previous research in CHR samples showing that this grouping reveals meaningful differences in brain developmental processes (Chung et al., in press).

Results

Preliminary Analyses & Covariates

Independent t-tests comparing males to females revealed no significant sex differences in positive prodromal symptoms (PosTotal) or sleep disturbance at any time point. The same analyses repeated with the Par/Hal composite revealed significant sex differences only on Par/HalT1 ($p=0.0003$), such that females showed significantly higher mean symptom severity than males. Bivariate correlations between age and the variables under investigation (i.e., sleep disturbance and positive prodromal symptoms) were calculated. Statistically significant correlations were observed only for PosTotal at Time 1 and age ($r=0.107$, $p=0.003$), such that age was positively correlated with symptom severity. These results suggest that age and sex may have impacts on the relationship between sleep and positive prodromal symptoms and thus both variables were explored as potential covariates. Correlations between sleep problems at time 1, time 2, and time 3, with positive symptoms at time 1, time 2, and time 3 reveal that positive symptoms and sleep problems are positively correlated across all time points, with those at closer time points showing stronger correlations (see Table 1 and Table 2). Both the total positive symptoms composite and the paranoia/hallucination composite show similar patterns of correlations with sleep that suggest linear associations over time. Thus, a linear autoregressive

panel model and a linear latent growth curve model were fitted to the data and assessed for best fit.

Evaluating Fit of Autoregressive Model and Growth Curve Model

Total positive symptom score composite (PosTotal): According to the previously mentioned criteria, neither the full autoregressive panel model using the PosTotal composite, nor the full growth curve model using the PosTotal composite achieved acceptable fit to the data, although the autoregressive panel model came close with an RMSEA of .083. See Table 3 for summary of the relevant fit statistics.

Paranoia/hallucinations composite (Par/Hal): A similar pattern was observed when evaluating fit of the autoregressive and growth curve models using the Par/Hal composite. In this case, the autoregressive panel model reached acceptable fit to the data (RMSEA = 0.075), but the growth curve model (RMSEA = 0.130) continued to show poor fit. Thus, the autoregressive panel model using the Par/Hal composite was selected as the better representation of the sleep-psychotic symptom relationship over time. See Table 3 for summary of the relevant fit statistics.

Table 3. Fit Statistics of Autoregressive Panel Models and Growth Curve Models

	-2LL	*df*	RMSEA	RMSEA 90% CI	AIC	SABIC	CFI	TLI
Full Autoregressive Panel Model (PosTotal)	24.879	4	0.083	.053;.115	15195.228	15228.880	0.969	0.890
Growth Curve Model (PosTotal)	114.986	7	0.142	.120;.166	15279.335	15308.598	0.842	0.662
Full Autoregressive Panel Model (Par/Hal)	21.123	4	0.075	.045;.108	13219.817	13253.523	0.974	0.910
Growth Curve Model (Par/Hal)	96.970	7	0.130	.108;.153	13289.718	13318.981	0.871	0.723

To further explore the relationship of sleep and positive prodromal symptoms over time, post-hoc modifications were applied to the model and changes in fit statistics were evaluated for these various modifications. The model using Par/Hal was the only model that achieved adequate fit to the data and was selected a priori based on previous research specifically focused on sleep problems and psychotic symptoms. However, the PosTotal composite is often used in CHR studies, thus further exploration was completed on models using both the usual 5-P symptom composite (PosTotal) and our more specific 2-Psymptom composite (Par/Hal).

Comparing Autoregressive Panel Model Modifications

Total positive symptom score composite (PosTotal):

Model A2 is the same as model A1, except with model A1's 3 non-significant paths removed (i.e., the SleepT1-PosTotalT2 path, SleepT2-PosTotalT3 path, and PosTotalT2-SleepT3 paths were removed). Thus model A1 and model A2 stand in nested sequence and can be compared directly and the difference can be tested using the χ^2 difference test.

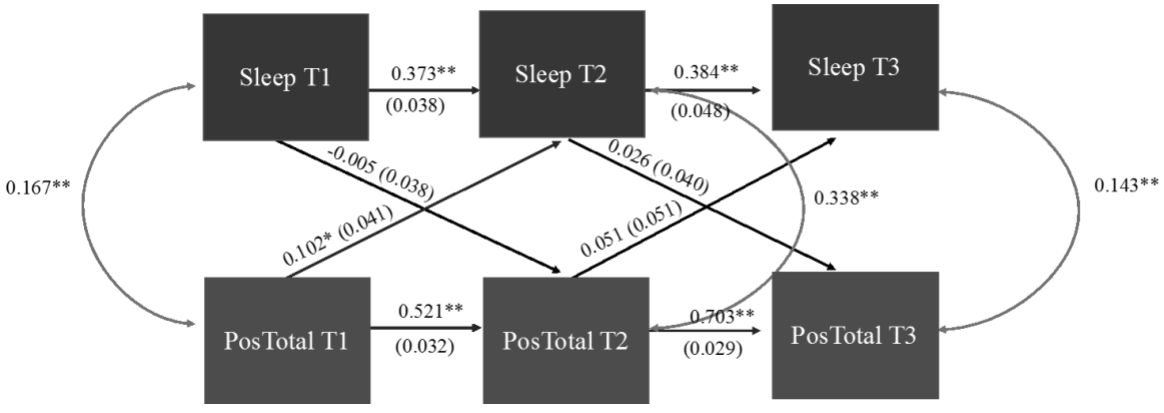

Figure 3. Model A1 including standardized path loadings (with standard error) using 5-P symptom composite (PosTotal). *p<0.05, **p<0.01

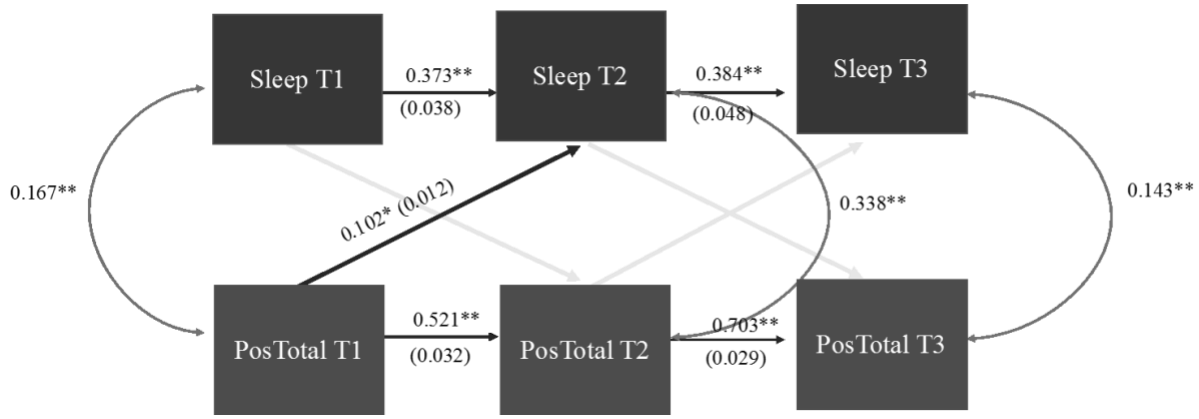

Figure 4. Model A2 including standardized path loadings (with standard error) using 5-P symptom composite

