Mental Health, Sleep, Physical Activity and Family Functioning in Adolescents with Narcolepsy

by

Arpita Parmar

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Institute of Medical Science
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Abstract

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Arpita Parmar
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Background: Pediatric narcolepsy is a lifelong sleep disorder that is associated with depressive symptoms. The factors associated with depressive symptoms are unclear. Research on family functioning in pediatric narcolepsy is also limited. The primary objective of this study was to evaluate sleep and physical activity (PA) as factors associated with depression scores in adolescents with narcolepsy and controls. The secondary objective was to assess family functioning in pediatric narcolepsy.

Methods: Adolescents with narcolepsy and controls were recruited from the Hospital for Sick Children and Toronto area respectively. Participants wore an actigraph and pedometer to measure sleep and PA respectively. Depression scores were evaluated with the Children’s Depression Inventory-2. Family Functioning was assessed using the PedsQL Family Impact Module.

Results: Sixty adolescents (30 narcolepsy; 30 controls) participated. Poor sleep quality, excessive daytime sleepiness, and low PA levels were associated with greater depression scores. Family functioning was impaired in pediatric narcolepsy patients.
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ADHD  attention-deficit hyperactivity disorder
BMI   body mass index
CBCL  Child Behaviour Checklist
CDI   Children’s Depression Inventory
CDI-2 Children’s Depression Inventory-2nd edition
DSM   Diagnostic and Statistical Manual of Mental Disorders
EDS   Excessive daytime sleepiness
EEG   Electroencephalogram
Epworth Scale Adapted Epworth Sleepiness Scale
HLA   Human leukocyte antigen
HRQOL Health-related quality of life
MSLT  Multiple sleep latency test
MET   Metabolic equivalent
NREM  Non-rapid eye movement
PA    Physical activity
PSG   Polysomnography
PSQ   Pediatric Sleep Questionnaire
REM   Rapid eye movement
SCARED Screen for Child Anxiety Related Disorders
SOREMP Sleep onset rapid eye movement period
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Chapter One: General Introduction

1.1 Overview

Narcolepsy is a devastating lifelong sleep disorder with typical onset during adolescence (Scammell, 2015). There has been an increase in the incidence of pediatric narcolepsy in the last decade, particularly amongst adolescents (Markku Partinen et al., 2012). Since 2010, the incidence of pediatric narcolepsy was 17 times higher (5.30 diagnoses per 100,000) than the average incidence between 2002 and 2009 (0.31 diagnoses per 100,000) (Markku Partinen et al., 2012). The hallmark feature of narcolepsy is excessive daytime sleepiness (EDS), which includes irresistible sleep episodes known as sleep attacks (Scammell, 2015). Sleep can occur at inappropriate times (e.g., in public places, while socializing or eating) significantly impacting daily function (Viorritto, Kureshi, & Owens, 2012). Cataplexy is also common in narcolepsy and is defined as the sudden loss of muscle tone in either the face, neck, limbs and trunk causing weakness and/or complete collapse (Nevsimalova, 2014). Nocturnal hallucinations and sleep paralysis—awakening unable to move, are further disturbing symptoms (Viorritto et al., 2012). Patients with narcolepsy also experience disturbed nocturnal sleep (Serra, Montagna, Mignot, Lugaresi, & Plazzi, 2008), which is characterized by frequent awakenings and sleep fragmentation (Roth et al., 2013). Disturbed nocturnal sleep may contribute to patients with narcolepsy feeling sleep deprived and unrested throughout the day, exacerbating the severity of daytime symptoms (Viorritto et al., 2012).

A common co-morbidity in pediatric narcolepsy is mental illness, specifically depression and anxiety (K. Maski et al., 2017). If left untreated, depression can have serious consequences such as poor school performance, obesity and suicide (Glied & Pine, 2002; X. Liu, 2004). The factors that are associated with depressive symptoms amongst adolescents with narcolepsy remain largely unknown. Sleep patterns (duration and quality) and physical activity (PA) levels are factors that are associated with depressive symptoms amongst otherwise healthy adolescents (Lofthouse, Gilchrist, & Splaingard, 2009) (Smagula, Stone, Fabio, & Cauley, 2016) (Biddle & Asare, 2011), however this association has not been examined amongst adolescents with narcolepsy. This knowledge is important for clinical teams working to improve overall clinical management of adolescents with narcolepsy.
Furthermore, pediatric illnesses are known to negatively impact the entire family’s functioning (Giallo, Roberts, Emerson, Wood, & Gavidia-Payne, 2014), however research on family functioning in the narcolepsy population is limited. This knowledge may provide valuable insight for clinical teams providing family centered care to patients.

The objectives of this theses are to:

1) Examine if sleep patterns (duration and quality), EDS and physical activity levels are associated with depression scores as the primary outcome and anxiety scores as the secondary outcome in adolescents with narcolepsy compared with healthy adolescents

2) Describe family functioning in adolescents with narcolepsy, in comparison to otherwise healthy adolescents (not seeking medical care) and other pediatric conditions

3) Examine the association between family functioning and depression and anxiety scores in adolescents with narcolepsy
1.2 Thesis Structure

