
UNIMORE
UNIVERSITÀ DEGLI STUDI DI
MODENA E REGGIO EMILIA

# UNIVERSITÀ DEGLI STUDI DI MODENA E REGGIO EMILIA

**Dottorato di ricerca in Neuroscienze**

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# *Sleep disturbances and psychiatric disorders: transdiagnostic markers and targets for intervention*

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**ABSTRACT**

Sleep disorders represent a crucial transdiagnostic domain, lying at the intersection between psychiatry and sleep medicine, with a decisive impact on individual vulnerability and the prognosis of mental disorders. This doctoral thesis systematically investigated the role of sleep as both a marker of vulnerability and a therapeutic target, considering psychiatric disorders with sleep alterations as well as sleep medicine conditions with psychiatric comorbidities. By integrating clinical and research perspectives from both fields, it combined original studies, analyses of large databases, and systematic literature reviews.

In the adolescent population, a study conducted on psychiatric inpatients showed that insomnia is an independent predictor of suicidality, along with depression, bullying, and physical inactivity. These findings were supported by a meta-analysis including over one million adolescents, which confirmed more than a threefold increase in suicide attempts and a more than twofold increase in suicidal ideation among those with sleep disturbances.

In adults experiencing a first episode of psychosis or bipolar disorder, a case-control study documented a high prevalence of sleep alterations. Subjective sleep quality was strongly correlated with depressive symptoms, prodromal features, and suicidality, while actigraphic data revealed distinct patterns between psychosis and bipolar disorder.

A systematic review of the literature further highlighted the pervasiveness of sleep disturbances in high-risk states and early psychosis, confirming their prognostic value and importance as early-phase markers of illness. Finally, a systematic review on therapeutic interventions in bipolar disorder summarized evidence regarding both pharmacological and non-pharmacological strategies. Results showed that non-pharmacological approaches are effective and safe in improving sleep quality and reducing depressive symptoms, whereas the use of hypnotics and antidepressants is associated with poorer outcomes and higher risks, including suicidality.

Another research line focused on the link between sleep disturbances and suicidality in the early phases of mental illness. The literature review revealed that, in first-episode psychosis, insomnia and poor sleep quality are significantly associated with suicidal ideation and behavior. All available studies confirm that sleep alterations represent a

modifiable risk factor and a potential preventive target in the initial stages of psychiatric disorders.

The research then explored narcolepsy type 1, an idiopathic central hypersomnia known also for its complex psychiatric comorbidities. In childhood and adolescence, a complementary study identified a distinct phenotype of narcolepsy with psychotic comorbidity, characterized by greater sleep–wake instability, reduced sleep efficiency, low orexin levels, and positive psychiatric family history. A subsequent study in adults with narcolepsy type 1 revealed a high co-occurrence of depressive and anxious symptoms, suicidal ideation, and hopelessness, delineating a profile of complex psychiatric vulnerability that warrants clinical attention and integrated care.

Overall, the results of this research pathway demonstrate that sleep disorders are not merely accessory symptoms but central pathogenic and clinical factors in psychiatric conditions. The integrated assessment of sleep, through both subjective and objective tools, enables the early identification of high-risk phenotypes and the development of multimodal therapeutic strategies. This thesis, therefore, underscores the need to systematically include sleep assessment in psychiatric clinical practice, opening new perspectives for prevention and intervention within a personalized medicine framework.

## CHAPTER 1 – INTRODUCTION

Sleep, a fundamental biological process essential for neural restoration, emotional regulation, and cognitive functioning, has long been viewed as an epiphenomenon within psychiatry, an accompanying feature rather than a core mechanism. However, evidence from the past two decades has greatly shifted this perspective. Disturbances in sleep are now understood not just as symptoms of mental disorders but as active factors that contribute to their development, persistence, and outcomes. Sleep affects nearly every aspect of mental health, from emotional regulation and stress response to learning, memory consolidation, and social cognition. When disrupted, it can trigger or worsen emotional instability, cognitive problems, and behavioral issues, key features of psychiatric disorders.

This paradigm shift has established sleep as a transdiagnostic domain, crossing traditional diagnostic boundaries and offering new insights into the shared mechanisms of vulnerability among mental disorders. The study of sleep–psychiatry interactions has evolved from mere descriptive observations to the identification of measurable biological and behavioral markers. Objective measures like actigraphy, polysomnography, and circadian rhythm analysis, combined with validated subjective scales, have enabled a more precise characterization of how changes in sleep quantity, quality, and timing relate to psychopathological states.

Clinically, sleep disturbances are among the most common and disabling symptoms in psychiatry. They affect nearly all diagnostic groups, including depression, anxiety, bipolar disorder, psychosis, and trauma-related disorders, and are often the first and last symptoms to appear during the course of illness. Their influence goes beyond subjective discomfort: poor sleep predicts relapse, suicide risk, cognitive decline, and diminished treatment response. However, despite their high prevalence and prognostic significance, sleep symptoms remain under-assessed and undertreated in psychiatric care, representing an overlooked opportunity for early detection and intervention.

From a neurobiological standpoint, sleep and mental health share common substrates within the brain's emotion-regulation and stress-response systems. Disruptions in neurotransmission, circadian clock genes, inflammatory pathways, and hypothalamic–pituitary–adrenal (HPA) axis activity underlie both insomnia and psychopathology.

Understanding these shared mechanisms offers a pathway to identify markers of risk that transcend categorical diagnoses and may inform a more dimensional, mechanism-based classification of mental disorders, consistent with the Research Domain Criteria (RDoC) framework.

Within this conceptual framework, sleep disturbances emerge as both markers of vulnerability and targets for intervention. They reveal early warning signs of psychopathology, often detectable before the full manifestation of clinical syndromes, and provide modifiable entry points for preventive and therapeutic strategies. For instance, insomnia and circadian misalignment have been shown to precede the onset of depression and psychosis, while specific sleep phenotypes, such as nightmares or REM dysregulation, predict suicidal behavior. Conversely, stabilizing sleep–wake patterns through behavioral and chronotherapeutic interventions can improve mood, cognitive functioning, and overall well-being.

The present thesis builds upon this transdiagnostic view. It explores the multifaceted role of sleep across developmental stages and psychiatric conditions, integrating data from original clinical studies, objective measurements, and systematic reviews. The research spans different populations and clinical scenarios—adolescents with psychiatric disorders, adults at the first episode of psychosis or bipolar disorder, and patients with narcolepsy type 1—to examine how sleep disturbances signal underlying vulnerability and how they can serve as therapeutic leverage points.

The following sections provide a theoretical and empirical foundation for this work.

## 1.1 The physiology and classification of sleep

Since ancient times, sleep has been a subject of great fascination. As early as the time of Aristotle and Hippocrates, attempts were made to understand its nature and investigate the role of dreams. The first true measurement of electrical activity in the human brain was conducted by Hans Berger, who recorded cortical electrical activity and described alpha and beta waves using the electroencephalogram (EEG) (Berger, 1930). Subsequently, in 1935, Loomis and his colleagues documented, through EEG observation, the main features of what is now known as non-rapid eye movement

(NREM) sleep, leading eventually to the discovery of rapid eye movement (REM) sleep (Loomis, 1935).

In the past, sleep was considered a state of cerebral inactivity caused by the reduction of sensory input (Dement, 2005). However, it was soon recognized that sleep is not a homogeneous state characterized merely by low-frequency EEG waves, but rather a far more complex and active phenomenon than initially assumed. As mentioned earlier, sleep is not uniform; it is composed of several cycles, each including an NREM (non-rapid eye movement) phase and a REM (rapid eye movement) phase. While the former typically occurs during the initial stages of sleep, the latter is characterized by a series of rapid eye movements that accompany dreaming.

REM sleep is not only important for enabling dreams, but also for regulating a range of bodily functions, including temperature, respiration, heart rate, blood pressure, and brain activity. In fact, during sleep, body temperature decreases by approximately 2°C, while respiration rate, heart rate, and blood pressure are reduced (Maki et al., 2020).

Returning to the initial distinction, NREM sleep accounts for about 75% of total sleep and is composed of three distinct stages:

- **Stage 1:** Transition from wakefulness to light sleep. Lasts approximately 1–7 minutes. Alpha waves (8–13 Hz), typical of wakefulness, disappear, and theta waves (4–7 Hz) emerge.
- **Stage 2:** Represents a deeper sleep state than stage 1, initially lasting about 10–25 minutes. Characterized by sleep spindles and K-complexes on the EEG, which indicate greater synchronization of neuronal activity. Memory consolidation is thought to occur mainly during this phase.
- **Stage 3:** Deep sleep, characterized by slow (delta) waves and high-voltage EEG activity. It lasts approximately 20–40 minutes in the first sleep cycle.

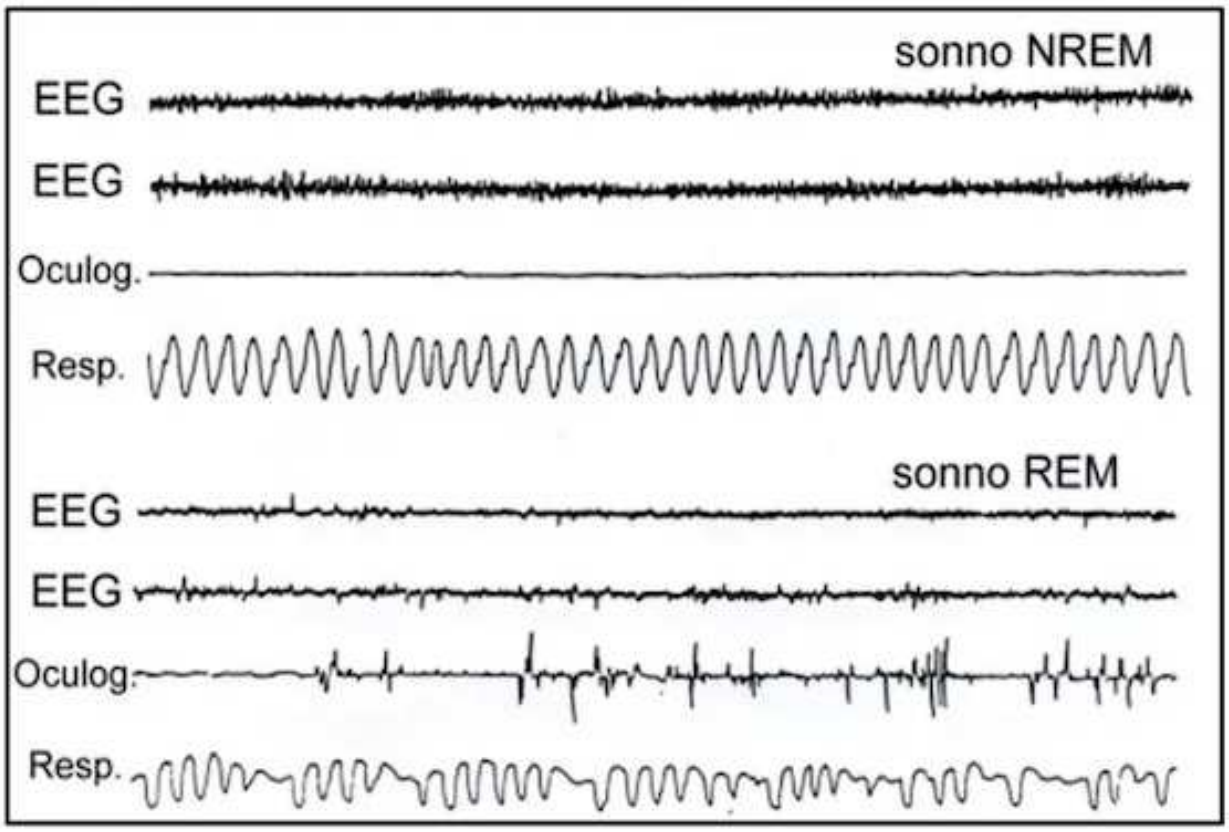


**Figure 1.** Polysomnographic parameters of REM and NREM sleep

Humans spend, on average, one-third of their lives sleeping. This simple fact highlights the fundamental importance of sleep in human life (Eide et al., 2021).
The Ascending Reticular Activating System (ARAS) is a key structure responsible for maintaining wakefulness. It consists of a network of neurons located in the brainstem, particularly in the central part of the midbrain and pons. It plays an essential role in regulating arousal and the sleep–wake cycle. For sleep to begin and be maintained, a reduction in ARAS activity is required (Carley et al., 2016). The main neurotransmitters involved in this system include noradrenaline, produced by the locus coeruleus; serotonin, originating from the median raphe nuclei; histamine, from the tuberomammillary nucleus; dopamine, synthesized in the ventral periaqueductal gray matter; acetylcholine, secreted by the pedunculopontine and laterodorsal tegmental nuclei of the pons; and orexin, released from the perifornical area (Poluektov et al., 2016). Even a single neurotransmitter alteration can cause sleep disorders. An example

is narcolepsy, characterized by orexin deficiency, leading to excessive daytime sleepiness, fragmented sleep, and episodes of cataplexy (Okechukwu et al., 2022).
Sleep disorders encompass a wide range of clinical conditions that can negatively affect the quality, quantity, and timing of sleep, with significant repercussions on both physical and mental health (Kryger et al., 2017). These disorders may range from mild, occasional sleep difficulties to chronic, debilitating conditions that require complex and ongoing medical management.
The American Academy of Sleep Medicine (AASM) has developed a classification system defining sleep disorders as pathological alterations of sleep that cause distress or impair daily functioning.
The most common sleep disorder is insomnia, characterized by difficulty initiating or maintaining sleep, or by early morning awakenings with the inability to return to sleep. Insomnia can be classified by duration into acute (short-term) or chronic (lasting at least three months) forms and may be associated with psychological, medical, or environmental factors (Morin et al., 2015).
Acute insomnia is generally linked to changes in usual sleep schedules, unsuitable environments, or stressful life events. It can be occasional (sporadic throughout life), transient (lasting a few nights), or short-term (lasting a few weeks), with a higher risk of progressing to chronicity.
The prevalence of insomnia in the general population is high: up to 30% of individuals experience occasional episodes, and about 10% suffer from chronic symptoms.
Among other frequent sleep disorders are circadian rhythm sleep–wake disorders, which are caused by a misalignment between an individual's internal circadian rhythm and the external environment (Wright et al., 2013). The circadian rhythm is the body's internal clock that operates on a roughly 24-hour cycle, influencing temperature, alertness, appetite, and hormone secretion.
These disorders can take various forms, such as delayed sleep–wake phase disorder, common among adolescents, or shift work disorder, affecting individuals working irregular or night shifts. Management often requires a combination of behavioral therapy, pharmacological interventions, and, in some cases, light therapy (Boivin et al., 2012).

According to the International Classification of Sleep Disorders, Third Edition (ICSD-3), six subtypes are recognized:

- Delayed Sleep–Wake Phase Disorder (DSWPD): a significant delay in sleep onset and awakening times relative to desired or required schedules.
- Advanced Sleep–Wake Phase Disorder (ASWPD): sleep onset and awakening occur earlier than desired.
- Irregular Sleep–Wake Rhythm Disorder (ISWRD): fragmented and disorganized sleep–wake patterns with multiple sleep episodes over 24 hours.
- Non-24-Hour Sleep–Wake Disorder (N24SWD): the circadian cycle fails to synchronize with the 24-hour day, gradually delaying each night.
- Shift Work Sleep Disorder (SWSD): associated with irregular work schedules or night shifts that disrupt natural circadian rhythms.
- Jet Lag Disorder: a transient misalignment following travel across multiple time zones.

Another major category of sleep disorders is parasomnias, which include abnormal behaviors or experiences occurring during sleep or partial awakenings. Common parasomnias are sleepwalking, night terrors, and sleep paralysis. These can be particularly distressing not only for the affected person but also for family members, as they often involve complex or even violent movements during sleep (Zadra et al., 2013).

Sleep-related movement disorders are characterized by abnormal, typically stereotyped movements that disrupt sleep quality. These include Restless Legs Syndrome (RLS), sleep bruxism, and Periodic Limb Movement Disorder (PLMD) (Chokrovery et al., 2010).

Understanding the etiology of sleep disorders is essential to ensure appropriate and effective treatment. Risk factors are multiple, genetic, environmental, psychological, or associated with pre-existing medical conditions, resulting in a multifactorial etiology that requires an integrated and personalized therapeutic approach (Plazzi et al., 2014).

Sleep disorders are associated with a wide range of health consequences, from an increased risk of chronic diseases to adverse effects on mental well-being, including the development of anxiety and depression. In recent years, growing evidence has also highlighted the role of sleep disturbances in psychiatric disorders.