	-2LL	*df*	$\Delta\chi^2$*	Δdf*	RMSEA	RMSEA 90% CI	AIC	SABIC	CFI	TLI
A1) PosTotal Full Panel Model	24.879	4			0.083	.053;.115	15195.228	15228.880	0.969	0.890
A2) PosTotal non-significant paths dropped	26.454	7	1.575	3	0.060	.037;.086	15190.803	15220.065	0.971	0.942

(PosTotal). *p<0.05, **p<0.01

Table 4. Fit Statistics Comparing Model A1 and A2
*in comparison to nested model above

When comparing model A2 to model A1, the change in χ^2 was 1.573 with a change of 3 degrees of freedom. This observed χ^2 was less than the critical value for 3 degrees of freedom (7.815), thus model A1 and model A2 are not significantly different. Since there is no significant difference between the models, the model A2 is selected above A1, because model A2 is the more parsimonious model (i.e., fewer parameters estimated). The remaining fit statistics (AIC, SABIC, CFI, and TLI) all showed better fit for model A2 (See Table 4). As seen in Figure 4 above, the better fitting model A2 shows that positive prodromal symptoms at baseline are a significant predictor of sleep problems at time 2. However, sleep problems at baseline are not predictive of positive symptoms at time 2, nor are sleep problems at time 2 predictive

of positive symptoms at time 3.

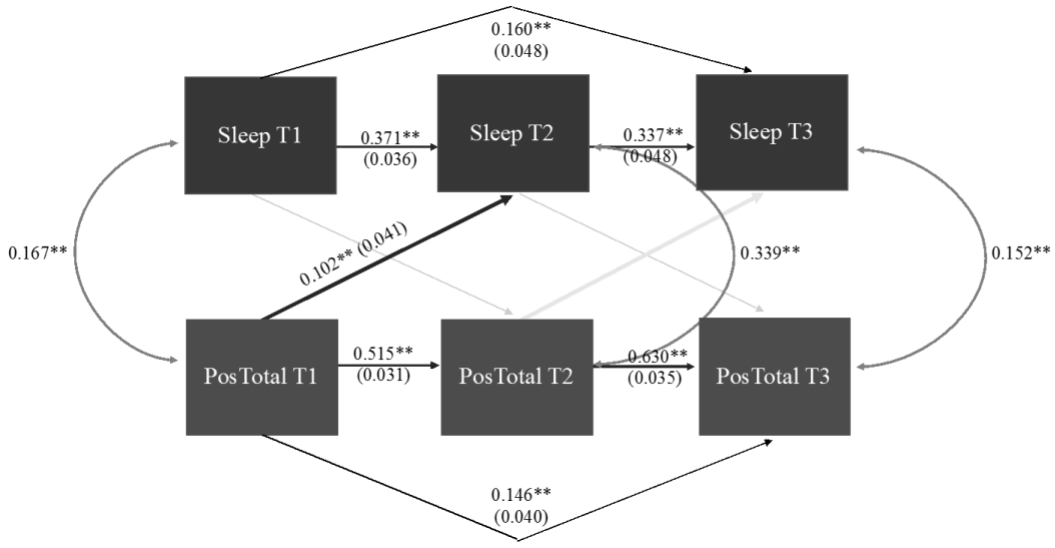

Figure 5. Model A3 including standardized path loadings (with standard error) using 5-P symptom composite (PosTotal). *p<0.05, **p<0.01

	-2LL	*df*	$\Delta\chi^2$*	Δdf*	RMSEA	RMSEA 90% CI	AIC	SABIC	CFI	TLI
A3) PosTotal non-sig paths dropped with AR2 added	3.302	5			0.000	0.000;.040	15171.651	15203.840	1.000	1.000
A2) PosTotal non-significant paths dropped	26.454	7	23.152	2	0.060	.037;.086	15190.803	15220.065	0.971	0.942

Table 5. Fit Statistics Comparing Model A3 and A2
*in comparison to nested model above

When comparing model A3 with model A2, the only difference was that model A3 specifies two additional parameters than A2 (i.e., A3 specifies AR2 relationships for both constructs: SleepT3-SleepT1 and PosTotalT3-PosTotalT1 paths were estimated), so again these were nested models and can be compared directly and tested using the χ^2 squared difference test. When comparing the fit of model A3 to model A2, the observed change in χ^2 was 23.152 with a difference of 2 degrees of freedom. The critical value (at p = 0.05) for 2 degrees of freedom is 5.991. The observed value (23.152) was above the critical value (5.991), and it was concluded that there is a significant difference between the two models. Model A3 has better fit than model A2, indicating

that the addition of the AR2 parameters enhances the model fit. Model A3 was selected as the best fitting PosTotal model. See Table 5 for fit statistics. As seen in Figure 5, the best fitting PosTotal model A3 shows not only that positive prodromal symptoms at baseline are a significant predictor of sleep problems at time 2, but also that both sleep problems and positive symptoms remain quite stable over time (more so than predicted by the original A1 model).

Paranoia/hallucinations composite (Par/Hal):

Model B2 is the same as model B1, except with model B1's 2 non-significant paths removed (i.e., the SleepT1-Par/HalT2 path and the SleepT2-Par/HalT3 path were removed). Thus model B1 (Figure 6) and model B2 (Figure 7) stand in nested sequence and can be compared directly and the difference can be tested using the χ^2 difference test.

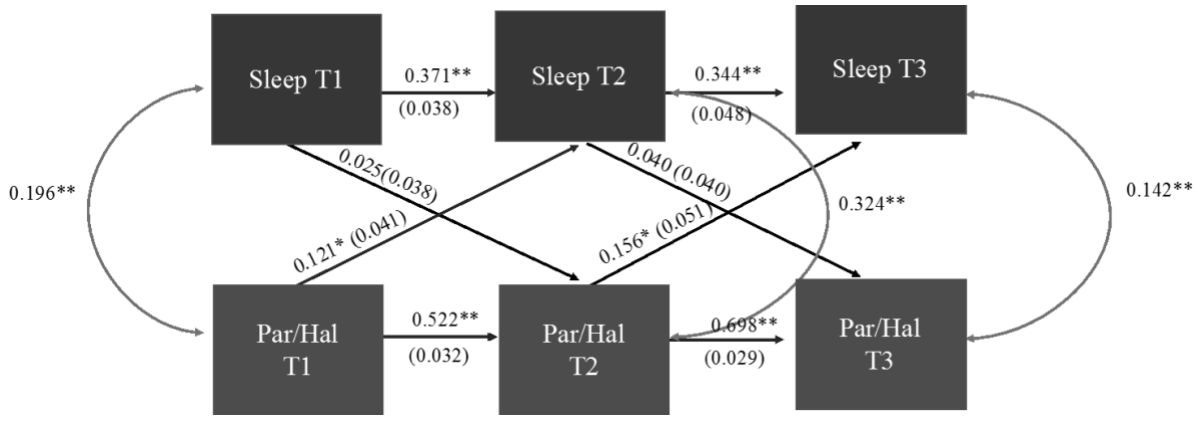

Figure 6. Model B1 including standardized path loadings (with standard error) using 2-P symptom composite (Par/Hal). *p<0.05, **p<0.01

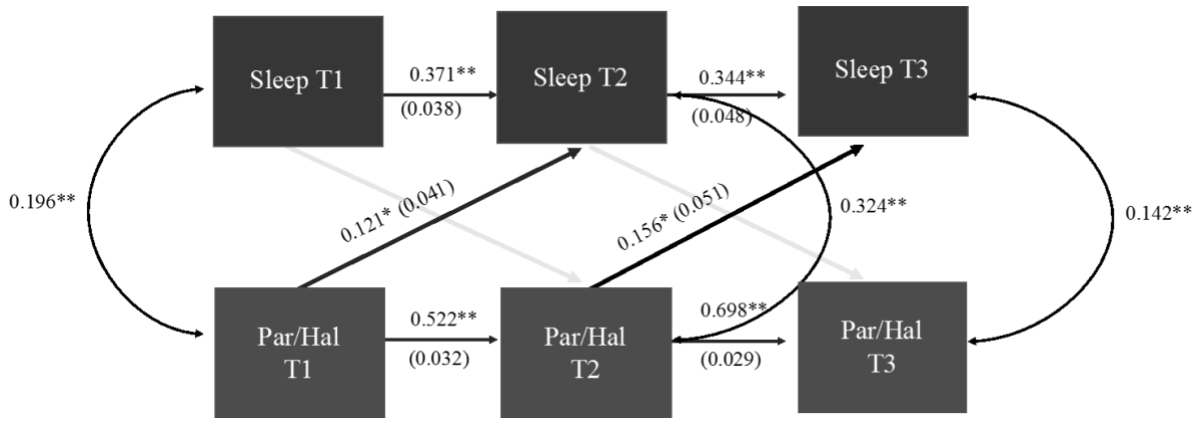

Figure 7. Model B2 including standardized path loadings (with standard error) using 2-P symptom composite (Par/Hal). *p<0.05, **p<0.01.

	-2LL	*df*	$\Delta\chi^2$*	Δdf*	RMSEA	RMSEA 90% CI	AIC	SABIC	CFI	TLI
B1) Par/Hal Full Model	21.123	4			0.075	.045;.108	13219.817	13253.523	0.974	0.910
B2) Par/Hal non-significant paths dropped	22.588	6	1.465	2	0.060	.035;.088	13217.336	13248.061	0.975	0.942

Table 6. Fit Statistics Comparing Model B1 and B2
*in comparison to nested model above

When comparing model B2 to model B1, the difference in χ^2 was 1.465 with a difference of 2 degrees of freedom. This observed χ^2 was less than the critical value for 2 degrees of freedom (5.991), thus model B1 and model B2 are not significantly different. Since there is no significant difference between the models, the model B2 is selected above B1, because model B2 is the more parsimonious model (i.e., fewer parameters estimated). The remaining fit statistics (AIC, SABIC, CFI, and TLI) all showed better fit for model B2. See Table 6 for fit statistics. As seen in Figure 7, the better fitting model B2 shows that positive prodromal symptoms at baseline are a significant predictor of sleep problems at time 2, and positive prodromal symptoms at time 2 are predictive of sleep problems at time 2. Once again, neither sleep problems at baseline, nor sleep problems at time 2 are predictive of later positive prodromal symptoms.

When comparing B3 to B2, again the only difference is that model B3 (Figure 8) specifies 2 additional parameters (specifically, in B3 the AR2 relationship between sleepT3 and sleepT1, and the AR2 relationship between Par/HalT3 and Par/HalT1 are specified whereas in B2 there are no AR2 relationships specified). So again, these are nested models, with B2 nested within B3.

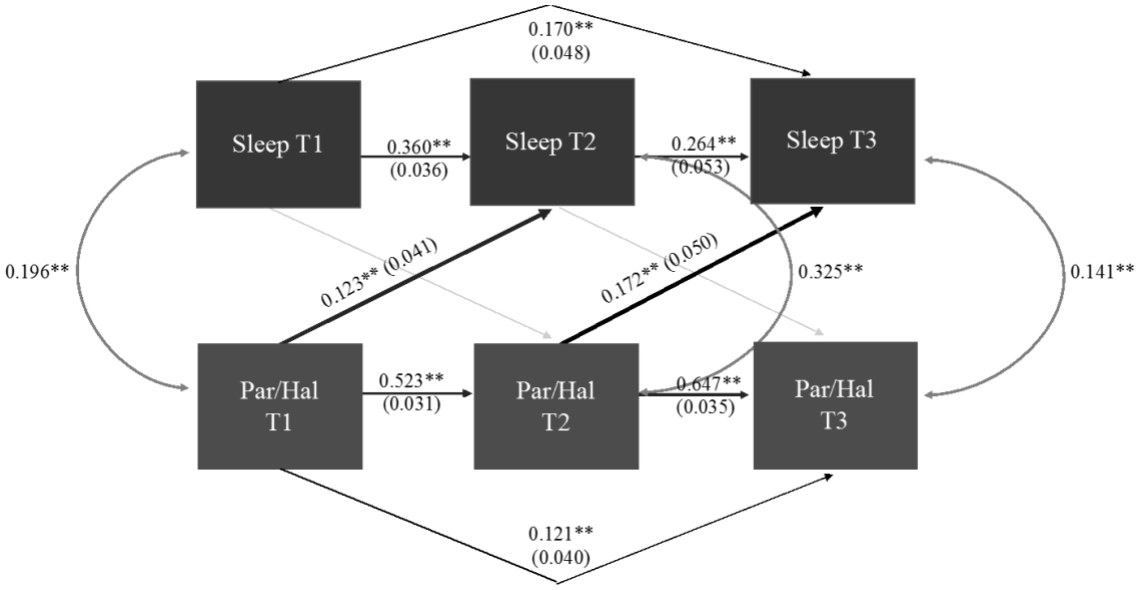

Figure 8. Model B3 including standardized path loadings (with standard error) using 2-P symptom composite (Par/Hal). *p<0.05, **p<0.01

	-2LL	*df*	$\Delta\chi^2$*	Δdf*	RMSEA	RMSEA 90% CI	AIC	SABIC	CFI	TLI
B3) Par/Hal non-sig paths dropped with AR2 added	1.807	2			0.000	0.000;.037	13200.555	13234.207	1.000	1.000
B2) Pal/Hal non-significant paths dropped	22.588	6	20.781	2	0.060	.035;.088	13217.336	13248.061	0.975	0.942

Table 7. Fit Statistics Comparing Model B3 and B2
*in comparison to nested model above

When comparing the fit of model B3 to model B2, the observed change in χ^2 is 20.781, which is above the critical value of 5.991. Therefore, B3 and B2 are significantly different, with B3 fitting the data better (see Table 7 for fit statistics). Model B3 was selected as the best fitting Par/Hal

model. Thus, as seen in Figure 8, the best fitting Par/Hal model B3 shows not only that positive prodromal symptoms predict later sleep problems, but also that both sleep problems and positive symptoms remain quite stable over time.

In summary, the autoregressive model best represented the longitudinal relationships in sleep and positive prodromal symptoms, as it was a better fit to the data than the growth curve model. Further, the originally hypothesized autoregressive panel model (which specified bidirectional effects of sleep and psychotic symptoms on each other) was improved by removing non-significant paths (specifically those from sleep to positive symptoms) and by adding AR2 paths. The improved fit of these modified models suggests that 1) sleep and psychotic symptoms are more stable over time than originally hypothesized, and 2) any cross-lagged effects are in the direction of psychotic symptoms predicting later sleep problems, not vice-versa.

Further, the same pattern of effects was present when using a composite of all 5 positive symptoms (PosTotal) as when using a composite of 2 positive symptoms (Par/Hal) previously found to be more specifically associated with sleep problems. However, models using the 2-positive symptom composite (Par/Hal) achieved better overall model fit. This supports the theory that paranoia/suspiciousness and hallucinations/perceptual abnormalities are more closely associated with sleep problems than other positive symptoms.