### 1.2 Sleep disturbances as a transdiagnostic domain

In the past two decades, the conceptualization of sleep within psychiatry has undergone a profound transformation. Sleep is no longer regarded as a passive state or a mere epiphenomenon of psychiatric illness, but rather as an active biological process that contributes to mental health and illness through shared neurobiological and behavioral pathways. Increasing evidence indicates that sleep disturbances represent a transdiagnostic domain, a dimension of vulnerability that cuts across traditional diagnostic categories and reflects underlying dysregulation in arousal, emotion, and circadian systems (Harvey et al., 2011; Hertenstein et al., 2020; Riemann et al., 2020). This paradigm aligns with the RDoC framework proposed by the National Institute of Mental Health, which aims to identify the mechanisms underlying multiple psychiatric conditions rather than focusing solely on categorical syndromes (Insel et al., 2010). Within the RDoC matrix, Arousal and Regulatory Systems are considered one of the core functional domains, encompassing sleep–wake dynamics, circadian rhythms, and the physiological systems that sustain alertness, emotion, and cognition. From this perspective, sleep becomes a measurable and modifiable component of mental functioning, capable of both reflecting and influencing psychological well-being.
Sleep disturbances are highly prevalent across psychiatric conditions. Insomnia and poor sleep quality are found in approximately 90% of patients with depression, 70% of those with anxiety disorders, and 50–80% of individuals with schizophrenia or bipolar disorder (Baglioni et al., 2016; Riemann et al., 2020). Beyond prevalence, the phenotypic overlap of sleep disturbances across disorders suggests shared pathophysiological roots. Insomnia, nightmares, hypersomnia, delayed sleep phase, and fragmented sleep recur as consistent features even when core psychiatric symptoms differ dramatically. These alterations rarely occur in isolation. Insomnia often coexists with emotional dysregulation, hyperarousal, and cognitive inflexibility; hypersomnia overlaps with fatigue and anergia, while circadian rhythm disruption contributes to affective instability and impulsivity.
Longitudinal research has shown that sleep problems often precede the onset of psychiatric illness and predict recurrence or poor recovery, supporting their role as early vulnerability markers (Hertenstein et al., 2020; Murray et al., 2020). For instance,

individuals with chronic insomnia are two to four times more likely to develop major depression, while disturbed circadian rhythms increase the risk of relapse and suicidal behavior in bipolar disorder (Perlis et al., 2016). Sleep fragmentation and delayed circadian phase have also been identified as early features in individuals at clinical high risk for psychosis, sometimes predating positive symptoms by several months (Reeve et al., 2019). These findings collectively indicate that sleep disturbances may represent a prodromal dimension signalling the transition from vulnerability to clinical expression.

The relationship between sleep and mental disorders is inherently bidirectional. Psychiatric symptoms interfere with sleep through heightened arousal, intrusive thoughts, medication effects, and altered circadian timing. Conversely, inadequate or dysregulated sleep exacerbates psychiatric symptoms by disrupting emotional regulation, attention, and stress resilience. Experimental sleep deprivation studies demonstrate that even modest sleep restriction can induce mood lability, anxiety, and cognitive impairment in healthy individuals (Goldstein & Walker, 2014). Sleep loss heightens amygdala reactivity to negative stimuli and reduces prefrontal regulatory control (Yoo et al., 2007), producing neural patterns analogous to those observed in depression and anxiety. Reduced slow-wave sleep and shortened REM latency are characteristic findings in depression, linked to affective instability and impaired cognitive performance. In schizophrenia, circadian disorganization and reduced sleep spindle activity correlate with negative symptoms and cognitive deficits, while in bipolar disorder, sleep–wake instability acts as both a trigger and consequence of mood episodes.

The neurobiological foundation of this transdiagnostic relationship involves overlapping regulatory systems. The sleep–wake cycle is governed by the interplay of homeostatic and circadian processes: the accumulation of sleep pressure during wakefulness and its dissipation during sleep (Process S), and the circadian rhythm driven by the suprachiasmatic nucleus (Process C) (Borbély, 1982). Dysregulation of these systems alters neurotransmitter balance, particularly in serotonergic, dopaminergic, and noradrenergic pathways that are also implicated in mood and cognitive regulation (Saper & Fuller, 2017). Reduced serotonergic tone contributes to insomnia and emotional hyperreactivity; dopaminergic dysregulation disrupts reward processing and

circadian synchronization; and orexin deficiency, as in narcolepsy, produces excessive sleepiness and emotional dyscontrol (Okechukwu et al., 2022).

Sleep disturbances also interact closely with stress and inflammatory pathways. Dysregulation of the HPA axis leads to hypercortisolemia and sympathetic overactivation, while chronic sleep loss increases proinflammatory cytokines such as IL-6 and TNF-α (Irwin & Opp, 2017). These physiological changes impair neuroplasticity, modulate mood-related neural circuits, and reinforce the cycle of insomnia and emotional dysregulation. Such biological convergence explains why disturbed sleep can trigger or sustain mental illness across diagnostic categories.

Beyond its neurobiological effects, sleep has broad psychological and behavioral impacts that further underscore its transdiagnostic nature. Poor sleep amplifies negative affectivity, impairs emotion recognition, and reduces cognitive flexibility, thereby weakening resilience to stress and interpersonal conflict (Goldstein & Walker, 2014). Insomnia fosters maladaptive cognitive processes such as rumination and catastrophizing, perpetuating both anxiety and depression. Sleep restriction also increases impulsivity and reward sensitivity—traits that cut across personality disorders, substance use, and suicidal behavior. During adolescence and early adulthood, periods of neurodevelopmental and social reorganization, irregular sleep patterns, and circadian delays are linked to heightened emotional reactivity and social withdrawal, both of which predict later depressive and psychotic outcomes (Carskadon, 2011). Similarly, in trauma-exposed individuals, recurrent nightmares and disrupted REM sleep maintain hypervigilance and intrusive memories, fueling post-traumatic stress.

Recognizing sleep as a transdiagnostic domain has significant methodological and clinical implications. In psychiatric assessment, sleep is often overlooked or documented superficially, despite being one of the most reliable indicators of symptom exacerbation. Standardized tools such as the Pittsburgh Sleep Quality Index (PSQI), Insomnia Severity Index (ISI), and actigraphy-based measures should therefore be incorporated into routine psychiatric evaluations (Riemann et al., 2020). In research, adopting a dimensional framework allows identification of shared biomarkers—such as reduced spindle density or circadian desynchrony—that traverse traditional diagnostic boundaries. Integrating objective sleep data into longitudinal psychiatric studies may

help refine predictive models, enable earlier intervention, and clarify the mechanisms underlying comorbidity.

Clinically, the transdiagnostic perspective highlights the potential of sleep as a therapeutic and preventive target. Behavioral and chronotherapeutic interventions—including Cognitive Behavioral Therapy for Insomnia (CBT-I), Interpersonal and Social Rhythm Therapy (IPSRT), light therapy, and digital CBT platforms—have demonstrated cross-diagnostic efficacy (Harvey et al., 2015; Frank et al., 2021). Importantly, improvements in sleep often precede and predict improvements in mood, anxiety, and cognitive functioning, underscoring sleep's causal influence on psychiatric outcomes. Because sleep disturbances frequently emerge before the onset of overt psychiatric symptoms, early detection and treatment of sleep problems may help prevent illness progression or relapse.

In summary, sleep disturbances embody a unifying framework that connects biological, psychological, and clinical dimensions of mental illness. They are simultaneously markers of vulnerability, mediators of symptom expression, and targets for therapeutic intervention. Conceptualizing sleep as a transdiagnostic domain not only advances our understanding of psychiatric mechanisms but also encourages a shift toward mechanism-based, preventive, and personalized psychiatry.

### 1.3 Epidemiology and clinical burden of sleep disturbances in mental disorders

Sleep disturbances represent one of the most common and disabling transdiagnostic dimensions in psychiatry, affecting individuals across all diagnostic categories and stages of illness. Epidemiological data consistently show that between 30% and 50% of the general population experiences at least one symptom of disturbed sleep, such as difficulty initiating or maintaining sleep, early morning awakenings, or non-restorative sleep, while approximately 10% meet criteria for chronic insomnia (Ohayon, 2013). These rates rise dramatically among individuals with mental disorders, where the prevalence of sleep disturbances exceeds 80% in most diagnostic groups (Riemann et al., 2020).

In major depressive disorder, insomnia and hypersomnia are cardinal features and among the most reliable predictors of relapse. Up to 90% of patients with depression

report poor sleep quality, while 40% experience early morning awakenings or reduced total sleep time. Conversely, hypersomnia occurs in roughly 15% of cases, more frequently in atypical or bipolar depression. Numerous longitudinal studies have shown that insomnia often precedes the first depressive episode by months or years, conferring a two- to fourfold increased risk of developing depression. Even after remission, residual sleep disturbances remain one of the strongest predictors of recurrence, treatment resistance, and suicidal behavior (Baglioni et al., 2016; Freeman et al., 2020).
Anxiety disorders are similarly characterized by pervasive alterations in sleep continuity and depth. Generalized anxiety disorder, panic disorder, and post-traumatic stress disorder (PTSD) are all associated with elevated arousal and sympathetic activation during sleep, resulting in prolonged sleep latency, reduced slow-wave sleep, and frequent nocturnal awakenings. In PTSD, recurrent nightmares and REM fragmentation are pathognomonic features, maintaining hypervigilance and intrusive re-experiencing (Germain, 2013). These findings highlight how sleep disturbances not only reflect the physiological expression of hyperarousal but also perpetuate emotional dysregulation and avoidance behaviors that define anxiety pathology.
In bipolar disorder, the prevalence of sleep alterations reaches 70–99% across phases. During manic or hypomanic episodes, decreased need for sleep and reduced sleep efficiency are hallmark symptoms, while hypersomnia and sleep inertia dominate depressive phases. Inter-episode periods are also characterized by irregular sleep–wake rhythms, delayed circadian phase, and increased variability in sleep duration from night to night. Such instability predicts mood episode recurrence and poorer functional outcomes. Furthermore, circadian misalignment and evening chronotype have been linked to greater impulsivity and suicidality in bipolar populations (Harvey, 2008; Gonzalez et al., 2014).
Patients with schizophrenia exhibit some of the most profound sleep–wake disruptions in psychiatry. Polysomnographic (PSG) studies reveal prolonged sleep latency, reduced sleep efficiency, altered spindle activity, and desynchronized circadian rhythms (Wulff et al., 2012). Actigraphic data confirm delayed sleep timing, irregular rest–activity cycles, and excessive time spent in bed, often dissociated from actual sleep. These disturbances are not merely secondary to antipsychotic medication or hospitalization: they are intrinsic to the disorder and correlate with negative symptoms, cognitive

deficits, and reduced social functioning. Moreover, poor sleep has been shown to exacerbate positive psychotic experiences such as hallucinations and delusions, and targeted treatment of insomnia with CBT-I can significantly reduce psychotic distress (Freeman et al., 2015).

Sleep abnormalities are also pervasive in neurodevelopmental and trauma-related conditions. In attention-deficit/hyperactivity disorder (ADHD) and autism spectrum disorders, irregular sleep timing, delayed circadian phase, and restless sleep are frequent and often persist into adulthood. These alterations have been associated with emotional dysregulation, executive dysfunction, and reduced quality of life (Cortese et al., 2020). Similarly, individuals exposed to early-life trauma frequently develop chronic insomnia, nightmares, and hyperarousal, which may mediate the link between adverse childhood experiences and later psychiatric morbidity.

The clinical and public health burden of sleep disturbances is considerable. Chronic insomnia increases the risk of developing depression, anxiety, substance use, cardiovascular disease, and metabolic disorders. From a functional perspective, impaired sleep contributes to cognitive deficits, daytime fatigue, irritability, and diminished occupational and social performance. The resulting reduction in quality of life is comparable to that observed in major chronic diseases such as diabetes or hypertension (Reimer et al., 2003). At the societal level, sleep disorders are associated with increased healthcare utilization, work absenteeism, and accident risk, translating into substantial economic costs.

Despite their prevalence and impact, sleep problems remain under-recognized and under-treated in psychiatric practice. Patients rarely report them spontaneously, and clinicians often attribute them solely to the primary disorder or its pharmacological treatment. Yet, mounting evidence indicates that sleep disturbances are not merely secondary symptoms but active components of psychopathology. Their persistence after clinical remission strongly predicts relapse and chronicity, while their improvement often precedes and facilitates broader recovery. Treating sleep problems as independent therapeutic targets therefore represents a crucial step toward precision psychiatry.

In summary, epidemiological and clinical evidence converge to show that sleep disturbances permeate virtually all mental disorders, shaping their onset, trajectory, and outcome. They represent both a marker of vulnerability and a determinant of prognosis.

Understanding their patterns and mechanisms across diagnostic boundaries not only refines our comprehension of psychopathology but also opens concrete opportunities for prevention and intervention through the systematic assessment and treatment of sleep.

### 1.6 Sleep in early psychosis and bipolar disorder

Numerous studies have demonstrated that sleep is closely connected to mood regulation, cognition, memory, and the ability to respond to stress (Walker, 2017). Alterations in sleep quality or quantity are frequently observed in association with various mental disorders and can act both as symptoms and as predisposing or aggravating factors.

The quality of life of individuals affected by sleep disorders is generally lower than that of the general population, particularly in domains related to energy and fatigue. This condition can be compared to that observed in individuals suffering from chronic illnesses such as hypertension or chronic obstructive pulmonary disease (Reimer et al., 2003). Sleep deprivation can lead to a range of negative effects, including decreased mood, difficulties in emotion regulation, heightened pain perception, negative interpretation of neutral stimuli, reduced working memory, and impaired problem-solving ability (Freeman et al., 2020).

One of the most significant roles of sleep in mental health, as previously mentioned, concerns mood regulation. Insufficient or disturbed sleep is closely linked to the onset of depressive and anxiety symptoms. Even short periods of sleep deprivation can cause irritability, decreased stress tolerance, and increased emotional sensitivity (Riemann et al., 2020). More specifically, sleep quality affects emotional regulation capacity, with sleep deprivation reducing the ability to modulate emotional responses, thereby increasing vulnerability to external stimuli.

The relationship between sleep and depression can be considered bidirectional: depression can cause sleep alterations such as insomnia or hypersomnia, and sleep disturbances can contribute to the development and maintenance of depression (Baglioni et al., 2016). Insomnia is one of the most common symptoms of depression and often precedes the onset of a depressive episode, suggesting that treating insomnia may have a preventive effect against depression.

In patients diagnosed with bipolar disorder, sleep alterations are common and can predict the onset of manic or depressive episodes. Reduced need for sleep is a core symptom of mania, while hypersomnia is frequently observed during depressive episodes (Harvey, 2008). Sleep disturbances are among the most frequent and specific symptoms of bipolar disorder and have been associated with a worse illness course, greater severity of affective episodes, and significant impairment in functioning and quality of life (Gonzalez et al., 2014).

Sleep alterations may represent potential biomarkers of bipolar disorder. Biomarkers of depressive episodes include increased REM sleep fragmentation, reduced REM latency, increased REM density, and higher percentages of nocturnal awakenings. Biomarkers of manic episodes, on the other hand, include reduced REM latency, increased stage I sleep, elevated REM density, fragmented sleep, reduced total sleep time, and longer periods of wakefulness in bed.

These REM sleep changes in bipolar disorder and other mood disorders, such as unipolar depression, suggest a central role of this sleep phase in mood regulation (Gold et al., 2016). Alterations of the sleep–wake rhythm are often residual symptoms persisting during inter-episode periods and are frequently reported by patients.

Sleep disturbances are also a common comorbidity in patients affected by psychosis, particularly in cases of first-episode psychosis. According to studies in the literature, sleep disturbances are among the most common prodromal symptoms of psychosis onset, with a prevalence of about 46% (Reeve et al., 2022). The most frequent sleep disturbances in individuals with psychosis are insomnia (both initial and terminal) and nightmares—recurrent awakenings following distressing dream content. A study by Lunsford-Avery showed that sleep abnormalities such as reduced sleep efficiency and increased wake time after sleep onset predict psychosis onset in individuals at high risk (Lunsford-Avery et al., 2017). These alterations not only reflect underlying neurobiological dysfunction but may also contribute to the exacerbation of psychotic symptoms. Insomnia, for example, has been associated with increased positive symptoms such as delusions and hallucinations. It has been hypothesized that sleep deprivation may elevate striatal dopamine levels, which are closely linked to psychotic activity.

Several studies have reported alterations in sleep architecture in populations at risk for psychosis and bipolar disorder. Individuals at ultra-high risk (UHR) show longer sleep latency compared to control groups. Actigraphic data reveal differences compared to the general population, such as increased wake time after sleep onset (WASO)—an index of sleep fragmentation and poor continuity—reduced sleep efficiency, more nocturnal movements, longer daytime naps, more fragmented circadian rhythms, and a delayed sleep onset. Notably, these parameters have been significantly associated with greater severity of positive symptoms. Finally, EEG studies have identified increased gamma activity during NREM sleep across a broad fronto-parieto-occipital area. Evidence regarding REM sleep remains limited, and the few existing studies have not reported significant differences between UHR individuals and control groups (Clarke et al., 2021).

| **Sleep disorder** | **Psychosis onset** | **Bipolar onset** |
|---|---|---|
| *Insomnia* | Prevalence up to 50%; difficulties in sleep initiation and maintenance | Prevalence around 50%; often an early signal of manic or depressive episodes |
| *Hypersomnia* | Less common; associated with negative symptoms and disorganization | Frequent during depressive episodes; non-restorative sleep |
| *Circadian rhythm alterations* | Delayed sleep phase, with impaired daytime functioning | Phase shifts and marked alterations in the sleep–wake cycle, particularly during mania |
| *Parasomnia* | Periodic limb movements during sleep and bruxism are more common | Rare parasomnias, often related to pharmacological treatment |

**Table 1.** *Main sleep disorders in early psychosis and bipolar onset.*

The presence of sleep disturbances has been associated with a worse psychopathological course, often leading to an exacerbation of positive symptoms. However, the relationship between sleep disorders and psychosis remains to be fully clarified.
In patients with schizophrenia, pharmacological treatment for sleep disorders mainly relies on the use of antipsychotics, which may act on both mental symptoms and sleep problems.
Circadian rhythm alterations and insomnia are the sleep disturbances most strongly associated with schizophrenia. Several studies have shown that individuals with schizophrenia often display delayed and/or desynchronized sleep–wake cycles, longer sleep onset latency, and increased total time spent in bed compared to control groups. These patients frequently exhibit an evening chronotype, whereas a morning chronotype appears to have a protective role against schizophrenia.
The bidirectional relationship between these disturbances and schizophrenia highlights the close connection between the circadian system and dopamine regulation. Dopaminergic activity is modulated by CLOCK genes in brain regions such as the retina, striatum, olfactory bulb, midbrain, and hypothalamus. Dopamine also appears to interact with adenosine and glutamate, which are key regulators of sleep and circadian rhythms. Some studies emphasize the central role of adenosine in the pathogenesis of schizophrenia, suggesting that reduced adenosine signaling may lead to excessive dopaminergic activity or decreased glutamatergic transmission (Singer et al., 2023; Pritchett et al., 2012).
Paliperidone has been shown to improve sleep quality, while olanzapine increases REM sleep and stage 3 NREM sleep without altering REM latency or density. Other drugs, such as zopiclone, a sedative-hypnotic, and melatonin, can enhance sleep efficiency and reduce nocturnal awakenings. Zopiclone, in particular, is preferred over benzodiazepines for short-term insomnia, since benzodiazepines can negatively affect slow-wave and REM sleep, both already impaired in patients with schizophrenia.
In individuals at risk of psychosis or with first-episode psychosis, pharmacological treatments for sleep disturbances include benzodiazepines and their agonists, antipsychotics for acute psychotic episodes, melatonin, and orexin receptor antagonists.
Non-pharmacological interventions represent a first-line strategy for managing sleep disorders in psychiatric patients. Among them, CBT-I is considered the most effective

treatment for insomnia in both schizophrenia and bipolar disorder (Furukawa et al., 2025). Other approaches include chronotherapy and IPSRT, particularly useful for circadian rhythm disturbances.

Chronotherapy aims to restore a regular sleep–wake cycle through techniques such as sleep deprivation, bright light therapy, dawn/dusk simulation, dark therapy, and integrative approaches. IPSRT, based on the theory of social zeitgebers, focuses on stabilizing daily biological and social rhythms, addressing interpersonal relationships and links between life events and mood fluctuations.

Even in individuals at risk of psychosis or with early psychotic episodes, non-pharmacological management, especially CBT-I, has proven effective. In addition to improving sleep, CBT-I helps reduce psychotic symptoms and alleviate anxiety and depression.

Treatment of sleep disturbances in bipolar disorder involves several classes of drugs, including benzodiazepines, benzodiazepine receptor agonists, antipsychotics, anticonvulsants, antidepressants, melatonin, and melatonin receptor agonists. Benzodiazepines and their agonists are primarily used for the acute management of insomnia. Among them, zolpidem is currently the most prescribed medication for sleep problems in bipolar disorder. However, benzodiazepine use should be limited in duration to avoid side effects such as dependence, tolerance, and rebound insomnia. For chronic insomnia, some studies support the cautious use of low-dose antidepressants, given the potential risk of inducing manic or hypomanic states. Anticonvulsants have also shown benefits on sleep—gabapentin, for example, improves REM sleep and increases slow-wave sleep duration. Finally, antipsychotics can be useful for improving sleep, either as primary treatments or in combination with other therapies.

In conclusion, the management of sleep disturbances should be regarded as an essential component of care for patients with early psychosis or mood disorders. Early and targeted treatment of these alterations may improve prognosis, reduce relapse risk, and enhance overall quality of life.

### 1.7 Narcolepsy and psychiatric comorbidity: a bidirectional model

Narcolepsy type 1 (NT1) is a rare chronic central disorder of hypersomnolence characterized by excessive daytime sleepiness (EDS), low levels of cerebrospinal (CSF) hypocretin, and cataplexy (i.e., loss of muscle control triggered by emotions during wakefulness), a pathognomonic disease symptom (American Academy of Sleep Medicine, 2023). Conversely, narcolepsy type 2 (NT2) shares EDS but presents with normal levels of hypocretin and the absence of cataplexy.

While traditionally classified within sleep medicine, narcolepsy has increasingly been recognized as a condition that lies at the crossroads between neurology and psychiatry. Its clinical expression extends well beyond sleep–wake instability, encompassing a range of affective, anxiety, and psychotic manifestations that often exert a greater impact on quality of life than the core symptoms themselves (Bassetti et al., 2019). Psychiatric comorbidities are highly prevalent in NT1, with depression and anxiety representing the most frequent (Vourdas et al., 2002; Fortuyn et al., 2010). Lifetime rates of depressive symptoms are estimated at around 40–60%, often fluctuating with disease course and sleep quality. Anxiety disorders, including social anxiety and panic attacks, are also common and may be aggravated by anticipatory fear of cataplexy or by experiences of social stigma (Ohayon et al., 2013). Emotional flattening and reduced motivation, sometimes mistaken for residual depression, may instead reflect the direct neurobiological effects of orexin deficiency on reward and arousal networks. The prevalence of suicidal ideation and attempts is consistently higher in patients with narcolepsy than in the general population, and this risk cannot be fully explained by comorbid depression (Barateau et al., 2025). Fragmented sleep, REM dysregulation, and chronic emotional instability appear to directly contribute to suicidal vulnerability, alongside feelings of hopelessness and loss of control frequently reported in individuals experiencing cataplexy.

Psychotic-like experiences can also occur in a subset of patients, particularly in adolescence and early adulthood. These include vivid hallucinations, dream-reality confusion, and transient delusional interpretations, which usually arise from REM intrusion into wakefulness. In most cases, such phenomena are self-limited, yet in vulnerable individuals—especially those with a family history of psychosis—they may

evolve into persistent psychotic symptoms (Plazzi et al., 2015). The resulting clinical picture can be complex, challenging traditional diagnostic boundaries and emphasizing the need for an integrated view of narcolepsy as both a sleep and psychiatric disorder. From a neurobiological perspective, the hypocretin/orexin system exerts widespread influence over circuits that regulate arousal, emotion, and motivation. Orexin neurons project to monoaminergic nuclei such as the locus coeruleus, dorsal raphe, and ventral tegmental area, orchestrating noradrenergic, serotonergic, and dopaminergic activity. Their degeneration leads to reduced activation of these systems, causing chronic hypoarousal, dysphoria, and instability of reward processing. Neuroimaging studies have shown altered amygdala and medial prefrontal activity during emotional tasks in NT1, consistent with impaired top-down modulation of affect. In parallel, the characteristic REM sleep dysregulation of narcolepsy—marked by premature REM onset and increased REM density—mirrors abnormalities described in mood disorders and post-traumatic stress disorder, where REM instability interferes with emotional memory processing and stress adaptation. These converging alterations help explain why patients with narcolepsy often experience mood swings, anxiety, or psychotic-like states even in the absence of major psychiatric diagnoses.

Psychiatric manifestations may further interact with the sleep–wake alterations typical of narcolepsy, creating a self-perpetuating cycle. Depression, anxiety, and stress can exacerbate excessive sleepiness and cataplexy by destabilizing circadian rhythms and increasing sympathetic activation. Conversely, fragmented sleep and disrupted REM regulation amplify emotional reactivity and cognitive biases, promoting the onset or recurrence of psychiatric symptoms. This mutual reinforcement supports the notion of a bidirectional relationship between narcolepsy and psychopathology, in which neurobiological vulnerability and psychosocial stressors act synergistically.

Developmental and environmental factors further shape this interaction. NT1 often begins in adolescence or early adulthood, a period marked by profound neurobiological and psychosocial change. The impact of excessive daytime sleepiness on academic performance, self-esteem, and social functioning can lead to isolation and depressive trajectories. Stigma and misunderstanding of the disease may increase anxiety and avoidance behaviors. Genetic predispositions, including HLA and immune-related

variants, may modulate both susceptibility to narcolepsy and vulnerability to psychiatric disorders, pointing to shared etiological pathways.

Clinically, this complex interplay implies that psychiatric symptoms in narcolepsy should not be considered secondary or reactive but integral to the disorder. Their recognition is essential for accurate diagnosis and effective treatment. A multidisciplinary approach combining pharmacological management with psychological and behavioral interventions offers the best outcomes.

In recent years, the understanding of narcolepsy has evolved from a purely neurological model to a biopsychosocial one, emphasizing its bidirectional links with mental health. Orexin deficiency and REM dysregulation create a neurophysiological substrate that predisposes to affective and psychotic symptoms, while psychiatric comorbidities in turn modulate disease expression and quality of life. This reciprocal relationship underscores the need for systematic psychiatric assessment in all patients with narcolepsy and for integrated care pathways bridging sleep medicine and psychiatry. By addressing both dimensions together, clinicians can move closer to a personalized approach that treats not only the disorder of sleep, but the disorder of being awake.

### 1.8 Sleep as a therapeutic and preventive target

The growing recognition of sleep as a modifiable determinant of mental health has profound implications for both clinical practice and prevention. Once regarded merely as a symptom of psychiatric disorders, sleep is now considered a central therapeutic and preventive target capable of influencing the trajectory of illness. Evidence from longitudinal, interventional, and neurobiological studies shows that improving sleep can reduce psychiatric symptoms, enhance emotional regulation, and prevent relapse, supporting the notion that sleep restoration acts as a gateway to mental stability (Freeman et al., 2017; Harvey et al., 2015).

In depression, insomnia treatment has proven to exert antidepressant effects independent of mood-focused interventions. CBT-I is the most effective non-pharmacological strategy and yields response rates comparable to those of antidepressant medications, without the associated side effects (Espie et al., 2018). Moreover, when CBT-I is combined with standard depression treatment, outcomes are

significantly improved, and remission is achieved earlier. The same holds true for bipolar disorder, where interventions aimed at regularizing circadian rhythms—such as IPSRT and chronotherapy—reduce mood episode recurrence and improve functional recovery (Frank et al., 2021). Light therapy, administered under controlled protocols, has also demonstrated efficacy in both unipolar and bipolar depression, suggesting that manipulating circadian cues can realign biological and affective rhythms.

In anxiety and trauma-related disorders, targeting sleep disruption can attenuate hyperarousal and intrusive memories. Imagery Rehearsal Therapy (IRT) for nightmares and CBT-I for insomnia have shown robust effects in reducing PTSD symptoms and improving overall functioning. Sleep-focused interventions appear to facilitate the extinction of fear memories by restoring REM sleep integrity, which is crucial for adaptive emotional processing (Germain, 2013; Walker & van der Helm, 2009). Pharmacological approaches that enhance slow-wave sleep or stabilize REM sleep, such as prazosin for nightmares or certain orexin receptor antagonists, have also contributed to symptom improvement in these populations.

In psychosis, behavioral interventions for insomnia represent one of the few non-pharmacological approaches capable of reducing both sleep problems and positive psychotic symptoms. Randomized controlled trials have demonstrated that CBT-I in individuals with schizophrenia leads not only to improved sleep continuity but also to decreased hallucinations and paranoia, likely mediated by reduced emotional distress and hypervigilance (Freeman et al., 2015). Similarly, early interventions targeting circadian irregularities in individuals at clinical high risk for psychosis have been associated with delayed or reduced transition to full-blown psychosis, reinforcing the preventive potential of sleep stabilization (Reeve et al., 2019).

From a neurobiological standpoint, therapeutic interventions on sleep may exert their benefits by restoring balance within the systems that regulate arousal, emotion, and stress. Improving sleep continuity normalizes activity in the amygdala–prefrontal circuit, enhances connectivity in limbic and executive networks, and reduces proinflammatory cytokine levels (Irwin & Opp, 2017). These changes translate into improved affective stability, cognitive control, and resilience to stress—core dimensions shared across psychiatric disorders. Sleep-focused treatments thus operate not only as

symptomatic relief but as true neuromodulatory interventions acting at the level of brain–body homeostasis.

The preventive implications of this perspective are equally significant. Sleep disturbances often precede the onset of major mental disorders by several years, providing an accessible window for early detection and intervention. Adolescence, in particular, represents a critical period in which irregular sleep patterns and delayed circadian phase interact with neurodevelopmental vulnerabilities, predicting later depression, bipolar disorder, and suicidality (Carskadon, 2011; Lovato & Gradisar, 2014). School- and community-based programs promoting sleep hygiene, digital behavioral interventions, and monitoring of at-risk youth have shown encouraging results in reducing anxiety, depressive symptoms, and self-harm behaviors.

Technological advances are also transforming sleep into a measurable biomarker and a vehicle for personalized psychiatry. Wearable devices, actigraphy, and digital phenotyping now allow the continuous monitoring of sleep–wake patterns, circadian regularity, and nocturnal physiology in naturalistic settings. These tools can identify early deviations from baseline, enabling timely preventive action before the onset of full clinical syndromes (Torous et al., 2014). Digital CBT-I and app-based sleep training programs are expanding accessibility to evidence-based interventions, bridging the gap between research and public health.

Altogether, the convergence of evidence positions sleep as a cornerstone of mental health intervention. Whether through behavioral therapy, chronotherapeutic modulation, pharmacological agents, or digital tools, targeting sleep offers a rare combination of efficacy, safety, and preventive potential. Beyond treating insomnia or hypersomnia, optimizing sleep means acting on the underlying mechanisms of affect regulation, cognition, and stress response that sustain psychiatric well-being. In this light, sleep should no longer be viewed as a passive state or secondary symptom, but as an active therapeutic system—one that, when nurtured, can restore balance to the mind itself.

### 1.9 Gaps in current knowledge and rationale of the thesis

Despite the growing evidence linking sleep and mental health, several conceptual and methodological gaps still limit our understanding of this relationship. Most existing

studies remain disorder-specific, focusing on single diagnostic categories such as depression, bipolar disorder, or schizophrenia, rather than examining sleep as a transdiagnostic dimension that cuts across traditional boundaries. As a result, findings are often fragmented and difficult to integrate within a unified framework of vulnerability and psychopathology. Furthermore, many investigations rely solely on subjective measures of sleep, which, although clinically relevant, are influenced by mood, cognition, and perception, and therefore cannot fully capture the complexity of sleep–wake regulation. Objective tools such as actigraphy and PSG are less frequently used in psychiatric research, and their integration with psychometric and clinical data is still limited.

Another major limitation concerns the temporal dimension of sleep disturbances. Longitudinal studies that clarify whether sleep alterations precede, accompany, or follow psychiatric symptoms remain scarce. This restricts our ability to establish causal inferences and to identify early markers of vulnerability. Similarly, there is insufficient research on how interventions targeting sleep may influence the onset, course, and prognosis of mental disorders, particularly in the early or prodromal stages. While randomized trials have shown that behavioral and chronotherapeutic strategies can improve psychiatric outcomes, the mechanisms underlying these effects, neurobiological, psychological, or circadian, are still poorly understood.

At the neurobiological level, the pathways linking sleep dysregulation to psychopathology are multifactorial and not yet clearly delineated. Dysfunctions in neurotransmitter systems, circadian clock genes, stress and inflammatory responses, and emotional regulation circuits all appear to play a role, but their relative contributions vary across disorders and developmental stages. Understanding how these mechanisms interact is crucial to move beyond descriptive correlations and toward mechanism-based interventions.

From a developmental and preventive perspective, adolescence and early adulthood represent critical windows during which sleep disturbances often emerge in parallel with affective or psychotic vulnerability. Yet, research on these transitional periods remains fragmented, and little is known about how early correction of sleep–wake instability could alter long-term trajectories of mental illness. Likewise, conditions at the interface between neurology and psychiatry, such as NT1, are rarely studied within a

transdiagnostic framework, despite offering a unique opportunity to explore the shared neurobiology of sleep and emotion.

Taken together, these gaps underscore the need for an integrated approach that bridges sleep medicine and psychiatry. The present doctoral thesis was conceived within this framework, aiming to investigate sleep disturbances as both markers of vulnerability and targets for intervention across diverse clinical contexts. Through a combination of original studies, secondary data analyses, and systematic reviews, it examines how sleep alterations manifest in different populations, from adolescents with psychiatric disorders, to adults in the early phases of psychosis and bipolar disorder, to patients with NT1, and how they relate to core psychopathological dimensions such as suicidality, mood instability, and emotional dysregulation.

By combining subjective and objective sleep measures with clinical and psychosocial factors, this work aims to clarify the mechanisms linking sleep and psychopathology, identify modifiable risk factors, and outline translational approaches for prevention and personalized treatment. In doing so, it adds to an increasing body of evidence supporting the idea that sleep is not just an epiphenomenon of psychiatric illness but a key factor influencing its onset, progression, and outcome.

## CHAPTER 2 – AIMS OF THE THESIS

The overarching aim of this doctoral thesis is to investigate the role of sleep disturbances as transdiagnostic markers and potential therapeutic targets in psychiatry, integrating evidence from different populations and methodological perspectives. Building upon the premise that alterations in sleep–wake regulation contribute to vulnerability, symptom expression, and prognosis across mental disorders, this work sought to delineate the clinical and neurobiological interfaces between sleep and psychopathology.

More specifically, the thesis pursued five interconnected objectives.

First, it examined the relationship between sleep disturbances and suicidality in adolescents with psychiatric disorders, identifying which dimensions of sleep quality independently predict suicidal ideation and behavior beyond depressive symptoms and psychosocial risk factors.

Second, it explored the prevalence, characteristics, and correlates of sleep disturbances in adults experiencing a first episode of psychosis or bipolar disorder, using both subjective (questionnaire-based) and objective (actigraphic) assessments, and investigated their association with symptom severity and clinical outcomes.

Third, it synthesized the available literature on sleep disturbances in early psychosis, outlining their main features, prognostic significance, and therapeutic implications.

Fourth, it investigated psychiatric comorbidities in NT1, with particular attention to the link between sleep–wake instability, emotional dysregulation, and suicidal vulnerability, describing distinct phenotypic profiles across developmental stages.

Finally, it reviewed the evidence on therapeutic strategies targeting sleep in bipolar disorder, including both pharmacological and non-pharmacological interventions, evaluating their impact on mood stabilization and suicidality.