Exploration of Potential Covariates

As the full autoregressive panel model using Par/Hal (Model B1) was the only original model to show adequate fit to the data, this was the model used to explore the potential effects of age and sex. Six different Par/Hal autoregressive panel models were run: males only, females only, 18 years and over, younger than 18, and psychotropic medication use, and no psychotropic

medication use. The covariates of age and sex will be discussed first, followed by a discussion of the medication use covariate.

Age & Sex: Most of the first 4 models (male, female, 18 and over, under 18) showed adequate fit to the data, with the exception of 'the under 18 years old' model. See Table 8 and 9 for fit statistics and Figures 9-12 for significant and non-significant paths including standardized coefficients and standard error. The pattern of the significant paths in each of these 4 models remained similar to previous analyses, such that where there were significant cross-lagged paths, they traveled in the direction of positive prodromal symptoms predicting sleep disturbances. No cross-lagged paths traveling in the opposite direction (i.e., sleep disturbance predicting later prodromal symptoms) were significant. It is noted that each of the 4 models showed only 1 significant cross-lagged effect from prodromal symptoms to sleep disturbance, although there was no consistency across models as to which specific path was significant. This is likely due to the fact that dichotomizing the groups resulted in smaller sample sizes and reduced power to detect all significant effects. Thus, the current exploration of potential covariates (i.e., age and sex) revealed no evidence that these variables impact the longitudinal relationships between sleep problems and prodromal symptoms in this sample. However, this may be due to reduced power or specifics of the current sample and future explorations of sleep and prodromal symptoms should assess utility of including these variables as covariate in analyses.

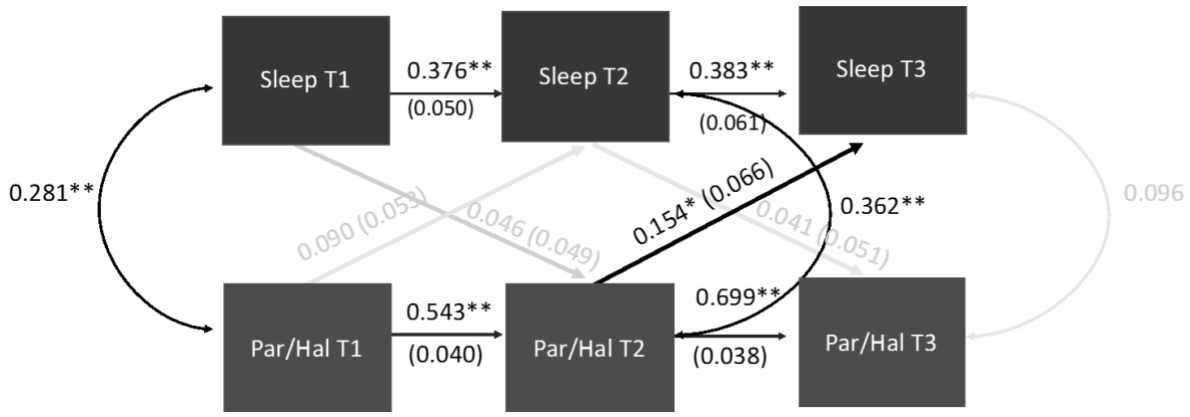

Figure 9. Full Par/Hal Autoregressive Panel Model (males only) showing standardized path loadings (with standard error). *p<0.05, **p<0.01.

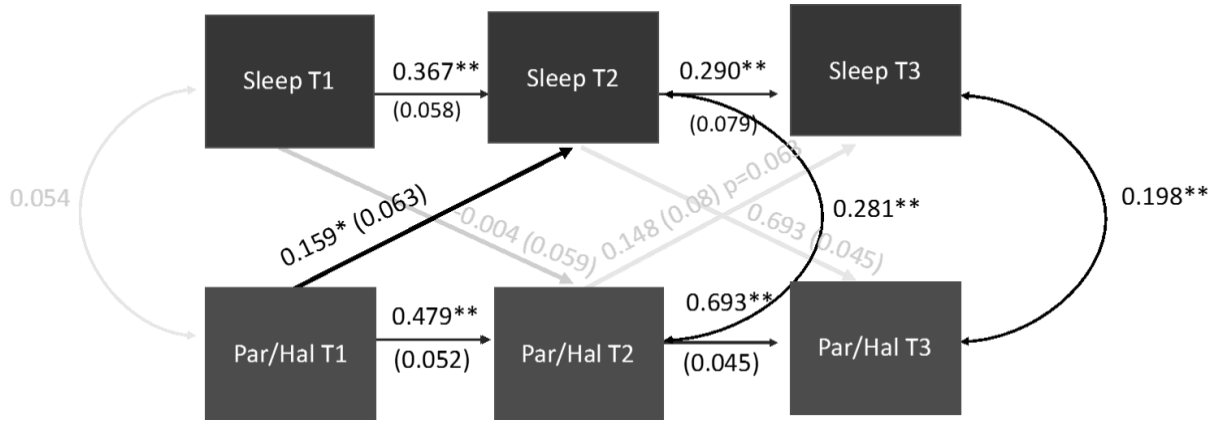

Figure 10. Full Par/Hal Autoregressive Panel Model (females only) showing standardized path loadings (with standard error). *p<0.05, **p<0.01

	RMSEA	RMSEA 90% CI	AIC	SABIC	CFI	TLI
Par/Hal Autoregressive Panel Model – Males Only	0.071	.029;.116	7564.386	7585.182	0.979	0.928
Par/Hal Autoregressive Panel Model – Females Only	0.067	.012;.121	5660.059	5674.343	0.975	0.912

Table 8. Fit Statistics of Par/Hal Autoregressive Panel Models – Exploring Sex as a Covariate

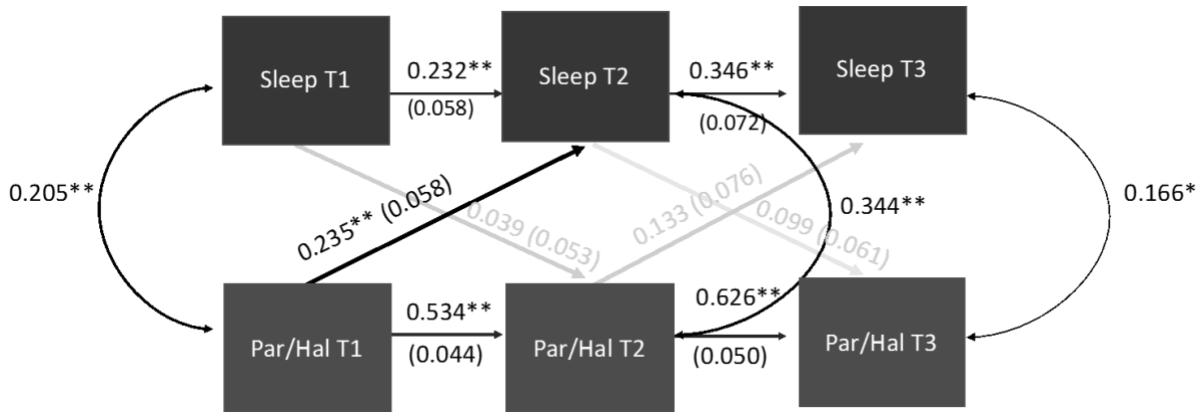

Figure 11. Full Par/Hal Autoregressive Panel Model (18 years and over) showing standardized path loadings (with standard error). *p<0.05, **p<0.01.