Through these complementary lines of inquiry, the thesis aims to offer an integrated framework connecting sleep and mental health, highlighting the relevance of sleep as a measurable and modifiable dimension within precision psychiatry and suicide prevention.

# CHAPTER 3 – MATERIAL AND METHODS

## 3.1 Studies design and overall approach

This doctoral thesis was designed as a multi-method research program combining clinical studies and systematic reviews. The main goal was to examine sleep disturbances as transdiagnostic markers of vulnerability and potential treatment targets across various psychiatric populations and stages of illness. The studies included in this work were conducted independently but were conceptually linked, each exploring different aspects of the sleep-psychopathology connection within a unified framework.
The first line of research focused on the association between sleep quality and suicidal risk in adolescents with psychiatric disorders. A cross-sectional study was carried out on inpatients admitted to a specialized psychiatric unit, integrating sociodemographic, clinical, and psychometric data. Standardized instruments were used to assess sleep quality, depressive symptoms, and suicidal ideation, enabling the identification of specific sleep dimensions that independently predicted suicidality. To strengthen these findings, a meta-analysis was subsequently performed, synthesizing evidence from large-scale studies on sleep disturbances and suicidal behavior in adolescents worldwide.
The second research line examined the prevalence, characteristics, and correlates of sleep disturbances in adults experiencing a first episode of psychosis or bipolar disorder. This study combined subjective assessments (questionnaires) with objective sleep measures (actigraphy) to capture the multidimensional nature of sleep–wake disruption in early phases of severe mental illness. The analysis explored associations between sleep alterations and key psychopathological features, including mood symptoms, suicidality, and functional outcomes. Complementarily, a systematic review of the literature was conducted to summarize current evidence on sleep disturbances in early psychosis and the therapeutic management of sleep disturbances in bipolar disorder.
The third line of research explored psychiatric comorbidities in both adults and adolescents with NT1. This work aimed to characterize the bidirectional relationship between sleep pathology and psychopathology, emphasizing narcolepsy as a model condition at the intersection between sleep medicine and psychiatry.

The integration of complementary methodologies—observational, experimental, and systematic—was conceived to provide a multidimensional view of sleep as a transdiagnostic phenomenon. By combining subjective and objective measures, cross-sectional and longitudinal perspectives, and clinical and meta-analytic evidence, this thesis sought to bridge the gap between theoretical models and practical applications. The overall approach reflects a translational perspective, in which sleep is not only studied as a correlate of psychiatric symptoms but as a central component of vulnerability, prevention, and treatment in mental health.

## 3.2 Study I – Sleep disturbances and suicidal risk in adolescents

### 3.2.1 Study design and participants

This prospective study was conducted at the Children and Adolescents Intensive Treatment Ward, "Villa Igea—il Nespolo," a tertiary-care facility specializing in intensive psychiatric treatment for adolescents. Participants were recruited between January 2020 and December 2024. Basic demographic information, including age and gender, was systematically recorded for all enrolled individuals. Ethical approval was obtained from the Institutional Review Board of the Medical University of Modena and Reggio Emilia, Italy, and all procedures complied with relevant guidelines for human research. The study adhered to the Declaration of Helsinki guidelines for ethical research.

Adolescents aged 12–18 years admitted for acute psychiatric care due to suicide attempts were eligible for inclusion. A suicide attempt is defined as a self-directed, harmful behavior to end one's life, regardless of the outcome, in line with DSM-5 criteria. In contrast, suicidal ideation is defined as recurrent or persistent thoughts of death or wishing to die without necessarily having a specific plan or intent to act on these thoughts. Patients were excluded if they had incomplete medical records, primary diagnoses of neurological disorders, or conditions directly affecting sleep independent of psychiatric symptoms (e.g., sleep apnea, narcolepsy).

### 3.2.2 Measures and instruments

Demographic and clinical data were extracted from electronic medical records. Psychiatric diagnoses, including depression and NSSI, were determined by attending psychiatrists using DSM-5 criteria during clinical interviews. Insomnia was defined as difficulty initiating or maintaining sleep or experiencing early morning awakenings, occurring at least three nights per week for a minimum of one month, accompanied by significant daytime impairment, according to the ICSD-3 criteria for insomnia.
Information about cannabis use and compulsive social media usage was gathered from electronic medical records, specifically documented during psychiatric intake interviews. Cannabis use was categorized as occasional or frequent based on patients' self-reports and clinical assessments. Compulsive social media use was evaluated qualitatively by psychiatrists, who considered patients' self-reported difficulties in managing their time on social media and its impact on daily functioning. During these clinical interviews, psychiatrists rated the presence of cannabis and social media misuse on a scale from 0 to 1.
Physical activity was classified as structured (e.g., participation in sports, gym workouts) or unstructured (e.g., walking, cycling), according to self-reported involvement in these activities.
These evaluations were part of the standard admission process and included detailed clinical interviews, patient history, and behavioral assessments.
Participants were divided into two groups: those with a reported suicide attempt (suicidal group) and those without (non-suicidal group). This classification was based on medical records and clinical evaluations conducted during hospitalization. Suicide risk was assessed clinically by attending psychiatrists based on structured clinical interviews and medical history as part of routine psychiatric evaluation. No specific psychometric scales were used for this assessment.
All clinical evaluations were performed during the first 48 hours of admission. Two independent researchers extracted information from electronic medical records to ensure data accuracy and cross-referenced findings to minimize errors. Any discrepancies were resolved through consensus discussions with a senior psychiatrist. A standardized protocol guided the data extraction process to maintain consistency, and regular quality

checks were conducted to verify the completeness and reliability of the extracted variables.

Descriptive statistics (means, standard deviations, frequencies) were utilized to summarize participant characteristics. Chi-square tests or Fisher's exact tests were employed to evaluate associations between insomnia and categorical variables, while independent t-tests or Mann-Whitney U tests were applied to continuous variables. Spearman's correlation coefficients were calculated to examine the relationships among insomnia, depression, non suicidal self-injury (NSSI), cannabis abuse, and compulsive social media use, considering the potential non-normal distribution of the data. Correlation coefficients (r) were reported with asterisks indicating statistically significant values, and the corresponding p-values ($p < 0.05$ or $p < 0.01$) were noted in the table legend for clarity.

A stepwise approach was employed for the logistic regression model to minimize multicollinearity, and independent variables were selected based on their clinical relevance and statistical significance from univariate analyses. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated to assess the strength of associations. Statistical significance was determined at $p < 0.05$. All analyses were carried out using JASP version 12.2.

### 3.2.3 Results

A total of 95 individuals were recruited, including 54 in the suicidal group and 41 in the non-suicidal group. Female participants were more prevalent among suicide attempters (90%) than in no-suicide attempters (75%), showing a statistically significant difference ($p = 0.04$). The median age did not differ significantly between the groups, centered at 16 years ($p = 0.40$). Family income distributions were comparable across the groups, with no significant difference ($p = 0.60$). A higher proportion of suicide attempters had a family psychiatric history (83%) compared to no-suicide attempters (63%) ($p = 0.04$). In contrast, although more suicide attempters reported a family history of suicide (26%) compared to no-suicide attempters (9%), this difference did not reach statistical significance ($p = 0.47$).

Insomnia was more common in suicide attempters (79%) than in non-suicide attempters (53%; p = 0.01). Although the subtypes of insomnia (initial, maintenance, and terminal) did not differ significantly between the groups, the frequency of nightmares was higher in suicide attempters (31%) compared to non-suicide attempters (12%; p = 0.02). Nighttime sleep duration showed no significant group differences (p = 0.68), with most participants in both groups reporting less than six hours of sleep per night.
Bullying was significantly more common among suicide attempters, with 26% reporting being bullied compared to 9% in the non-suicide attempters' group (p = 0.01). Physical activity was less common in suicide attempters (27%) than in non-suicide attempters (53%; p = 0.01). Tobacco use was more prevalent among suicide attempters (55%) than in the other group (39%), although this difference was not statistically significant (p = 0.09). Similarly, cannabis and alcohol use did not differ significantly between the groups. Depression was reported by nearly all suicide attempters (96%) compared to 70% of non-suicide attempters, a statistically significant difference (p = 0.01).

| *Variable* | Suicide attempters (n=54) | No-suicide attempters (n=41) | *p value* | $\chi^2$ |
|---|---|---|---|---|
| **Female sex,** n (%) | 49 (90) | 31 (75) | **0.04** | 3.15 |
| **Age,** *Median (IQR)* | 16 (1) | 16 (3) | 0.40 | - |
| **Family income,** n (%) | | | | 2.26 |
| Low | 7 (12) | 7 (17) | 0.60 | - |
| Lower-middle | 37 (68) | 22 (53) | | - |
| Upper-middle | 10 (18) | 12 (29) | | - |
| **Family psychiatric history,** n (%) | 45 (83) | 26 (63) | **0.04** | 4.50 |
| **Family suicide history,** n (%) | 14 (26) | 4 (9) | 0.47 | 2.07 |
| **Bullied,** n (%) | 14 (26) | 4 (9) | **0.01** | 5.00 |
| **Physically active,** n (%) | 15 (27) | 22 (53) | **0.01** | 6.50 |
| **Tobacco use**, n (%) | 30 (55) | 16 (39) | 0.09 | 2.05 |
| **Cannabis use**, n (%) | 16 (29) | 10 (24) | 0.53 | 1.30 |
| **Alcohol use**, n (%) | 9 (16) | 8 (19) | 0.71 | 0.01 |
| **Depression**, n (%) | 52 (96) | 29 (70) | **0.01** | 7.50 |
| **NSSI,** n (%) | 49 (90) | 34 (82) | 0.15 | 1.60 |
| **Insomnia**, n (%) | 43 (79) | 22 (53) | **0.01** | 4.75 |
| Initial insomnia | 37 (68) | 23 (56) | 0.21 | - |

| | | | | |
|---|---|---|---|---|
| Maintenance insomnia | 21 (38) | 17 (41) | 0.80 | - |
| Terminal insomnia | 5 (9) | 5 (12) | 0.64 | - |
| **Nighttime sleep duration**, n (%) | | | | 0.45 |
| < 6 hours | 33 (61) | 27 (65) | | - |
| 6 hours | 21 (38) | 10 (24) | | - |
| ≥ 7 hours | 0 | 4 (8) | 0.68 | - |
| **Nightmares,** n (%) | 17 (31) | 5 (12) | **0.02** | 3.02 |

**Table 2.** *Sociodemographic and clinical characteristics of the sample.*

Spearman correlations were calculated to evaluate the relationship among insomnia, depression, NSSI, cannabis abuse, and compulsive social media use (Table 3). A strong positive correlation was found between insomnia and depression ($r = 0.45$, $p < 0.05$), suggesting that higher levels of insomnia correspond to increased depressive symptoms. Depression exhibited a moderate positive correlation with NSSI ($r = 0.40$, $p < 0.05$), suggesting that increased depressive symptoms were linked to higher engagement in NSSI.

NSSI showed a weak to moderate positive correlation with cannabis abuse ($r = 0.25$, $p < 0.05$) and a moderate positive correlation with compulsive social media use ($r = 0.22$, $p < 0.05$), both indicating a statistically significant relationship.

These findings emphasize the significant connection between insomnia and depression, suggesting that NSSI may be related to both cannabis abuse and compulsive social media use. Conversely, other relationships appear weak or non-significant.

| Variable | Insomnia | Depression | NSSI | Cannabis abuse | Compulsive social media use |
|---|---|---|---|---|---|
| **Insomnia** | 1.00 | **0.45*** | 0.10 | -0.05 | 0.12 |
| **Depression** | **0.45*** | 1.00 | **0.40*** | 0.20 | 0.18 |
| **NSSI** | 0.10 | **0.40*** | 1.00 | **0.25*** | **0.22*** |
| **Cannabis abuse** | -0.05 | 0.20 | **0.25*** | 1.00 | -0.10 |
| **Compulsive social media use** | 0.12 | 0.18 | **0.22*** | -0.10 | 1.00 |

**Table 3.** *Spearman correlation analysis between insomnia and clinical variables.*

The logistic regression analysis identified several significant predictors of the outcome, as shown in Table 4. Age was significantly associated with the outcome (p = 0.05), with each additional year increasing the odds by 11% (OR = 1.11).
Insomnia emerged as a significant predictor (p = 0.01), with individuals experiencing insomnia having 73% higher odds of the outcome (OR = 1.73). Similarly, depression was strongly associated with the outcome (p = 0.01), with individuals diagnosed with depression being more than twice as likely to experience the outcome (OR = 2.34). Physical activity demonstrated a protective effect (p = 0.02), reducing the odds of the outcome by 34% (OR = 0.66). Family psychiatric history showed a trend toward significance (p = 0.07), with individuals having a family history of psychiatric conditions being 39% more likely to experience the outcome (OR = 1.39). Conversely, gender (p = 0.12, OR = 1.24) and economic status (p = 0.18, OR = 0.90) were not statistically significant predictors in this model.

These findings highlight the significant roles of age, insomnia, depression, and physical activity in influencing the outcome, with physical activity serving as a protective factor. While family psychiatric history showed a potential association, gender and economic status were not significant predictors.

| *Variable* | Coefficient (β) | Standard error | *p value* | Odds ratio |
|---|---|---|---|---|
| **Age** | 0.10 | 0.05 | **0.05** | 1.11 |
| **Gender** | 0.22 | 0.15 | 0.12 | 1.24 |
| **Family psychiatric history** | 0.33 | 0.19 | 0.07 | 1.39 |
| **Insomnia** | 0.55 | 0.20 | **0.01** | 1.73 |
| **Economic status** | -0.10 | 0.08 | 0.18 | 0.90 |
| **Physically active** | -0.42 | 0.18 | **0.02** | 0.66 |
| **Depression** | 0.85 | 0.28 | **0.01** | 2.34 |

**Table 4.** *Logistic regression analysis.*

### 3.3.4 Meta-analysis on sleep disturbances and suicidality in adolescents

This meta-analysis aimed to quantitatively synthesize the evidence on the relationship between sleep disturbances and suicidal behaviors in adolescents. The study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and was prospectively registered on PROSPERO (CRD42023415526). A systematic search was conducted in PubMed, EMBASE, CENTRAL, and PsycINFO from inception to August 2024, including observational studies reporting suicidal ideation or suicide attempts among adolescents aged 12 to 21 years. To ensure consistency, studies focusing on participants with diagnosed psychiatric disorders were excluded, as the aim was to evaluate the association between sleep problems and suicidality in the general adolescent population.

Sleep disturbances were defined as insomnia symptoms, poor sleep quality, short sleep duration, frequent awakenings, nightmares, or other indicators of disrupted sleep. Suicidal behaviors were identified through validated self-report instruments or structured interviews. Data extraction and quality assessment were independently conducted by two reviewers using the Newcastle–Ottawa Scale (NOS), and disagreements were resolved through discussion with a senior investigator. Random-effects meta-analyses were performed using *R* software, calculating pooled ORs and

95% CIs for suicidal ideation and suicide attempts. Between-study heterogeneity was assessed with the $I^2$ statistic, and meta-regressions were used to explore the influence of demographic and behavioral moderators such as age, sex, bullying, and substance use. Publication bias was evaluated through funnel plots and Egger's test.

Nineteen studies met the inclusion criteria, encompassing a total of 1,196,271 adolescents (628,525 with sleep disturbances and 567,746 controls) from nine countries. The mean age across samples was 15.2 years, and females accounted for 46.3% of participants. Thirteen studies were rated as low risk of bias, and six as moderate, according to the NOS. The pooled analysis revealed that adolescents with sleep disturbances had significantly higher odds of suicide attempts (OR = 3.10; 95% CI = 2.43–3.95) and suicidal ideation (OR = 2.28; 95% CI = 1.76–2.94) compared to controls.

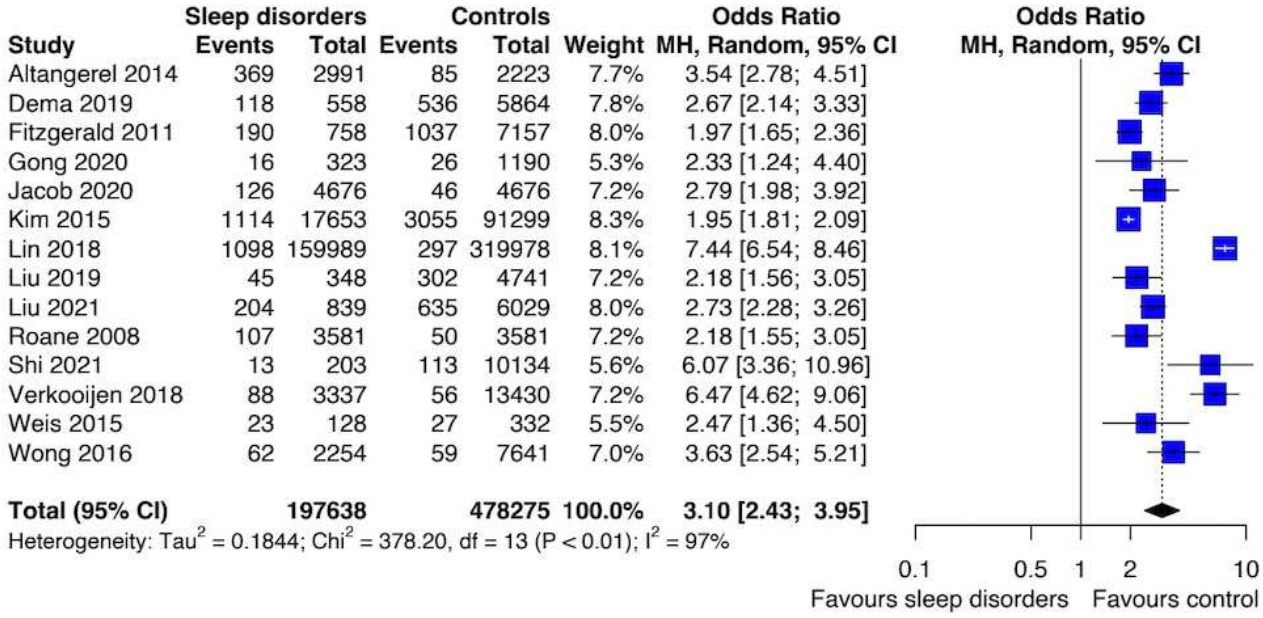


**Figure 2.** *Forest plot of the primary analysis of the association of suicide attempt and sleep disturbances.*

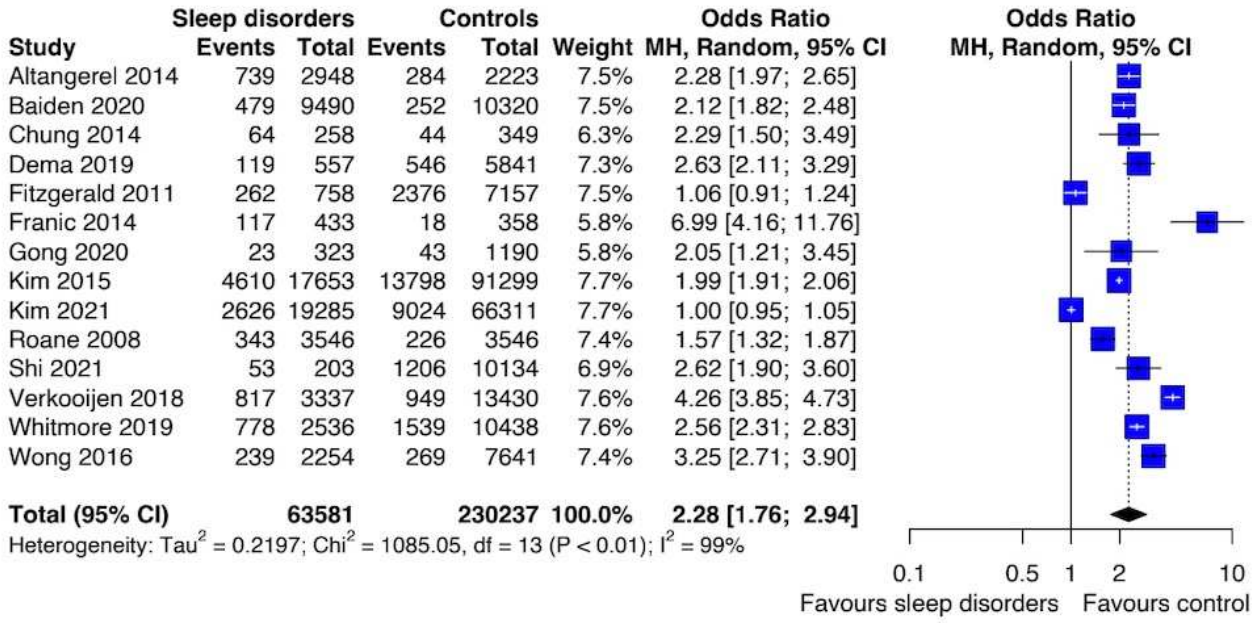


**Figure 3.** *Forest plot of the primary analysis of the association of suicide ideation and sleep disturbances.*

Sensitivity analyses confirmed the robustness of the results, with minimal variation after exclusion of lower-quality studies. Heterogeneity was substantial across studies, reflecting differences in methodology and sleep assessment tools, yet no significant publication bias was detected.

Meta-regression analyses indicate that the association between sleep disturbances and suicidality remained stable across sex, age, and other demographic variables, suggesting a pervasive relationship that is independent of sample composition. Data on non-suicidal self-injury and completed suicide were insufficient for quantitative synthesis but consistently pointed in the same direction.

### 3.3 Study II – Sleep disturbances in first-episode psychosis and bipolar disorder

#### 3.3.1 Study design and participants

This was a cross-sectional observational study conducted at the Bologna Department of Mental Health in Northern Italy, in collaboration with the Narcolepsy Center at the IRCCS Institute of Neurological Sciences of Bologna. The study took place from March 2024 to September 2025, as part of routine outpatient mental healthcare for adults recently diagnosed with psychosis or bipolar disorder.

Patients were consecutively recruited from community mental healthcare services in Bologna.

Inclusion criteria were: (i) age 18-35 years; (ii) diagnosis of first-episode psychosis or bipolar disorder, according to the DSM-5 criteria; (iii) illness episode duration of 12 months or less; and (iv) ability to provide informed consent. Exclusion criteria included: (i) intellectual disability, neurodegenerative disease, or major neurological disorder; (ii) comorbid substance use disorder; (iii) inability to complete self-report questionnaires; and (iv) fewer than seven valid nights of actigraphy monitoring.

Sociodemographic and clinical information (such as age, sex, education, employment, living situation, tobacco use, illness duration, and current medications) was collected using a structured data sheet. Medication use was not limited, and patients received standard pharmacological treatments as indicated in the international guidelines for the treatment of psychosis and bipolar disorder by their psychiatrists.

A group of healthy controls was recruited from university students and young adults in the local community who responded to online postings and word of mouth. Eligibility was verified through a brief clinical interview conducted by a psychiatrist to rule out current or past psychiatric disorders, as well as major neurological or medical conditions affecting sleep. Controls underwent the same actigraphic monitoring protocol as patients. Self-report questionnaires were not administered to controls, as they were only included to provide an objective benchmark for actigraphic sleep parameters.

### 3.3.2 Measures and instruments

Sleep quality was assessed using the PSQI, a 19-item self-report questionnaire evaluating subjective sleep quality over the previous month across seven domains: perceived quality, latency, duration, efficiency, sleep disturbances, use of hypnotics, and daytime dysfunction. Total scores range from 0 to 21, with higher values indicating poorer sleep quality; scores above 5 were considered indicative of clinically relevant sleep disturbance. The validated Italian version of the PSQI was used in this study. Subjective daytime sleepiness was measured with the *Epworth Sleepiness Scale (ESS)*, which asks participants to rate the likelihood of dozing off in eight everyday situations. Each item is scored from 0 (no chance of dozing) to 3 (high chance of dozing), yielding a total score between 0 and 24. A score of 11 or higher denotes pathological sleepiness. Depressive symptoms were evaluated using the *Beck Depression Inventory (BDI)*, a 21-item self-report scale assessing cognitive, affective, and somatic features of depression, with total scores ranging from 0 to 63. A cut-off score of 14 or higher indicates at least mild depressive symptomatology. Suicidal ideation was examined separately through item 9 of the BDI, which, despite its brevity, provides a validated and low-burden indicator of suicidal thoughts in clinical and research settings. Lifetime manic and hypomanic features were screened with the *Mood Disorder Questionnaire (MDQ)*, a 13-item self-report instrument in which yes/no responses identify the presence of characteristic bipolar symptoms. The MDQ also evaluates symptom clustering and functional impact, allowing identification of individuals with bipolar spectrum features without providing a formal diagnosis.

Prodromal and subthreshold psychotic symptoms were assessed using the *Prodromal Questionnaire-16 (PQ-16)*, a brief screening tool that captures positive, negative, and general symptoms associated with emerging psychosis. Each item is answered on a yes/no basis, and higher total scores indicate greater risk for prodromal manifestations. Consistent with previous studies, a cut-off score of six or higher was used to define clinically relevant subthreshold symptomatology.

Objective sleep–wake activity was recorded using wrist-worn actigraphs, which participants wore continuously on the non-dominant wrist for seven consecutive nights, including both weekdays and weekends. They also completed a sleep diary to assist in

the interpretation of actigraphic data. Recordings were analyzed using validated algorithms to derive parameters such as total sleep time (TST), sleep efficiency (SE), sleep onset latency (SOL), WASO, and indices of circadian rest–activity rhythm. Nights were considered valid if the device was worn for at least 90% of the nocturnal period, and participants with fewer than five valid nights were excluded from analyses.

The study received approval from the Independent Ethics Committee of the Area Vasta Emilia Centro (CE-AVEC, protocol no. 36330/AUSLBO). All participants provided written informed consent before enrollment and were free to withdraw at any time, in accordance with the principles of the Declaration of Helsinki and the General Data Protection Regulation (GDPR 2016/679).

Sociodemographic and clinical data were summarized as means and standard deviations for continuous variables, and as frequencies and percentages for categorical ones. Comparisons between groups—patients with psychosis and those with bipolar disorder—were performed using independent-samples *t*-tests or Mann–Whitney *U* tests for continuous variables, and chi-square or Fisher's exact tests for categorical data. Along with *p*-values, effect sizes were reported using Cohen's *d* for continuous variables and OR with 95% CI for categorical comparisons. Associations between sleep measures, depressive symptoms, prodromal features, and suicidal ideation were examined through Spearman's rank correlation coefficients. Logistic regression models were then applied to identify predictors of clinical variables, with validated cut-offs used for binary categorization (PSQI > 5, ESS ≥ 11, BDI ≥ 14, PQ-16 ≥ 6, and presence of suicidal ideation on BDI item 9). Actigraphic variables were averaged across valid nights and compared between patients and healthy controls, as well as between psychosis and bipolar subgroups. All statistical tests were two-tailed, with significance set at $p < 0.05$, and analyses were performed using JASP software (version 12.2, Amsterdam, The Netherlands).

### 3.3.3 Results of the study

The final clinical sample had a mean age of 25.00 ± 3.90 years. Slightly more than half were male (55%). Most participants had completed high school (90%), while a small percentage held a university degree (10%). The majority lived with their families (90%), and 30% were employed at the time of assessment. Tobacco use was reported by 15% of the sample.

As for clinical features, 11 subjects had a first episode of psychotic onset, while 9 had a first episode of bipolar. Regarding pharmacological treatment, the mean proportions of prescribed medications were as follows: 55% received second-generation antipsychotics, 45% mood stabilizers, 30% antidepressants, and 15% benzodiazepines.

| **Variable** | **Total sample (n=20)** | **Psychosis (n=11)** | **Bipolar (n=9)** |
|---|---|---|---|
| **Gender,** n (%) | | | |
| *Male sex* | 11 (55) | 7 (64) | 4 (44) |
| **Age –** M (SD) | 25 (3.9) | 23 (3.1) | 26 (4.6) |
| **Level of education,** n (%) | | | |
| *High school* | 18 (90) | 11 (100) | 6 (67) |
| *Degree* | 2 (10) | 0 | 3 (33) |
| **Employed,** n (%) | | | |
| *Yes* | 6 (30) | 1 (9) | 5 (56) |
| *No* | 14 (70) | 10 (91) | 4 (44) |
| **Living situation,** n (%) | | | |
| *Alone* | 2 (10) | 0 | 2 (22) |
| *With family* | 18 (90) | 11 (100) | 7 (78) |
| **Tobacco use,** n (%) | 3 (15) | 2 | 1 (11) |
| **Type of onset,** n (%) | | | |
| *Psychotic* | 11 (55) | - | - |
| *Bipolar type I* | 7 (35) | | |
| *Bipolar type II* | 2 (10) | | |
| **Illness duration since onset,** n (%) | | | |
| *< 12 months* | 12 (60) | 7 (64) | 5 (56) |
| *≥ 12 months* | 8 (40) | 4 (36) | 4 (44) |

| **Pharmacologic treatment,** n (%) | | | |
|---|---|---|---|
| First-generation antipsychotics | 1 (5) | 1 (5) | 0 |
| Second-generation antipsychotics | 11 (55) | 7 (64) | 4 (44) |
| Mood stabilizers | 9 (45) | 1 (5) | 8 (89) |
| Antidepressants | 6 (30) | 3 (27) | 3 (33) |
| Benzodiazepines | 3 (15) | 2 (18) | 1 (11) |

**Table 5.** *Sociodemographic and clinical characteristics of the clinical sample.*

There were no statistically significant differences between patients with first episode psychosis and those with bipolar onset in both sleep and psychopathological self-reported measures. Also, the prevalence rate of suicidal ideation, assessed through the BDI item 9, was comparable. However, lifetime MDQ manic/hypomanic features tended to be higher in the bipolar group, although this difference did not reach significance ($p = 0.67$). At the same time, PQ-16 scores were higher in the psychosis group, although not statistically significantly so. Consistently, our results on clinical cut-offs confirmed these findings.

The correlation matrix among clinical variables is presented in Table 4. Worse sleep quality (i.e., higher PSQI scores) was strongly linked to more severe depressive symptoms (BDI total score; $r = 0.76$, $p < 0.001$) and increased prodromal features (PQ-16 total symptom score; $r = 0.69$, $p < 0.01$). PSQI also had a moderate positive correlation with suicidal ideation, as indicated by the BDI item 9 subscore ($r = 0.45$, $p < 0.05$).

Depressive symptoms were strongly linked to both suicidal ideation ($r = 0.52$, $p < 0.05$) and prodromal symptoms ($r = 0.64$, $p < 0.01$), further emphasizing the connection between affective distress and subthreshold psychotic features. Meanwhile, excessive daytime sleepiness (ESS) and manic/hypomanic features (MDQ) did not show significant links with other clinical variables.

| Variable | Psychosis (n=11) | Bipolar (n=9) | p-value | Effect size (Cohen's d) | 95% CI |
|---|---|---|---|---|---|
| **PSQI**, M (SD) | 7.0 (3.3) | 8.0 (2.7) | 0.83 | 0.33 | –0.62 – 1.24 |
| **ESS**, M (SD) | 7.0 (4.2) | 5.0 (2.9) | 0.35 | –0.54 | –1.47 – 0.43 |
| **BDI total**, M (SD) | 15.0 (10.6) | 18.0 (10.4) | 0.46 | 0.28 | –0.68 – 1.18 |
| **BDI item 9 positive,** n (%) | 8 (66%) | 5 (62%) | 0.89 | OR=1.20 | 0.21 – 6.80 |
| **MDQ**, M (SD) | 0.2 (0.4) | 0.8 (0.3) | 0.67 | 1.64 | 0.46 – 2.73 |
| **PQ-16**, , M (SD) | 12.0 (8.8) | 7.0 (6.7) | 0.76 | –0.63 | –1.60 – 0.42 |

**Table 6.** *Comparison of clinical scale scores according to the type of onset.*

When compared to healthy controls, patients exhibited a significantly shorter average of TST (388.6 ± 68.4 vs. 449.7 ± 31.8 minutes; $p < 0.01$). No other actigraphic parameters showed significant differences between these two subgroups (Table 5).

| Variable | Patients (n=20) | Healthy controls (n=20) | p value |
|---|---|---|---|
| TST (min) | 388.6 (68.4) | 449.7 (31.8) | **<0.01** |
| SOL (min) | 157.7 (110.2) | 190.4 (95.6) | 0.49 |
| SE (%) | 34.1 (26.4) | 39.7 (32.6) | 0.55 |
| WASO (min) | 254.6 (199.4) | 229.7 (200.1) | 0.69 |
| Wake episodes (n) | 5.9 (4.4) | 4.7 (2.39) | 0.31 |
| Sleep episodes (n) | 5.4 (4.6) | 4.2 (3.1) | 0.33 |

**Table 7.** *Actigraphic analyses between patients and healthy controls.*

Within the clinical sample, patients with bipolar onset showed significantly longer sleep latency compared to those with psychotic onset (160.8 ± 110.5 vs. 80.1 ± 61.4 minutes; $p < 0.01$). Other actigraphic variables did not differ significantly between groups, although there were trends toward lower sleep efficiency and a higher number of wake and sleep episodes in the psychosis group (Table 6).

| **Variable** | **Psychosis (n=11)** | **Bipolar (n=9)** | **p value** |
|---|---|---|---|
| TST (min) | 392.6 (30.9) | 383.6 (89.3) | 0.78 |
| SOL (min) | 80.1 (61.4) | 160.8 (110.5) | **<0.01** |
| SE (%) | 26.7 (17.8) | 43.1 (33.1) | 0.17 |
| WASO (min) | 276.3 (212.8) | 228.4 (190.8) | 0.60 |
| Wake episodes (n) | 7.5 (4.9) | 4.1 (3.4) | 0.08 |
| Sleep episodes (n) | 7.1 (4.9) | 3.3 (3.2) | 0.06 |

**Table 8.** *Differences in actigraphic analyses between psychosis and bipolar patients.*

### 3.3.4 Systematic review of sleep disturbances in early psychosis

This systematic review investigated the nature, prevalence, and clinical implications of sleep disturbances in individuals with first-episode psychosis (FEP) and those at clinical high risk (CHR) for developing psychosis. Mounting evidence suggests that sleep abnormalities are not merely consequences of psychiatric illness or medication but may constitute early indicators and modifiable mechanisms underlying psychotic vulnerability. The aim of this review was therefore to integrate findings from subjective and objective studies to clarify the patterns of sleep disruption characterizing early psychosis and their associations with clinical and cognitive outcomes.

The review was conducted in accordance with PRISMA guidelines and was registered on PROSPERO (CRD42024623913). A comprehensive search was performed in PubMed, Web of Science, EMBASE, and PsycINFO up to December 2024. Keywords combined terms related to “first-episode psychosis,” “clinical high risk,” “prodrome,” and “sleep” or “circadian rhythm.” Eligible studies included original empirical research assessing sleep parameters in FEP or CHR participants, with or without a healthy control group. Both subjective instruments (e.g., PSQI, ISI, sleep diaries) and objective measures (PSG, actigraphy) were accepted. Studies were excluded if they focused exclusively on chronic schizophrenia, examined sleep under pharmacological challenge, or lacked clear diagnostic or methodological information. Data extraction and quality assessment were independently performed by two reviewers, with the NOS applied to evaluate bias in sampling, comparability, and outcome measurement.