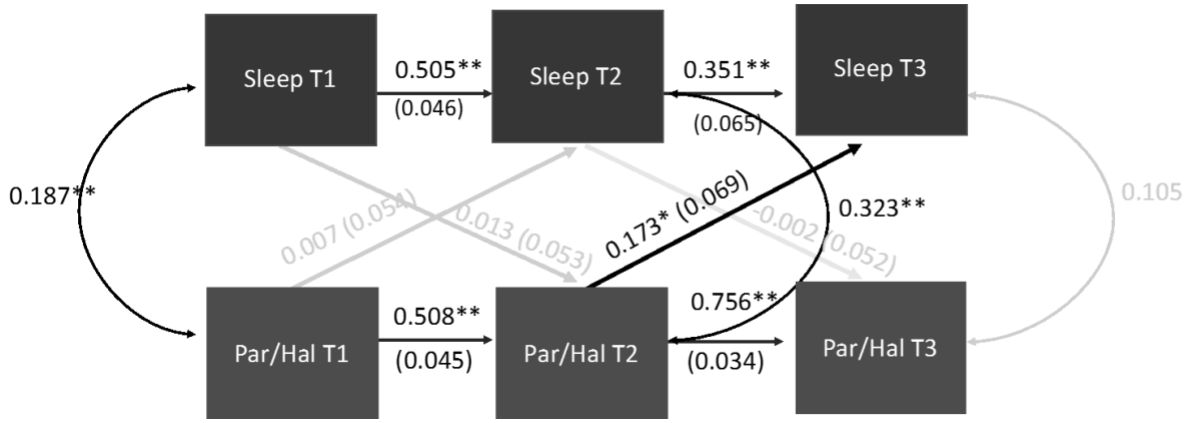

Figure 12. Full Par/Hal Autoregressive Panel Model (younger than 18 years) showing standardized path loadings (with standard error). *p<0.05, **p<0.01.

	RMSEA	RMSEA 90% CI	AIC	SABIC	CFI	TLI
Par/Hal Autoregressive Panel Model – 18 years and over	0.073	.029;.121	6724.366	6742.668	0.973	0.904
Par/Hal Autoregressive Panel Model – Under 18 years	0.100	.057;.147	6508.687	6525.911	0.962	0.866

Table 9. Fit Statistics of Par/Hal Autoregressive Panel Models – Exploring Age as a Covariate

Psychotropic Medication Use: Analyses were also performed to test whether psychotropic medication use at baseline impacted the longitudinal association of sleep problems and prodromal symptoms. See table 10 for fit statistics and figures 13 and 14 for significant and non-significant paths including standardized coefficients and standard error. When the model was run for only the group who reported no psychotropic medication use at baseline (n = 300), the model fit was poor and no cross-lagged effects were observed in either direction. However, when the model was run for only the group who reported psychotropic medication use at baseline (n = 464), the model achieved good fit to the data and the pattern of cross-lagged effects was such that prodromal symptoms at each time point predicted sleep problems at a later time point. This is the same pattern observed in the initial analyses with no covariates. These results suggest that the use of psychotropic medications at baseline has an impact on the longitudinal relationship between sleep problems and prodromal symptoms. Specifically, those who do not report baseline psychotropic medication use show no associations between sleep problems and prodromal symptoms over time, whereas those who report using psychotropic medications at baseline show significant associations between prodromal symptoms and sleep problems over time, with prodromal symptoms predicting later sleep problems. There are several possible interpretations for this result that will require further analysis. Firstly, many psychotropic medications have side effects that that are known to cause sleep problems. Thus, if psychotropic medications are being prescribed to treat prodromal symptoms (and associated symptoms such as depression, anxiety, and cognitive issues), and the dosage increases depending on prodromal symptom severity, then the correlated increase in side effects may explain why sleep problems follow prodromal symptoms. However, it may also be that psychotropic medication use is an indicator of more severe prodromal symptomology at baseline, and perhaps the association of

prodromal symptoms and sleep problems is only noticeable in those CHR individuals with more severe symptoms or poorer premorbid functioning. Further analyses should be conducted to understand more about how and why psychotropic medications appear to impact the longitudinal association of sleep and prodromal symptoms in this sample.

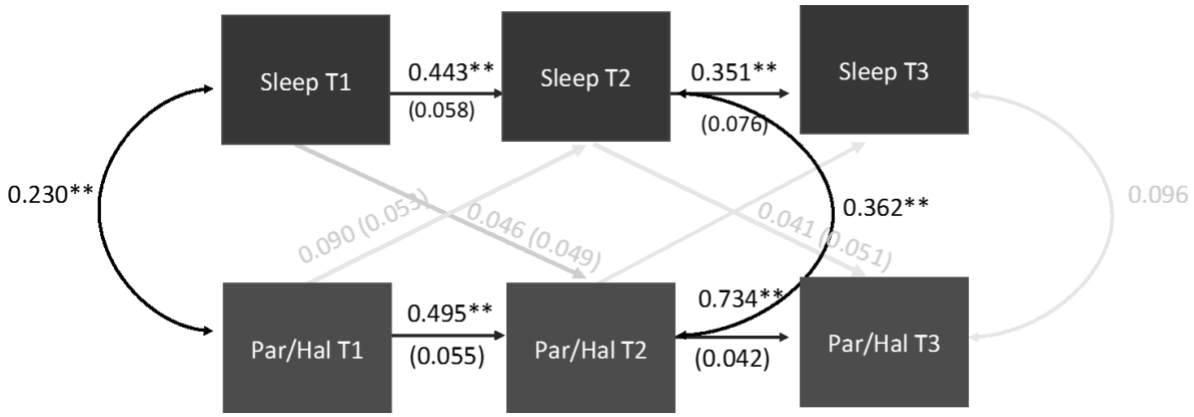

Figure 13. Full Par/Hal Autoregressive Panel Model (no psychotropic medication use at baseline) showing standardized path loadings (with standard error). *p<0.05, **p<0.01. n=300

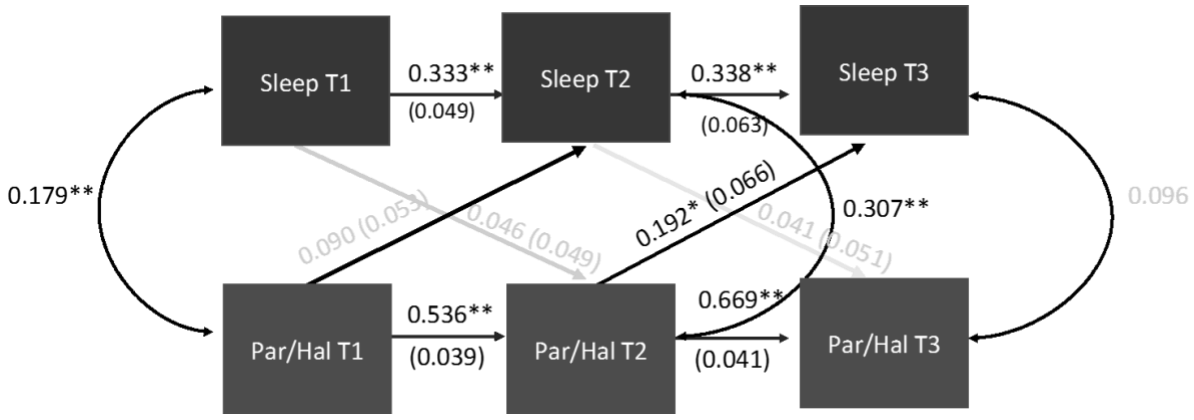

Figure 14. Full Par/Hal Autoregressive Panel Model (psychotropic medication use at baseline) showing standardized path loadings (with standard error). *p<0.05, **p<0.01. n=464

	RMSEA	RMSEA 90% CI	AIC	SABIC	CFI	TLI
Par/Hal Autoregressive Panel Model – no medication use	0.107	.060;.160	5125.751	5137.995	0.949	0.821
Par/Hal Autoregressive Panel Model – medication use	0.057	.011;.102	8121.040	8143.261	0.985	0.947

Table 10. Fit Statistics of Par/Hal Autoregressive Panel Models – Exploring Psychotropic Medication Use at Baseline as a Covariate

Discussion

The current study is the first to assess bidirectional associations of sleep problems and positive prodromal or psychotic-like symptoms over three consecutive time points. Interestingly, the results indicate that positive prodromal symptoms predict later sleep disturbance, and sleep disturbance does not have a significant impact on later positive prodromal symptoms. This result runs counter to previous theories and hypotheses that predict sleep problems will cause worsened psychotic symptoms (e.g., Lunsford-Avery & Mittal, 2013). However, there are several potential explanations for the observed direction of the sleep-psychotic symptom relationship.

It is conceivable that the experience of positive prodromal symptoms, especially suspiciousness and perceptual abnormalities, interferes with sleep directly (e.g., ruminating about the possibility that someone intends harm, or seeing things that are not there, could interfere with the ability to fall asleep). In addition, the experience of positive prodromal symptoms may also have an effect on sleep through indirect pathways such as through increased general stress and/or abnormalities in cortisol (a stress-response hormone which is associated with both dopamine abnormalities and resulting psychotic symptoms, as well as with circadian disruption). Understanding of these relationships and potential mediators of the association between positive prodromal symptoms and sleep problems requires further analysis with longitudinal data. The

exploration of possible covariates also indicates that future explorations of sleep and prodromal symptoms should include psychotropic medication use as a covariate in analyses.

The present findings also appear counter the previously discussed longitudinal and experimental findings that suggest sleep problems predict later psychotic or psychotic-like symptoms. There are several potential reasons for the apparent discrepancy. First and probably most relevant, the current study is the first to actually assess for possible bidirectional effects of sleep and psychotic symptoms on each other, whereas previous studies have focused only on unidirectional effects (i.e., sleep problems predicting later psychotic symptoms). Second, this study made use of the largest sample size of CHR participants to date, which allowed greater power to detect possible bidirectional effects. Third, the current study was the first to utilize data from three separate time points, and by using all three time points in an autoregressive panel model design, we were able to explore cross-lagged effects, while controlling for effects from the construct at the previous time point. This is especially important as our data show that both sleep disruption and positive prodromal symptoms are significantly correlated with each other at each time point, and both constructs also show a high level of stability over time. By using the autoregressive panel model design, we were able to conclude that the cross-lagged effects were not simply due to the high correlations between variables at the previous time point. Investigations using only two time points and testing only one directional prediction (i.e., sleep problems predicting psychotic symptoms) would likely suffer from conflation of these effects.

Finally, it is important to consider that the present CHR sample is, by intent, enriched for individuals who are at elevated statistical risk for serious mental illness. Their baseline level of psychotic-like symptoms is higher than that of healthy samples from the general population. Most of the longitudinal research findings and all of the experimental research findings

providing evidence that sleep deprivation augments psychotic-like symptoms come from studies of healthy samples. It may be that there is a symptom-severity threshold for this effect, and that most CHR individuals have exceeded the threshold. In other words, the predominant direction of the relationship between sleep disturbance and psychotic-like symptoms may shift when symptom severity reaches/exceeds the level required for CHR designation. So, in healthy samples, the relation between sleep and psychotic-like symptoms may be primarily due to the adverse effects of sleep disturbance. In contrast, for CHR samples, symptom severity levels may be driving the relationship and reversing the direction of causality. The present findings are consistent with this interpretation.

Despite the previously discussed strengths of this study, there are also limitations that may be addressed by future investigations. One major limitation of the current study is that only one indicator of sleep disruption was used in analyses. The sleep disruption variable used in this study includes problems of sleeping too much, as well as problems of sleeping too little, and even circadian abnormalities (e.g., sleeping at socially inappropriate times) within the same variable. It is possible that these specific sleeping problems have different relationships with positive prodromal symptoms. For example, there is evidence that circadian dysfunction may be associated with worsening of psychotic symptoms in CHR samples (Lunsford-Avery et al., 2017). However, in the current dataset there was no way to disentangle circadian disruption from other sleep problems such as insomnia or hypersomnia. In addition, the current study did not assess duration of sleep problems at each time point, and thus did not differentiate the impacts of chronic sleep problems versus acute or short-term sleep disruption. Future studies may benefit from using more indicators of sleep dysfunction, perhaps including latent constructs, and assessing the impacts of chronicity of sleep dysfunction on positive psychotic symptoms.

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Appendix B: Manuscript 2 Tables & Figures

Table 1. Table of correlation coefficients for sleep disturbance and positive symptoms (using the 5-P symptom composite PosTotal). *p<0.05, **p<0.01

Variable	1	2	3	4	5	6
1. Sleep Time 1	1					
2. Sleep Time 2	0.387**	1				
3. Sleep Time 3	0.295**	0.401**	1			
4. Total positive symptoms T1	0.167**	0.165**	0.076	1		
5. Total positive symptoms T2	0.083*	0.349**	0.191**	0.516**	1	
6. Total positive symptoms T3	0.094*	0.265**	0.234**	0.467**	0.709**	1

Table 2. Table of correlation coefficients for sleep disturbance and positive symptoms (using the 2-P symptom composite Par/Hal). *p<0.05, **p<0.01

Variable	1	2	3	4	5	6
1. Sleep Time 1	1					
2. Sleep Time 2	0.391**	1				
3. Sleep Time 3	0.299**	0.289**	1			
4. Paranoia/Hallucinations T1	0.196**	0.194**	0.161**	1		
5. Paranoia/Hallucinations T2	0.127**	0.363**	0.289**	0.524**	1	
6. Paranoia/Hallucinations T3	0.132**	0.293**	0.307**	0.459**	0.710**	1