Twenty-five studies met the inclusion criteria, representing 1,255 patients and 342 healthy controls. Sample sizes ranged from small PSG studies ($n \approx 20$) to larger actigraphic cohorts (>100 participants). Across methodologies, results converged on a consistent finding: sleep disturbances are pervasive in early psychosis, present in 70–90% of patients, and often precede the onset of frank psychotic symptoms.

Subjective data indicated that insomnia symptoms—particularly difficulty initiating sleep, frequent awakenings, and non-restorative sleep—were among the most prevalent complaints. In both FEP and CHR groups, poor sleep quality correlated with higher scores on positive and negative symptom scales, greater emotional dysregulation, and reduced quality of life. A subset of studies also reported that self-reported sleep

disruption predicted the persistence of attenuated psychotic symptoms and functional decline over 6–12 months.

Objective studies provided converging physiological evidence. PSG revealed prolonged sleep latency, decreased total sleep time, and reduced sleep efficiency in both CHR and FEP populations compared with controls. Abnormal sleep architecture was a recurrent finding: diminished slow-wave sleep (N3), increased light sleep (N1–N2), and alterations in REM parameters (shorter latency, higher density, and fragmentation). Several investigations observed decreased spindle density and amplitude, particularly over frontal and centroparietal regions, suggesting thalamocortical dysregulation that may contribute to cognitive impairment and sensory gating deficits typical of psychosis. Actigraphy studies further confirmed fragmented rest–activity cycles, delayed circadian phase, and lower amplitude of the 24-hour rhythm, reflecting impaired biological synchrony. These circadian alterations were linked to mood instability, anhedonia, and higher rates of suicidal ideation.

From a developmental perspective, evidence from CHR samples underscores that sleep disruption frequently predates the onset of psychosis. Longitudinal data showed that insomnia, nightmares, and irregular sleep timing predict transition to psychosis within 1–2 years, even after adjusting for baseline symptom severity. These findings support the hypothesis that sleep disturbance acts as an early warning marker of psychotic conversion, possibly through its impact on emotion regulation, stress reactivity, and dopaminergic modulation.

At the clinical level, poor sleep was associated not only with positive symptoms such as hallucinations and paranoia, but also with negative and affective dimensions, including anhedonia, depressive symptoms, and suicidal ideation. Cognitive impairments—especially in working memory, attention, and executive functioning—were consistently linked to objective markers such as reduced spindle activity and diminished slow-wave power. These results suggest that sleep abnormalities may contribute directly to neurocognitive dysfunction in psychosis through disrupted neural plasticity during NREM sleep.

Importantly, sleep disturbances persisted despite clinical remission of acute psychotic episodes and were only partially responsive to antipsychotic treatment, indicating that they may represent trait-like features rather than transient symptoms. The convergence

of subjective, actigraphic, and PSG evidence across independent cohorts strengthens the conceptualization of sleep disturbance as a transdiagnostic and mechanistically relevant domain in early psychosis.

Collectively, the reviewed evidence highlights three central points. First, sleep disturbances are widespread and multifaceted in early psychosis, involving both homeostatic and circadian dysregulation. Second, these alterations have meaningful clinical consequences, influencing symptom expression, cognition, and daily functioning. Third, they provide actionable targets for early intervention. Preliminary studies suggest that CBT-I, light therapy, and social rhythm stabilization can ameliorate sleep parameters and yield parallel improvements in psychotic and affective symptoms. Although the literature remains dominated by cross-sectional designs and small samples, the consistency of results across modalities underscores the potential for sleep-focused interventions in preventive psychiatry.

| **Sleep domain** | **Typical alterations observed** | **Associated clinical features** | **Type of evidence** |
|---|---|---|---|
| **Sleep continuity** | Reduced sleep efficiency, prolonged sleep latency, increased wake after sleep onset (WASO) | Positive and negative symptoms, depressive symptoms, cognitive impairment | Polysomnography, actigraphy, self-report |
| **Sleep architecture** | Decrease in slow-wave sleep (N3), reduced spindle density and duration, REM abnormalities (shorter latency, higher density) | Cognitive deficits, negative symptoms, poorer functional outcomes | Polysomnography |
| **Circadian rhythm** | Irregular rest–activity patterns, delayed sleep phase, reduced amplitude of circadian rhythm | Emotional dysregulation, suicidality, mood instability | Actigraphy, self-report |
| **Subjective sleep quality** | Poor overall sleep quality, insomnia symptoms, daytime fatigue | Lower quality of life, higher distress, depressive symptoms | PSQI, ISI, sleep diaries |
| **Prodromal/at-risk phase** | Early complaints of insomnia and circadian misalignment preceding psychosis onset | Transition to psychosis, heightened stress reactivity | Longitudinal and high-risk cohort studies |

**Table 9.** *A synthesis of the main domains of alteration and their associated clinical correlates.*

### 3.3.5 Systematic review on therapeutic interventions in bipolar disorder

This systematic review investigated the efficacy and safety of pharmacological and non-pharmacological interventions specifically targeting sleep disturbances in individuals with bipolar disorder. Sleep alterations are among the most pervasive features of bipolar disorder, influencing the course of the illness, the risk of relapse, and suicidality. Despite their clinical relevance, sleep problems in bipolar disorder are often underdiagnosed and inadequately treated, and evidence-based guidance remains limited. Following the PRISMA 2020 guidelines, a systematic search was conducted on PubMed, Embase, Web of Science, and PsycINFO from January 2015 to May 2025, including randomized controlled trials and observational studies assessing interventions designed to improve sleep parameters or regulate circadian rhythms in patients with BD. The protocol was pre-registered on PROSPERO (CRD420251024576).

A total of twelve studies met the inclusion criteria, including ten randomized controlled trials and two observational studies. These trials explored both pharmacological and non-pharmacological approaches, with sample sizes ranging from 19 to 124 participants and durations of treatment varying between two weeks and nine months. Participants were predominantly in euthymic or inter-episode phases, although some studies included individuals in depressive or acute affective states.

Non-pharmacological interventions yielded the most consistent and clinically relevant improvements. Cognitive Behavioral Therapy for Insomnia adapted for bipolar disorder (CBTI-BD) emerged as the intervention with the strongest evidence base, significantly improving sleep efficiency, latency, and total sleep time, while also reducing depressive symptoms and relapse risk. The intervention was well tolerated, with only mild transient increases in sleepiness during early sessions. Relaxation-based protocols, such as the Benson Relaxation Technique, produced significant reductions in PSQI scores and improved emotional regulation, accompanied by a parallel decrease in aggressive and hostile behaviors. Bright light therapy and blue-blocking glasses also demonstrated some benefit on sleep and mood symptoms, although findings were heterogeneous across studies, likely due to variability in treatment intensity, timing of light exposure, and individual chronotype. Importantly, none of the behavioral or chronotherapeutic

interventions were associated with polarity switches or severe adverse events, confirming their favorable safety profile.

Pharmacological strategies showed more heterogeneous results. Melatonin, administered to euthymic patients with delayed sleep–wake phase disorder, was associated with earlier sleep onset, increased total sleep time, and improved circadian alignment without mood destabilization. Suvorexant, a dual orexin receptor antagonist, produced modest increases in total sleep time but failed to yield consistent subjective or affective improvements. Conversely, benzodiazepines and Z-drugs demonstrated limited efficacy on validated sleep outcomes and were associated with a higher risk of suicidality during acute affective episodes, especially when used in polytherapy with other psychotropic agents. Antidepressant exposure was linked to poorer subjective sleep quality and greater impulsivity during euthymic phases, supporting the hypothesis that pharmacological modulation of sleep requires careful phase-specific consideration.

Taken together, the evidence indicates that behavioral and chronotherapeutic interventions represent the most effective and safest strategies for managing sleep disturbances in bipolar disorder, particularly in stabilized phases of illness. By acting on both the cognitive–behavioral and circadian dimensions of sleep dysregulation, these interventions contribute to mood stabilization and improved daytime functioning. Pharmacological treatments may serve as useful adjuncts when non-pharmacological options are insufficient, but they require tailored application based on mood state, chronotype, and comorbidities.

The review also highlights that improvements in sleep frequently parallel reductions in depressive symptoms, suggesting that targeting sleep represents not only a symptomatic approach but also a preventive strategy against relapse and suicidality. Given the bidirectional relationship between sleep and mood regulation, systematic assessment of sleep patterns and circadian rhythm should become routine in the clinical management of BD. Interventions such as CBTI-BD, IPSRT, and melatonin-based chronotherapy should be integrated into multidisciplinary treatment plans, with an emphasis on personalized, phase-adapted approaches.

In conclusion, sleep-focused interventions play a central role in the long-term stabilization of bipolar disorder. Non-pharmacological strategies, particularly CBTI-BD, consistently improve sleep continuity, reduce depressive burden, and show

excellent tolerability. Pharmacological treatments remain valuable in selected cases but must be prescribed with caution due to potential adverse behavioural effects.

| Intervention domain | Main strategies investigated | Typical effects on sleep | Clinical impact | Type of evidence |
|---|---|---|---|---|
| **Cognitive-behavioral interventions** | CBT for Insomnia adapted for BD (CBTI-BD), psychoeducation, IPSRT elements | Improved sleep efficiency, reduced latency, increased total sleep time, greater regularity of sleep–wake cycles | Reduction of depressive symptoms, better mood stability, decreased relapse risk | Randomized controlled trials, follow-up studies |
| **Relaxation-based techniques** | Benson Relaxation Technique, mindfulness relaxation | Improved subjective sleep quality, shorter sleep latency, reduced arousal and aggression | Decreased hostility and irritability, improved emotional regulation | Randomized controlled trials |
| **Chronotherapeutic approaches** | Bright Light Therapy, blue-blocking glasses, structured daily routines | Phase advance, improved sleep timing, variable impact on subjective sleep quality | Reduction of depressive symptoms in some studies, better circadian alignment | Randomized controlled trials, pilot studies |
| **Melatonin and chronobiotic agents** | Exogenous melatonin (2–5 mg), melatonin agonists | Earlier sleep onset, prolonged total sleep time, improved circadian stability | Stable mood during treatment, absence of polarity switch | Small RCTs and open-label trials |
| **Sedative-hypnotics** | Benzodiazepines, Z-drugs | Minimal or transient improvement in sleep continuity | Increased risk of suicidality during affective episodes, poor long-term efficacy | Observational and cohort studies |
| **Orexin receptor antagonists** | Suvorexant | Slight increase in objective total sleep time, limited subjective improvement | Neutral on mood symptoms, good short-term tolerability | Randomized controlled trial |

| Intervention domain | Main strategies investigated | Typical effects on sleep | Clinical impact | Type of evidence |
|---|---|---|---|---|
| **Antidepressants (adjunctive use)** | SSRIs, SNRIs, other antidepressants during euthymia | Worsened sleep quality, delayed sleep phase, reduced efficiency | Increased impulsivity and emotional dysregulation | Cross-sectional and observational studies |

**Table 10.** *Summary of intervention domains and their effects on sleep and clinical outcomes in bipolar disorder.*

## 3.4 Study III – Psychiatric comorbidities in Narcolepsy Type 1 during childhood and adolescence

### 3.4.1 Study design and participants

This study adopted a retrospective case–control design conducted at the Narcolepsy Center of the IRCCS Institute of Neurological Sciences of Bologna. The sample included pediatric patients diagnosed with NT1 before the age of 18, evaluated between January 2014 and January 2025. All participants had comprehensive clinical documentation and at least two years of follow-up after the initial diagnostic hospitalization.

Children and adolescents who developed psychotic symptoms either at NT1 onset or within one year of diagnosis were classified as the NT1+psychosis group. Psychotic symptoms were confirmed by board-certified child and adolescent psychiatrists through longitudinal clinical observation and diagnostic interviews based on DSM-5 criteria. Only cases showing persistent hallucinations, delusional ideation, or severe behavioral disorganization outside sleep–wake transitions were included. A control group of NT1 patients without psychotic symptoms was selected from the same time span, matched for age and sex.

All participants underwent a standardized diagnostic work-up for NT1, including neurological examination, anthropometric assessment, two-night continuous PSG, and Multiple Sleep Latency Test (MSLT) following the AASM guidelines. When available,

CSF hypocretin-1 levels and HLA-DQB106:02* typing were also obtained. NT1 diagnosis was confirmed according to the ICSD-3 or its text revision (ICSD-3-TR). Psychiatric assessments were conducted during diagnostic hospitalization and follow-up visits, with systematic evaluation of emotional, cognitive, and behavioral functioning. Particular attention was devoted to differentiating NT1-related hypnagogic or hypnopompic hallucinations from true psychotic phenomena, considering their temporal and phenomenological characteristics.
Family psychiatric history was collected through structured interviews with caregivers and medical record review, focusing on mood, psychotic, anxiety, and neurodevelopmental disorders in first-degree relatives.

### 3.4.2 Measures and instruments

Clinical and demographic data were extracted from the patients' medical records, including age at diagnosis, sex, disease duration, and family psychiatric history. Anthropometric parameters such as body mass index (BMI) and the presence of cataplexy, sleep paralysis, hypnagogic or hypnopompic hallucinations, and automatic behaviors were recorded during clinical evaluation.
Objective sleep parameters were obtained through nocturnal PSG followed by a Multiple Sleep Latency Test (MSLT) performed according to the AASM scoring criteria. PSG variables included TST, sleep latency, SE, WASO, number of awakenings, and time spent in each sleep stage (N1, N2, N3, and REM). The MSLT provided data on mean sleep latency and the number of sleep-onset REM periods (SOREMPs). All recordings were visually inspected and manually scored by experienced sleep technologists blinded to participants' psychiatric status.
CSF hypocretin-1 levels were measured when available using standardized radioimmunoassay techniques, and HLA-DQB1*06:02 typing was performed through polymerase chain reaction sequence–specific oligonucleotide analysis. Hypocretin deficiency was defined as values < 110 pg/mL.
Psychiatric symptoms were identified through longitudinal evaluation by specialized child and adolescent psychiatrists. Psychotic features were classified according to *DSM-5* criteria, based on the persistence and content of hallucinations or delusional beliefs.

The onset timing, clinical course, and response to pharmacological or behavioral interventions were also documented.

Sleep–wake patterns during follow-up were characterized by calculating composite indices of nocturnal instability derived from the hypnogram. These included the total number of transitions between wake and NREM stages (tW-NR-index), wake and REM (tW-R-index), and between NREM and REM (tNR-R-index), providing a measure of sleep fragmentation and instability.

All clinical and physiological data were reviewed by two independent investigators to ensure accuracy and completeness.

### 3.4.3 Results of the study

The final sample included 105 pediatric patients with a diagnosis of NT1, 9 of whom presented with clinically significant psychotic symptoms (psychosis+NT1 group) and 96 without psychiatric comorbidity (control-NT1 group). The two groups did not differ in age, sex distribution, age at NT1 onset, or duration of illness. However, a positive family history of psychiatric disorders was markedly more frequent among psychotic patients (55.6% vs. 2.2%, $p < 0.01$).

Biological parameters revealed that CSF hypocretin-1 levels were significantly lower in the psychotic group (mean 4.9 ± 9 pg/mL) compared to controls (18.9 ± 24.2 pg/mL, $p = 0.02$), whereas body mass index, HLA-DQB1*06:02 positivity, and daytime sleepiness (ESS-CHAD) did not show significant differences.

| | **Psychotic NT1 phenotype (n=9)** | **Non-psychotic NT1 (n=96)** | *P-value* |
|---|---|---|---|
| **Sex,** (male), n (%) | 5 (55.5) | 58 (60.4) | 0.27 |
| **BMI,** (kg/m$^2$), Mean (SD) | 24.15 (3.26) | 23.37 (5.20) | 0.39 |
| **Narcolepsy duration** (years), Mean (SD) | 2.89 (2.44) | 1.98 (2.14) | 0.35 |
| **Age at diagnosis** (years), Mean (SD) | 10 (4.1) | 10.95 (2.78) | 0.45 |
| **Age the onset of narcolepsy** (years), Mean (SD) | 9.1 (3.5) | 9 (2.52) | 0.92 |
| **ESS-CHAD,** (total score) Mean (SD) | 14.88 (2.64) | 14.36 (3.72) | 0.81 |
| **CSF Hypocretin** (pg/mL), Mean (SD) | 4.95 (9) | 18.89 (24.17) | **0.02** |
| **HLA-DQB1*06:02,** n (%) | 9 (100) | 89 (94.7) | 1.00 |
| **Positive psychiatric family history,** n (%) | 5 (55.6) | 2 (2.2) | **< 0.01** |
| **Frequency of cataplexy,** n (%) | | | |
| ≥ 1 day | 6 (67) | 44 (46) | 0.50 |
| 1/week - 1/day | 2 (22) | 42 (44) | |
| 1/month - 1/week | 1 (11) | 8 (9) | |
| 1/year - 1/month | 0 | 1 (1) | |
| **Frequency of time of cataplexy,** n (%) | | | |
| 2min - 10min | 2 (22) | 8 (9) | 0.65 |
| 10s - 2min | 0 | 20 (20) | |
| < 10s | 7 (78) | 69 (71) | |

| | | | |
|---|---|---|---|
| **Emotional triggers of cataplexy,** n (%) | | | |
| Angry | 5 (55.5) | 42 (43.5) | 0.53 |
| Laughter | 7 (78) | 91 (95) | 0.10 |
| While telling a joke | 8 (89) | 70 (73) | 0.38 |
| Sudden surprise | 1 (11) | 14 (15) | 0.77 |
| Unexpected encounter | 1 (11) | 10 (10.5) | 0.96 |
| **Body distribution of cataplexy**, n (%) | | | |
| Generalized weakness | 8 (89) | 61 (64) | 0.21 |
| Partial weakness of the face/jaw | 9 (100) | 84 (87) | 0.36 |
| Partial weakness of the neck | 8 (89) | 76 (79) | 0.72 |
| Partial weakness of the knees | 7 (78) | 76 (79) | 0.68 |
| Partial weakness of the arms/hands | 4 (44) | 66 (69) | 0.10 |

**Table 11.** *Demographic and clinical characteristics of the groups.*

Regarding nocturnal PSG, children with psychosis exhibited shorter total sleep time (430.8 ± 86.5 vs. 503.7 ± 76.8 min, $p = 0.03$) and lower sleep efficiency (75.6% ± 15.6 vs. 89.5% ± 7.6, $p = 0.02$) than non-psychotic peers. They also had more frequent daytime naps (3.7 ± 1.8 vs. 2.6 ± 1.7, $p = 0.04$). Sleep–wake instability indices were markedly elevated, with higher values for both the transition index between wakefulness and sleep (tW-S-index) and the composite wake–NREM–REM transition index (tW-NR-R-index) (both $p < 0.01$), indicating increased fragmentation of nocturnal sleep architecture.

Trends toward longer REM latency, reduced N2 sleep percentage, and fewer MSLT SOREMPs were observed in the psychotic group, though not statistically significant. These findings collectively point to a phenotype characterized by more disrupted nocturnal sleep, greater daytime sleep propensity, and unstable transitions between vigilance states.

Clinically, psychotic manifestations encompassed early-onset schizophrenia, psychosis not otherwise specified, obsessive-compulsive disorder with psychotic features, autism spectrum disorder with psychotic traits, and psychotic depression. Despite this heterogeneity, all cases shared the presence of persistent hallucinations or delusional beliefs beyond the sleep–wake boundary. Social withdrawal emerged as a frequent prodromal feature, documented in 62.5% of psychotic patients. In most cases, psychiatric symptoms developed within months after NT1 treatment initiation, whereas in others they appeared one to three years later.

Overall, these results delineate a distinct pediatric NT1 phenotype marked by familial psychiatric vulnerability, severe hypocretin deficiency, and profound sleep–wake instability, suggesting shared neurobiological mechanisms between narcolepsy and psychotic disorders.

| | **Psychotic NT1 phenotype (n=9)** | **Non-psychotic NT1 (n=96)** | *P-value* |
|---|---|---|---|
| **NIGHTTIME,** Mean (SD) | | | |
| n-TST (min) | 430.83 (86.48) | 503.71 (76.79) | **0.03** |
| n-SL (min) | 6 (6.13) | 3.84 (3.64) | 0.25 |
| SE (%) | 75.6 (15.62) | 89.47 (7.60) | **0.02** |
| WASO (min) | 110.2 (78.5) | 59.42 (48.89) | 0.10 |
| N1% (% of TST) | 15.06 (12.37) | 10.54 (5.19) | 0.30 |
| N2% (% of TST) | 27.59 (16.09) | 38.48 (7.32) | 0.07 |
| N3% (% of TST) | 32.76 (14.66) | 27.25 (9.20) | 0.29 |
| REM% (% of TST) | 18.1 (9.16) | 23.78 (6.50) | 0.10 |
| n-REML (min) | 8.1 (17.4) | 24.45 (52.34) | 0.08 |
| **Sleep-wake transitions,** Mean (SD) | | | |
| tW-S-index (n/hour of TIB) | 11.57 (5.33) | 6.41 (3.08) | **< 0.01** |
| tNR-R-index (n/hour of TIB) | 2.88 (1.81) | 3.05 (1.10) | 0.48 |
| W/N1-index (n/hour of TIB) | 5.10 (1.78) | 4.61 (1.38) | 0.48 |

| | | | |
|---|---|---|---|
| tW-NR-R-index (n/hour of TIB) | 27.11 (10.04) | 17.11 (6.33) | **< 0.01** |
| **DAYTIME,** Mean (SD) | | | |
| d-Nap (n) | 3.68 (1.82) | 2.64 (1.68) | **0.04** |
| d-SOREMP (n) | 2.11 (1.90) | 2.88 (1.46) | 0.26 |
| d-TST (min) | 181.4 (85.9) | 126.17 (72.42) | 0.09 |
| MSLT | | | |
| MSLT mSL (min) | 3.57 (4.17) | 3.25 (2.59) | 0.73 |
| MSLT SOREMPs (n) | 2.11 (1.90) | 4.32 (0.92) | 0.08 |

**Table 12.** *Comparison of nighttime, sleep-wake instability, and daytime sleep parameters between NT1 patients with and without psychiatric comorbidities.*

## 3.5 Study IV – Psychiatric comorbidities in Narcolepsy Type 1 during adulthood

### 3.5.1 Study design and participants

This study employed a cross-sectional case–control design to evaluate the prevalence and co-occurrence of depressive symptoms, anxiety, suicidal thoughts, and hopelessness in adults with NT1 compared with healthy controls. Participants were recruited as part of the Psychological Impact of Narcolepsy project, conducted at the Narcolepsy Center of the IRCCS Institute of Neurological Sciences of Bologna.

A total of 127 adults with NT1 (mean age 38.2 ± 15.5 years; 53.5% female) and 131 healthy controls (mean age 37.4 ± 14.3 years; 59.5% female) matched for age, sex, and educational level were enrolled. The NT1 diagnosis was confirmed by overnight PSG followed by a Multiple Sleep Latency Test (MSLT) and measurement of CSF hypocretin-1 levels, according to the criteria of ICSD-3. All patients were followed and treated by the same team of neurologists specialized in central disorders of hypersomnolence.

Control participants were recruited from relatives and acquaintances of patients attending the neurology outpatient clinic, provided they had no history of sleep disorders or psychiatric conditions. Exclusion criteria for both groups included neurological diseases other than NT1, intellectual disability, and major medical conditions that could influence sleep or mood.

Sociodemographic data (age, sex, educational level) and clinical characteristics were collected through structured interviews and chart reviews. For NT1 patients, disease-specific features such as age at onset, disease duration, presence of cataplexy, hypnagogic/hypnopompic hallucinations, sleep paralysis, and pharmacological treatment were systematically recorded. The majority of patients (92.3%) were under active treatment for narcolepsy, with approximately one quarter receiving low-dose antidepressants for anticataplectic purposes.

All participants completed a battery of validated self-report questionnaires assessing depressive symptoms, anxiety, and hopelessness. Data collection took place during routine clinical visits in a quiet setting, and completion required approximately 20–30 minutes. The study protocol was approved by the Intercompany Ethical Committee of Bologna-Imola (protocol no. 16181), and written informed consent was obtained from all participants prior to enrollment, in accordance with the Declaration of Helsinki and the European General Data Protection Regulation (GDPR 2016/679).

### 3.5.2 Measures and instruments

Psychological assessment focused on the evaluation of depressive symptoms, anxiety, hopelessness, and suicidal ideation. All instruments were validated in Italian and widely used in both clinical and research settings.

Depressive symptoms were assessed using the *Beck Depression Inventory–II (BDI-II)*, a 21-item self-report scale that measures affective, cognitive, and somatic components of depression. Each item is rated on a four-point Likert scale ranging from 0 to 3, yielding a total score between 0 and 63. A cut-off score of 14 or higher was adopted to indicate at least mild depressive symptomatology. Item 9 of the BDI-II, which specifically assesses suicidal thoughts, was analyzed separately to determine the presence of suicidal ideation.

Anxiety was measured through the *State–Trait Anxiety Inventory (STAI)*, which consists of two subscales assessing state (STAI-S) and trait (STAI-T) anxiety. Each subscale includes 20 items rated on a four-point scale, with total scores ranging from 20 to 80. A cut-off of 45 was applied to identify clinically relevant anxiety.

Hopelessness was evaluated using the *Beck Hopelessness Scale (BHS)*, a 20-item true/false questionnaire that explores negative expectations about the future and loss of motivation. Total scores range from 0 to 20, with values of 9 or higher denoting moderate to severe hopelessness.

Sociodemographic and clinical information, including age, sex, education, disease duration, and NT1-related symptoms, were obtained through structured interviews and medical record review.

All questionnaires were administered during the same session, under the supervision of a trained psychologist. Participants were instructed to respond based on their experiences in the two weeks preceding the assessment.

Statistical analyses were performed using SPSS version 28.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as means ± standard deviations, and categorical data as frequencies and percentages. Between-group comparisons (NT1 vs. controls) were conducted using *t*-tests or Mann–Whitney *U* tests for continuous variables and chi-square or Fisher's exact tests for categorical variables. Logistic regression models were applied to estimate the ORs and 95% CIs for the association between NT1 and each psychological outcome, adjusting for age, sex, and education. Spearman's correlation coefficients were calculated to explore the relationships among depressive, anxiety, and hopelessness scores. All statistical tests were two-tailed, and significance was set at $p < 0.05$.

### 3.5.3 Results of the study

The final sample comprised 127 adults with NT1 and 131 healthy controls, matched for age, sex, and education. Sociodemographic variables did not differ significantly between the two groups. Among NT1 patients, the mean age at disease onset was 24.8 ± 13.2 years, and the mean disease duration was 13.4 ± 11.5 years. Cataplexy was present in all participants, while 72% reported hypnagogic or hypnopompic hallucinations and 59% reported sleep paralysis.

Patients with NT1 exhibited significantly higher levels of depressive symptoms, anxiety, and hopelessness compared with healthy controls. Mean BDI-II scores were 14.7 ± 9.8 in the NT1 group versus 7.1 ± 6.4 in controls ($p < 0.001$), and depressive symptomatology above the clinical cut-off (BDI-II ≥14) was observed in 38.6% of NT1

patients versus 13.0% of controls ($p < 0.001$). Similarly, STAI-T scores were elevated in patients (mean 49.6 ± 9.7) compared with controls (43.2 ± 10.6, $p < 0.001$), with trait anxiety reaching clinical levels in 54.3% of cases versus 31.3% of controls ($p = 0.001$). Moderate to severe hopelessness (BHS ≥9) was detected in 28.3% of NT1 patients and 9.9% of controls ($p < 0.001$).

Suicidal ideation, as measured by item 9 of the BDI-II, was endorsed by 20.5% of NT1 patients compared with 3.1% of controls ($p < 0.001$). Suicidal thoughts were more frequent among patients with concurrent depressive symptoms and higher hopelessness, and they showed strong correlations with both BDI-II ($\rho = 0.64$, $p < 0.001$) and BHS ($\rho = 0.53$, $p < 0.001$) scores.

| | Narcolepsy (N = 127) | Controls (N = 131) | |
|---|---|---|---|
| | Median (IQR) or N (%) | Median (IQR) or N (%) | *P-value* |
| **BDI score** | 9 (3–18) | 5 (1–11) | <0.001 |
| **BDI level** | | | **0.002** |
| Absent <13 | 86 (67.7 %) | 113 (86.3 %) | |
| Mild 13-18 | 18 (14.2 %) | 8 (6.1 %) | |
| Moderate 19-29 | 15 (11.8 %) | 9 (6.9 %) | |
| Severe ≥30 | 8 (6.3 %) | 1 (0.8 %) | |
| **BDI item 9 level** | | | **<0.001** |
| *"I do not have thoughts of killing myself"* = 0 | 100 (80.0 %) | 125 (96.9 %) | |
| *"I have thoughts of killing myself, but I would not carry them out"*=1 | 19 (15.2 %) | 3 (2.3 %) | |
| *"I would like to kill myself"*=2 | 5 (4.0 %) | 1 (0.8 %) | |
| *"I would kill myself if I had the chance"* = 3 | 1 (0.8 %) | 0 (0.0 %) | |
| **STAI-trait anxiety score** | 43 (34–51) | 38 (32–46) | **0.009** |
| **STAI-trait anxiety level** | | | **0.025** |
| Absent <30 | 16 (12.6 %) | 21 (16.0 %) | |
| Mild 30-37 | 30 (23.6 %) | 46 (35.1 %) | |
| Moderate 38-44 | 27 (21.3 %) | 31 (23.7 %) | |
| Severe ≥45 | 54 (42.5 %) | 33 (25.2 %) | |
| **STAI-state anxiety score** | 36 (32–49) | 34 (29–42) | **0.011** |
| **STAI-state anxiety level** | | | **0.003** |
| Absent <30 | 19 (15.0 %) | 38 (29.1 %) | |
| Slight 30-37 | 55 (43.3 %) | 43 (32.8 %) | |
| Moderate 38-44 | 15 (11.8 %) | 26 (19.8 %) | |
| Serious ≥45 | 38 (29.9 %) | 24 (18.3 %) | |
| **BHS score** | 5 (3–10) | 4 (2–6) | **<0.001** |
| **BHS levels** | | | **0.002** |
| Absent <4 | 47 (37.0 %) | 62 (47.3 %) | |
| Slight 4-8 | 41 (32.2 %) | 52 (39.7 %) | |
| Moderate 9-14 | 23 (18.1 %) | 16 (12.2 %) | |
| Serious 15-20 | 16 (12.6 %) | 1 (0.8 %) | |
| **Coexistence of BDI≥13 and STAI- trait≥38** | 40 (31.5 %) | 20 (15.3 %) | **0.002** |
| **Coexistence of BDI ≥13 and STAI- state≥38** | 32 (25.2 %) | 18 (13.7 %) | **0.020** |

**Figure 4.** *Depressive symptoms, suicidal thoughts, anxiety, and hopelessness: comparisons*

*between patients and controls.*

Multivariate logistic regression analyses confirmed that NT1 diagnosis independently predicted the presence of depression (OR = 3.23, 95% CI: 1.72–6.04), trait anxiety (OR = 1.91, 95% CI: 1.09–3.32), and moderate-to-severe hopelessness (OR = 2.95, 95% CI: 1.48–5.87) after adjustment for age, sex, and education. The co-occurrence of depressive and anxiety symptoms was also more frequent among NT1 patients (OR = 2.72, 95% CI: 1.29–5.73).

Within the NT1 group, hopelessness and suicidal ideation were associated with older age and longer disease duration, while sleep paralysis, hallucinations, and nocturnal sleep disruption were more common among those with higher affective symptom scores. Neither cataplexy frequency nor pharmacological treatment (stimulants or antidepressants) showed significant associations with psychological outcomes.

Overall, these findings demonstrate that adults with NT1 experience a substantial psychiatric burden characterized by high rates of depression, anxiety, hopelessness, and suicidal ideation. The co-occurrence of these emotional dimensions suggests a shared vulnerability, potentially linked to orexin deficiency and dysregulation of arousal and emotional circuits. These results underscore the need for systematic psychiatric screening and integrated psychological care in sleep medicine settings to reduce affective distress and suicide risk in this population.

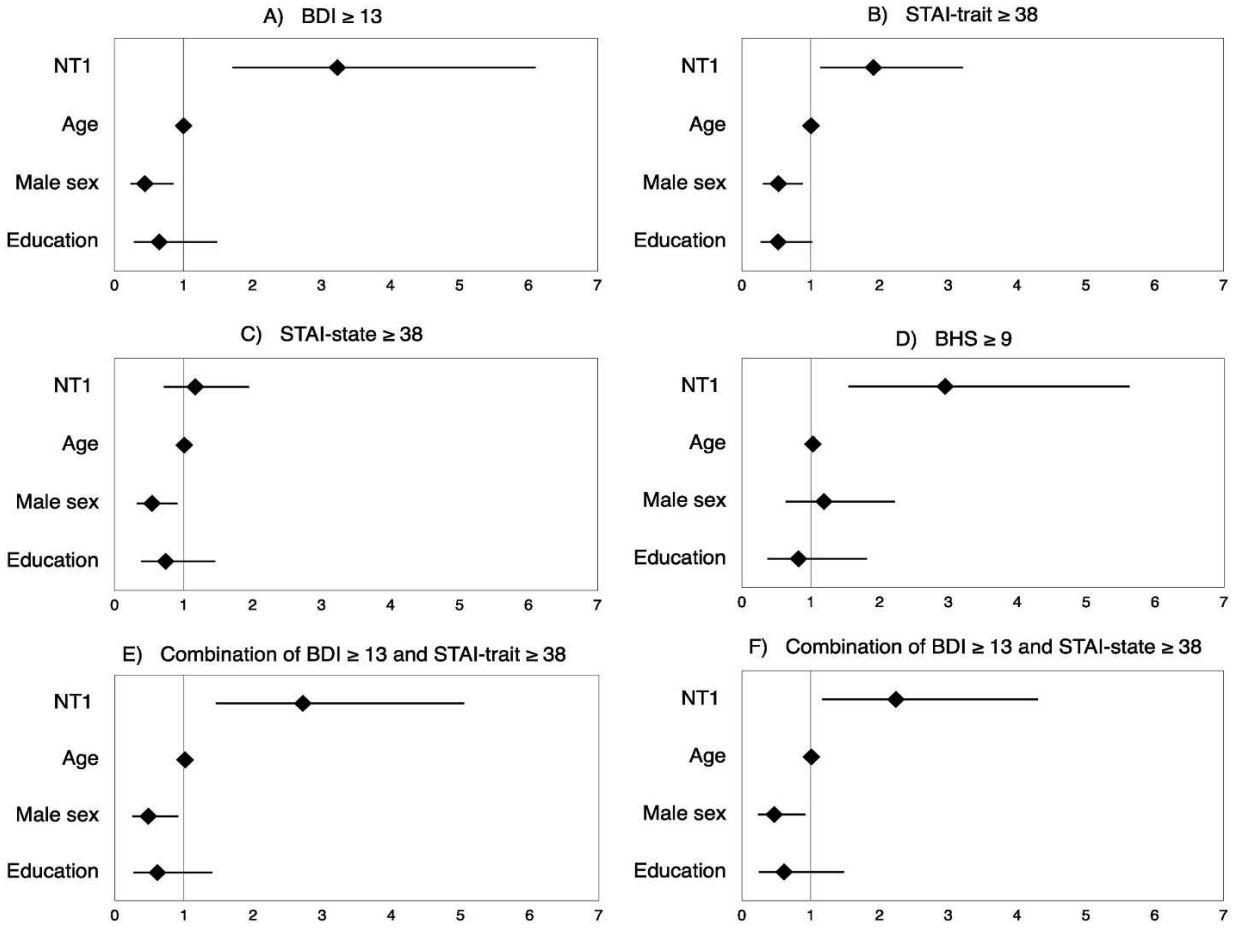


**Figure 5.** *Multivariable analysis of the relation between narcolepsy and depressive symptoms, anxiety, hopelessness, and comorbid symptoms of depression and anxiety, expressed as odds ratio and 95 % confidence interval.*

# CHAPTER 4 – GENERAL DISCUSSION AND CONCLUSION

## 4.1 Integrative overview of the research program

This doctoral thesis examined sleep disturbances as both transdiagnostic markers of vulnerability and potential therapeutic targets across psychiatric and sleep medicine domains. The project integrated multiple methodologies—clinical studies, actigraphic monitoring, and systematic reviews—spanning distinct but conceptually linked populations: adolescents with psychiatric disorders, adults in the early stages of psychosis and bipolar disorder, and individuals with NT1.