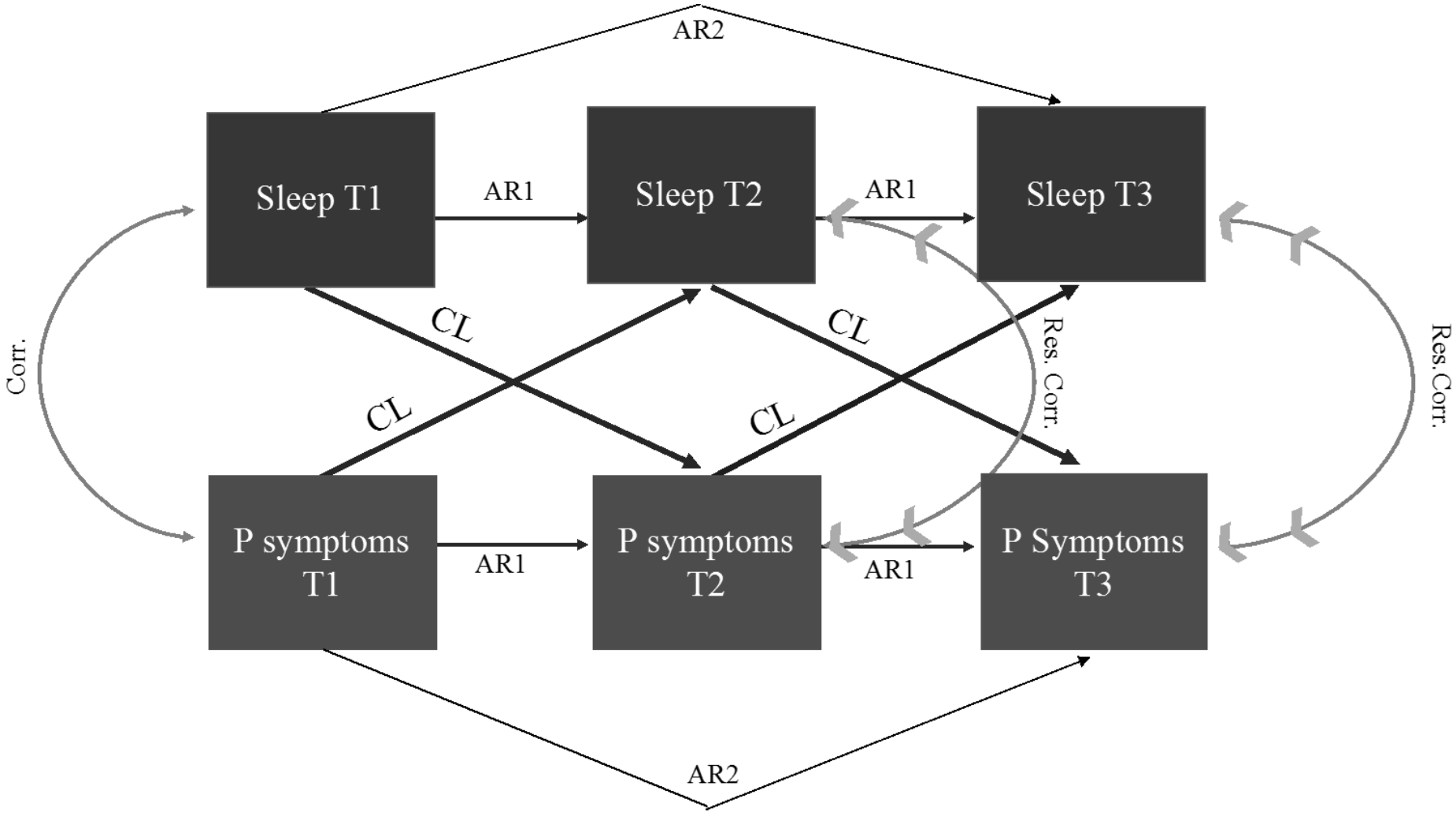

Figure 1. Theoretical autoregressive panel model with all effects labeled. Autoregressive path between constructs 1 time period apart (AR1); Autoregressive path between constructs 2 time periods apart (AR2); Cross-lagged path (CR); curved, single-headed arrows represent correlation (Corr.) between constructs; Curved double-headed arrows present residual correlations (Res. Corr.) between constructs.

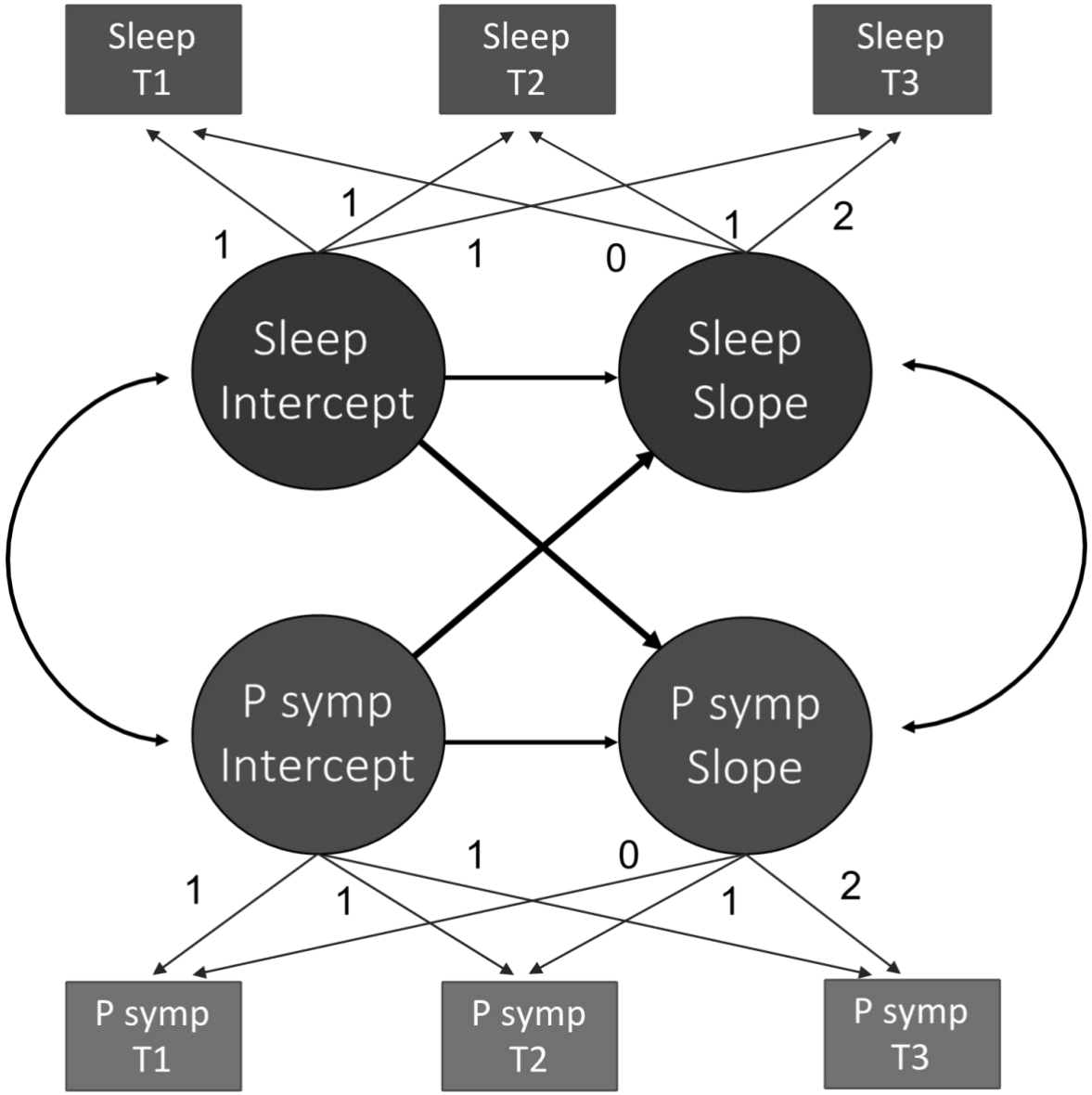

Figure 2. Theoretical growth curve model. Intercept factor loadings are fixed at 1, and slope factor loadings are fixed to estimate a linear slope.