The rationale guiding this program stemmed from the recognition that sleep, once considered an ancillary symptom, is in fact an active determinant of mental health. Over the past two decades, advances in neuroscience, psychophysiology, and chronobiology have converged on the notion that sleep and psychopathology share overlapping biological substrates—ranging from emotion regulation networks to circadian and stress-response systems (Riemann et al., 2020; Harvey et al., 2011). This thesis built upon that conceptual shift by investigating how sleep disruptions can signal vulnerability, mediate psychopathological processes, and offer novel preventive or therapeutic entry points.

The first line of research focused on adolescence, a critical developmental period characterized by profound neurobiological and psychosocial reorganization. In this phase, the architecture of sleep undergoes changes in timing, duration, and regulation that interact with emotional and cognitive maturation (Carskadon, 2011). The study conducted on psychiatric inpatients demonstrated that insomnia is an independent predictor of suicidality, even when controlling for depressive symptoms and psychosocial factors such as bullying or physical inactivity. This finding was reinforced by the meta-analysis of over one million adolescents, which showed that sleep disturbances more than triple the risk of suicide attempts and double that of suicidal ideation. These converging results emphasize that poor sleep represents not just a correlate but an early, modifiable driver of suicidal vulnerability.

The second research axis examined sleep disturbances in adults within the first year of psychosis or bipolar disorder onset. This is a crucial stage in which neurobiological plasticity, stress sensitivity, and symptom consolidation interact. Subjective and actigraphic measures revealed high prevalence and disorder-specific profiles of sleep disruption: patients with first-episode psychosis exhibited fragmented and phase-delayed sleep, while those with bipolar disorder showed reduced total sleep time and greater intraindividual variability. Importantly, subjective sleep quality correlated with depressive symptoms, suicidal ideation, and prodromal features, confirming sleep as an early warning signal in severe mental illness.

The systematic review on sleep disturbances in early psychosis synthesized evidence that sleep disruption not only accompanies illness onset but often precedes it, acting as a prodromal marker. Parallelly, the review of therapeutic strategies for bipolar disorder highlighted that non-pharmacological approaches—particularly CBT for Insomnia and

Interpersonal and Social Rhythm Therapy—improve both sleep and affective stability, whereas chronic hypnotic use correlates with poorer outcomes and heightened suicidality (Frank et al., 2021; Espie et al., 2018).

Finally, the studies NT1 extended the analysis to a neurological condition characterized by intrinsic sleep–wake instability. In pediatric and adolescent NT1, a distinct psychotic phenotype emerged, defined by greater REM dysregulation, low orexin levels, and positive psychiatric family history—suggesting an inherited vulnerability to both sleep and emotional dysregulation. In adults, depressive and anxious symptoms, hopelessness, and suicidal ideation were highly prevalent. Together, these findings position narcolepsy as a paradigmatic interface disorder that blurs the boundary between neurology and psychiatry (Bassetti et al., 2019; Barateau et al., 2025).

Across these diverse settings, a consistent pattern emerges: sleep alterations mirror and magnify psychiatric vulnerability. Whether manifested as insomnia, hypersomnia, circadian misalignment, or REM instability, disturbed sleep predicts affective dysregulation, cognitive disorganization, and suicidal thinking. Sleep thus represents a shared dimension that traverses diagnostic categories and developmental stages—a biological "common language" of mental illness.

Taken together, the four research lines developed in this thesis form a coherent, multilayered exploration of how sleep disturbances signal and shape psychiatric vulnerability across different ages, diagnoses, and neurobiological substrates.

Study I (adolescents with psychiatric disorders) identified insomnia as an independent predictor of suicidality even after accounting for depression, bullying, and physical inactivity. This study provided the first clinical demonstration within this thesis that sleep problems are not merely correlates of emotional distress but active, modifiable risk markers in a population undergoing intense developmental reorganization. The subsequent meta-analysis, involving over one million adolescents, strengthened the generalizability of this finding and positioned sleep disturbances as one of the most robust behavioral predictors of suicidal thoughts and attempts during adolescence.

Study II, focused on early psychosis and bipolar disorder, expanded this framework into the early stages of severe mental illness. By combining subjective measures and actigraphy, it demonstrated that sleep alterations in these conditions are not only pervasive but show distinct profiles across diagnoses, correlating with depressive

symptoms, prodromal features, and suicidal ideation. This study bridged adolescent vulnerability with the onset of adult psychiatric disorders, pointing to sleep–wake disruption as a shared early marker that persists across diagnostic transitions.

The two studies on NT1 further extended the model beyond conventional psychiatric diagnoses, providing a unique "boundary condition" where sleep–wake dysregulation is intrinsic and biologically determined. The pediatric/adolescent NT1 study identified a specific psychotic phenotype characterized by REM instability, low orexin levels, and psychiatric family history—traits that resonate with mechanisms observed in both adolescent suicidality and early psychosis. The adult NT1 dataset showed high rates of depression, anxiety, hopelessness, and suicidal ideation, suggesting that chronic REM disruption and hypocretin deficiency may amplify the same affective–cognitive vulnerabilities detected in the other populations.

Across the four studies, a conceptual continuity emerges: sleep alterations consistently accompany—or precede—domains of vulnerability such as emotional dysregulation, prodromal psychotic symptoms, and suicidal thinking. Each study examines a different segment of the lifespan and a different neurobiological background, yet all converge on a shared pattern in which disrupted sleep acts as an early indicator, mediator, and potential lever for intervention.

This integrative perspective positions sleep not as a by-product of psychiatric illness but as a transdiagnostic dimension that traverses developmental stages and diagnostic boundaries, offering a unifying explanatory layer to otherwise heterogeneous psychiatric phenomena.

### 4.2 Synthesis across levels of analysis

A key strength of this research program is its integration of multiple analysis levels—clinical, behavioral, psychometric, objective, and neurobiological—within a cohesive transdiagnostic framework. Rather than looking at sleep disturbances from just one approach, the studies used complementary methods that each capture different but related aspects of vulnerability.

At the clinical level, the four studies explored populations ranging from adolescents in acute psychiatric crisis to adults in the early phases of psychosis and bipolar disorder, and

individuals with NT1, establishing sleep disruption as a recurring feature across heterogeneous diagnostic and developmental contexts.

At the behavioral and symptom level, standardized psychometric instruments (PSQI, ISI, BDI, PQ-16, MDQ) quantified subjective sleep difficulties, affective symptoms, prodromal psychotic features, and suicidal thoughts, revealing consistent co-variation between sleep quality and core psychopathological dimensions.

At the objective level, actigraphy provided continuous, ecologically valid measures of sleep–wake cycles, circadian regularity, fragmentation, and intraindividual variability. These data complemented subjective assessments and revealed disorder-specific patterns—such as delayed phase and instability in first-episode psychosis, or reduced total sleep time and high irregularity in bipolar disorder—that would not have been detectable using self-report tools alone.

At the neurobiological level, the studies on narcolepsy introduced a mechanistic layer grounded in orexin deficiency and REM instability, offering a unique model in which sleep–wake dysregulation is directly linked to emotional and cognitive vulnerability. This biological anchor strengthens the interpretation that sleep alterations observed across the thesis are not merely psychological correlates, but reflect deeper disruptions in arousal-regulation systems.

Finally, at the population and evidence-synthesis level, the meta-analysis on adolescent suicidality and sleep disturbances integrated data from over one million individuals, validating the generalizability of the associations observed in the original studies and placing them within a broader epidemiological context.

Across these interconnected layers, a unified picture emerges: disruptions in sleep–wake regulation reflect a multi-level dysregulation spanning neural circuitry, physiology, cognition, and affect. By examining sleep simultaneously as a subjective experience, a behavioral pattern, a measurable physiological rhythm, and a biologically grounded vulnerability, this thesis demonstrates how the integration of diverse methodologies can reveal the coherence of sleep as a transdiagnostic domain underlying psychiatric risk.

### 4.3 Sleep as a transdiagnostic domain

The results obtained across studies align with the conceptualization of sleep as a transdiagnostic domain, as proposed within the RDoC framework (Insel et al., 2010). Rather than being disorder-specific, sleep alterations reflect dysregulation within the broader "Arousal and Regulatory Systems" dimension, which modulates both physiological and psychological stability.

This transdiagnostic perspective provides a unifying lens through which phenomena as diverse as adolescent suicidality, psychotic relapse, and narcoleptic affective lability can be interpreted. In all these contexts, sleep disturbance operates as both a marker and a mediator—reflecting vulnerability while simultaneously amplifying it. Insomnia, for instance, enhances hyperarousal and emotional dysregulation; circadian misalignment disrupts social rhythm synchronization and reward processing; and REM instability interferes with adaptive emotional memory consolidation (Walker & van der Helm, 2009).

These cross-cutting features challenge the traditional boundaries of psychiatric nosology. The consistent correlations observed across diagnostic groups in this thesis echo previous evidence that sleep disruption predicts onset and recurrence of depression (Baglioni et al., 2016), worsens anxiety (Goldstein & Walker, 2014), and exacerbates psychotic symptoms (Freeman et al., 2015). The recurrence of these mechanisms across illnesses reinforces the need for a dimensional, rather than categorical, approach to mental disorders.

Moreover, sleep offers a rare example of a measurable, modifiable construct linking molecular, behavioral, and experiential levels. From a translational standpoint, it connects neural circuitry (prefrontal–amygdala regulation), endocrine rhythms (cortisol, melatonin), inflammatory signaling, and subjective distress into a coherent framework (Irwin & Opp, 2017). This multidimensionality makes sleep an ideal target for precision psychiatry: it can be quantified, monitored longitudinally, and modified through behavioral, chronotherapeutic, or pharmacological interventions.

### 4.4 Neurobiological mechanisms and shared vulnerability

The convergence of findings across populations suggests a shared neurobiological architecture underpinning both sleep regulation and psychiatric vulnerability. Sleep disturbances and psychopathology intersect in three primary domains: emotion regulation circuits, circadian timing systems, and stress/inflammatory pathways.

Functional neuroimaging and experimental sleep deprivation studies show that sleep loss amplifies amygdala reactivity and reduces prefrontal control, producing neural signatures indistinguishable from those of mood and anxiety disorders (Yoo et al., 2007; Goldstein & Walker, 2014). Chronic sleep restriction disrupts dopaminergic and serotonergic tone, while circadian desynchrony alters CLOCK gene expression and neurotransmitter release (Saper & Fuller, 2017). These neurochemical shifts foster cognitive inflexibility, impulsivity, and affective instability—core dimensions of many psychiatric syndromes.

In the early psychosis sample of this thesis, reduced actigraphic regularity and delayed sleep phase reflect precisely this circadian desynchronization, likely involving dysregulated dopaminergic transmission (Clarke et al., 2021). In bipolar disorder, alterations in REM architecture mirror underlying disruptions in mood-regulating limbic circuits (Harvey, 2008; Gonzalez et al., 2014). In narcolepsy, orexin neuron loss disorganizes arousal networks, producing chronic hypoarousal that paradoxically coexists with emotional volatility (Okechukwu et al., 2022).

Inflammatory signaling further bridges sleep and psychopathology. Insomnia and circadian disruption elevate proinflammatory cytokines, which impair synaptic plasticity and modulate mood-regulating neural pathways (Irwin & Opp, 2017). Adolescents experiencing both poor sleep and depression show increased cortisol reactivity and altered autonomic balance—biomarkers of stress-system dysregulation that parallel suicidal vulnerability.

Taken together, these findings illustrate how diverse clinical phenomena—ranging from adolescent suicidality to narcoleptic psychosis—emerge from converging neurobiological dysfunctions affecting arousal, emotion, and circadian regulation.

### 4.5 Clinical, preventive, and translational implications

From a clinical perspective, these results advocate for a paradigm shift: sleep should be systematically assessed and treated as a core dimension of psychiatric care, not a secondary complaint. Despite its high prevalence, insomnia remains underdiagnosed in mental health services (Freeman et al., 2020). Routine screening with validated instruments such as the PSQI, ISI, or actigraphy-based monitoring could provide valuable markers of clinical status and treatment response.

Sleep-focused interventions demonstrate broad therapeutic and preventive potential. CBT-I and IPSRT are evidence-based, low-risk treatments that improve not only sleep continuity but also mood, cognition, and suicidality across disorders (Harvey et al., 2015; Frank et al., 2021). Their integration into early intervention programs for psychosis or mood disorders could prevent symptom escalation and relapse. In high-risk adolescents, promoting sleep hygiene and circadian regularity through psychoeducation or digital programs has shown measurable reductions in depressive and suicidal symptoms (Lovato & Gradisar, 2014).

In narcolepsy and other neurological conditions, multidisciplinary approaches are essential. Psychiatric symptoms are intrinsic components of the disorder and require coordinated management by sleep physicians and psychiatrists. Recognition of orexin deficiency's emotional sequelae can guide more comprehensive care models, addressing not only excessive sleepiness but also mood instability and social functioning.

The thesis also holds implications for *precision medicine*: sleep parameters—captured via actigraphy or wearable devices—may serve as digital biomarkers for early detection and personalized treatment adjustment (Wang et al., 2022). Combining such monitoring with ecological momentary assessment could enable real-time prediction of relapse or suicidal risk, transforming clinical practice toward proactive, individualized models.

### 4.6 Methodological reflections and limitations

This research program's strengths lie in its integrative, multi-method design and its focus on early stages of illness—windows where prevention is still possible. By bridging

epidemiological, clinical, and neurobiological perspectives, the thesis provides converging evidence for the centrality of sleep in mental health.

However, several limitations warrant discussion. Most original studies were cross-sectional, limiting causal inference. Longitudinal or experimental designs are needed to determine whether sleep disturbances precede psychiatric symptoms or represent epiphenomena. Sample sizes, though clinically meaningful, were moderate, and generalizability may be constrained by demographic and cultural factors. Subjective assessments such as the PSQI and BDI, while validated, are prone to bias; combining them with actigraphy improved accuracy but remains a proxy for PSG.

In the meta-analyses, heterogeneity across studies in definitions of sleep disturbance, measurement tools, and control for confounders introduces residual uncertainty. Publication bias, although minimal, cannot be excluded. Nevertheless, the convergence of results across methodologies and populations strengthens confidence in the overall conclusions.

### 4.7 Final conclusions

Across different populations and methodologies examined in this thesis, a clear narrative emerges: sleep disturbances are not just secondary symptoms of psychiatric disorders but fundamental mechanisms that influence vulnerability, symptom presentation, and clinical outcomes. Insomnia and circadian disruption in adolescents, sleep–wake instability in early psychosis and bipolar disorder, and orexin-related dysregulation in narcolepsy all reflect a common architecture where arousal systems, emotional regulation, and stress reactivity come together as transdiagnostic factors driving mental illness.

The empirical findings indicate that sleep problems often precede the onset of major psychiatric symptoms, frequently act as early warning signs of clinical deterioration, and consistently predict suicidality, emotional instability, and cognitive–emotional dysregulation. This temporal and mechanistic significance suggests that sleep may serve as both a trait-like marker of vulnerability and a state-like amplifier of psychological distress.

From a clinical perspective, these findings highlight the urgent need to incorporate systematic sleep assessments into routine psychiatric care. Sleep is a rare therapeutic

target that can be measured, modified, and has a significant impact across diagnostic categories. When applied early, behavioral and chronotherapeutic treatments have the potential to decrease relapse rates, reduce suicidal risk, and improve functional recovery. Finally, the translational implications of this work go beyond the specific studies presented here. Sleep parameters measured through actigraphy, digital phenotyping, and wearable technologies can act as early risk biomarkers, supporting the development of preventive, personalized, and real-time interventions. Future research that combines objective measures, ecological monitoring, and mechanistic studies of arousal regulation will be crucial to understanding how stabilizing sleep may influence the long-term pathways of psychiatric disorders.

In summary, this thesis highlights a transformative yet straightforward idea: understanding mental illness requires understanding both the biology and phenomenology of sleep. By placing sleep at the core of the clinical and theoretical framework, we move closer to a psychiatry that can predict vulnerability, prevent deterioration, and promote recovery—not just by treating symptoms, but by reestablishing the fundamental rhythms that support the mind.

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