General Conclusion

This dissertation explored the association between sleep problems and positive prodromal symptoms in a sample at CHR for psychosis. Most previous research in this area has been cross-sectional, thus limiting the inferences that can be drawn about causal relations between sleep abnormalities and psychosis-spectrum symptoms. Although there are some experimental studies that indicate a causal effect of sleep disturbance on the occurrence of psychotic-like symptoms, the participants in these studies were healthy adults, who are presumably at low risk for psychotic symptoms. Further, while there are also some reports on the relation of sleep disturbance with positive symptom severity in schizophrenia patients, these do not address the question of whether sleep problems contribute to the development of psychotic symptoms or disorders. Finally, all previous longitudinal studies of the association between sleep problems and psychotic symptoms only tested the association across two time points, and in one direction (i.e., only analyzed whether sleep problems predict later psychotic symptoms). No previous studies have attempted to test the reverse relationship (i.e., psychotic symptoms predict later sleep problems), or a bidirectional relationship. By testing the longitudinal relations between sleep disturbance and positive symptoms at three time points in CHR youth, the present study more directly addresses the potential relation of sleep with the changing severity of attenuated positive symptoms. It is noteworthy that the two previous published studies on sleep and prodromal symptoms in a CHR sample were limited by their small sample sizes and were cross-sectional rather than longitudinal designs. Thus, by nature of the large sample size and multiple follow-ups after baseline, the studies described in this dissertation address several limitations in the extant research literature on sleep and psychotic symptoms.

The present findings from the cross-sectional analyses are largely consistent with previous findings from CHR, psychotic, and general population samples. Specifically, the current investigation found that sleep disruption and positive prodromal symptoms show significant cross-sectional associations. However, sleep problems were more closely associated with the specific prodromal symptoms of suspiciousness, perceptual abnormalities, and disorganized speech than with other positive prodromal symptoms. Further, although depression has been found to be a mediator in many previous studies of sleep and psychotic symptoms (see Reeve, Sheaves & Freeman, 2015 for review), the current cross-sectional study of the direct and indirect effects found this only to be the case in the relationship between sleep problems and suspiciousness. In fact, the indirect effect of sleep problems on total positive prodromal symptoms through depression was not significant in this sample. This suggests that any mediation effect of depression on the association of sleep problems and psychotic symptoms may be specific to only certain psychotic symptoms (e.g., suspiciousness/paranoia).

Perhaps most noteworthy, the findings from the present longitudinal analyses differ from results that generated the currently prevailing theories and hypotheses, which suggest sleep problems cause worsening of psychotic symptoms over time. In fact, longitudinal analyses from this dissertation revealed the opposite effect; positive prodromal symptoms predicted sleep problems at later time points. Further, when CHR subjects were categorized based on clinical outcome, no evidence was found that sleep problems at baseline were associated with conversion to psychosis. In sum, these findings from a CHR population suggest that the longitudinal relations between positive prodromal symptoms and sleep problems are likely at least bidirectional, if not predominantly in the direction of prodromal symptoms predicting later sleep problems.

It is important to consider the characteristics of the current sample when interpreting the results of this study. In particular, CHR samples are enriched for individuals at risk for severe mental illness. By definition, baseline levels of psychotic-like symptoms are higher in CHR samples than in healthy samples, and it is assumed that a significant subgroup of CHR individuals are characterized by a neurobiological vulnerability to psychosis. Thus, it is understandable that associations between sleep and psychotic-like symptoms may be quite different in CHR samples, than in healthy populations. Whereas studies show that sleep problems may be associated with transient psychotic-like symptoms in a general population, sleep problems may have a different association with the more severe and often escalating types of psychotic-like symptoms seen in CHR samples. Indeed, in CHR samples, sleep problems may be best explained as a correlate or consequence of the underlying neuropathology that confers risk for psychosis, rather than as contributor to psychotic illness.

Taking a broader perspective, these findings also highlight the important role of longitudinal research in helping to understand causation and directionality of associations. It is clear even from this dissertation that cross-sectional and longitudinal analyses focused on similar questions can lead to very different conclusions. Longitudinal data from several time points has the distinct advantage of allowing for more nuanced and more ecologically valid portrayals of change over time.

The current finding that positive prodromal symptoms predict later sleep problems also points to new possible avenues for future research. For example, investigators may need to consider different mediators of the sleep and psychosis association, as many of the potential mediators of the sleep-psychosis relationship mentioned in the literature (e.g., cognitive mediators such as depression, and neural mediators such as neuroinflammatory process and

synaptic pruning) seem to have been chosen based on the assumption of sleep problems causing later worsening of psychosis. Thus, it may make sense to investigate new and different meditational processes, such as the possibility that cortisol dysregulation produced by the stress of positive symptoms is disrupting sleep. Future investigations on the topic of sleep and psychotic symptoms may also benefit from exploring potential subgroups. The current study explored the relations of sleep problems and prodromal symptoms in the entire CHR sample as a group. However, it is possible that some individuals are more affected by sleep problems than others (e.g., a 'bipolar-type' CHR group), and these groups may show different trajectories over time. Exploring 'hidden groups' through growth curve modeling is one way to investigate this possibility. In addition, circadian dysfunction was not directly assessed in this study and this issue still warrants attention. It may be that those CHR individuals who report complete day-night reversal make up a group that specifically has sleep problems as a result of dysfunctional circadian processes. As day-night schedules appear to be more variable in CHR and psychotic samples than the general population, it is worth investigating whether there is any association between circadian dysfunction and psychosis. Rapid Eye Movement (REM) sleep behavior disorder is a type of sleep problem that specifically effects REM sleep and is associated with unusual experiences such as sleep paralysis, hypnagogic hallucinations, and dissociative episodes during wakefulness. It is possible that some of the CHR participants also experience disruptions to REM sleep or other specific sleep phase disorders that are not simply captured by sleep length or subjective quality. Participants belonging to any of these potential subgroups could conceivably display a different sleep and prodromal symptom association than those found in the sample overall. Advances in these future areas of study may also inform intervention efforts and

help to ensure that interventions are appropriate for the specific issues and possible subgroups present in CHR and psychotic samples.

Finally, it may also be worthwhile to switch the focus to exploring the functional consequences of sleep problems in CHR and psychotic groups and addressing the need for effective early intervention efforts that enhance functioning in these vulnerable groups. Future research could assess whether currently used sleep interventions are also appropriate for CHR and psychotic samples. This path of investigation is more in line with the "recovery orientation" to psychotic disorders, which has become popular recently. This orientation entails focusing less on reducing psychotic symptoms and more on increasing functioning and helping individuals live fulfilling lives, despite the possibility of residual psychotic symptoms. This change in focus is particularly relevant as many people with psychotic disorders do not experience complete remittance of their positive psychotic symptoms, even when receiving appropriate treatment. Thus, focusing on reducing the functional impairments that are most prevalent in those with psychosis and at risk for psychosis, such as sleep problems, may be a practically effective early intervention. Given the findings from the current studies, optimal strategies for improving sleep in this population may include interventions aimed at reducing the severity of positive symptoms, especially suspiciousness and perceptual abnormalities, potentially by altering the attributions CHR individuals make about these experiences (e.g., Cognitive Behavior Therapy strategies). Understanding more about the specific associations between sleep and prodromal symptoms in a CHR sample may help to inform future intervention effects so that they can be most relevant and effective for this at-risk population.