Chapter two is the literature review, which outlines several key integrated concepts that produce the background of this thesis. The first section presents an overview of pediatric narcolepsy and discusses the diagnoses and symptoms, diagnostic tools, pathophysiology, epidemiology, treatment and comorbidities associated with narcolepsy. Chapter two also discusses current knowledge on mental health in adolescents with narcolepsy and otherwise healthy adolescents, and the relationship between mental health, sleep and physical activity levels. This section also discusses current knowledge on family functioning in pediatric narcolepsy. Chapter three presents the rationale, objectives and study hypotheses. Chapter four outlines the methodology, including the eligibility criteria for the study population and study design. This section also describes the study measures in detail, which includes actigraphy, a pedometer and validated questionnaires to assess depression scores, anxiety scores and family functioning in pediatric populations. Chapter five summarizes study results, where sleep patterns, physical activity levels, depression and anxiety scores, and family functioning were assessed amongst adolescents and controls. The factors associated with depressive symptoms are also described. Family functioning amongst adolescents with narcolepsy was also compared to a community sample (not seeking medical care) and other pediatric conditions. Chapter six is the conclusion and the general discussion, strengths and limitations and avenues for future research related to this thesis.
Chapter Two: Literature Review

2.1 Pediatric Narcolepsy

2.1.1 Diagnosis and Symptoms

Narcolepsy is a sleep disorder that typically onsets between the ages of 10 and 20 years (Scammell, 2015). The mean delay in diagnosis in pediatric narcolepsy is approximately two years (Dias Costa et al., 2014), however can be longer than ten years in some adults (Thorpy & Krieger, 2014). The time between disease onset and diagnosis can be a challenge in narcolepsy because of its rarity and lack of symptom recognition (Thorpy & Krieger, 2014).

The International Classification of Sleep Disorders Diagnostic and Coding Manual (3rd edition) describes narcolepsy as a central disorder of hypersomnia, and divides narcolepsy into two categories: Type 1—narcolepsy with cataplexy and Type 2—narcolepsy without cataplexy (AASM, 2014). Cataplexy is the sudden loss of muscle tone in either the face and neck and/or limbs and trunk, which leads to weakness and the loss of voluntary muscle control (Nevsimalova, 2014). Episodes of cataplexy are triggered by strong emotions, which are usually positive (e.g., laughter) but can also be negative (e.g., anger, fear) (Scammell, 2015). Episodes of cataplexy also vary in severity and range from cataplectic facies, which includes repetitive mouth opening, tongue protrusion, and drooping eyelids (Nevsimalova, 2014; Viorritto et al., 2012) (See Figure 1). Complete cataplexy may result in weakness and loss of tone in larger muscles of the limbs and trunk which cause patients to collapse (See Figure 2). Patients with narcolepsy also remain entirely conscious during episodes of cataplexy (Nevsimalova, 2014).

The hallmark feature of both type 1 and 2 narcolepsy is excessive daytime sleepiness (EDS), which must persist daily for greater than three months (Babiker & Prasad, 2015). EDS is characterized by the sudden onset of irresistible sleep episodes known as sleep attacks. Sleep attacks can occur at inappropriate times (e.g., in public places, while socializing or eating) significantly impacting daily functioning (Viorritto et al., 2012).

Other features of both types of narcolepsy include hypnagogic/hypnopompic hallucinations, which is dreamlike imagery that is exclusive to falling asleep and/or awakening (Peterson & Husain, 2008). Hypnagogic hallucinations occur just before falling asleep and
hypnopompic hallucinations occur upon waking (Peterson & Husain, 2008). Hallucinations occur in up to 50 per cent of pediatric patients with narcolepsy and are multi-sensory (e.g., auditory, visual, kinetic). In pediatric patients with narcolepsy, hallucinations are not usually frightening and have simple forms (e.g., colored circles, images of animals or people) that can appear to be very realistic (Peterson & Husain, 2008). Hallucinations also frequently occur in relation to sleep paralysis (Guilleminault & Pelayo, 2000). Sleep paralysis is the temporary inability to move voluntary muscles during sleep-wake transitions, while being conscious (Viorritto et al., 2012). Episodes of sleep paralysis can last in a duration of seconds or minutes and end spontaneously, which can be frightening and confusing for young patients (Viorritto et al., 2012). Sleep paralysis can also be interrupted by physical or verbal contact with the affected individual (Stores, 2009).

Disturbed nocturnal sleep is also a common symptom in narcolepsy and occurs in approximately 89 per cent of pediatric narcolepsy patients (Serra et al., 2008). Disturbed nocturnal sleep is characterized by nightly awakenings and greater periods of wakefulness after sleep onset resulting in sleep fragmentation and overall poor sleep quality (Roth et al., 2013). Disturbed nocturnal sleep results in reduced sleep efficiency which is the amount of time spent sleeping divided by the time spent lying in bed (Xu et al., 2017). Distributed nocturnal sleep may also cause patients with narcolepsy to feel unrested in the morning and throughout the day, exacerbating the severity of daytime symptoms (Viorritto et al., 2012).
**Figure 1:** Narcolepsy Patients Presenting with Cataplectic Facies: (A) Facial weakness, onward head and trunk flexion with active shoulder raising (B) head drop and opposing neck hyperextension (C) Mouth opening and tongue protrusion. Figure adapted from Postiglione et al (Postiglione et al., 2017).
Figure 2: Cataplexy across Differing Levels of Severity. Figured adapted from Scammell et al (Scammell, 2015)
2.1.2 Diagnostic Tools

Multiple tests can be used to diagnose narcolepsy including a comprehensive clinical interview; an overnight sleep study, also called polysomnography (PSG), followed by a multiple sleep latency test (MSLT) conducted during the day. Other tests include hypocretin levels, Human leukocyte antigen (HLA) typing, the modified Epworth Sleepiness Scale (Epworth scale) score and actigraphy (Nevsimalova, 2014).

Polysomnogram

PSG is conducted in sleep laboratories, and provides a comprehensive recording of biophysiological changes during sleep including an electroencephalogram (EEG), eye movements, muscle activity, respiratory events and heart rhythms (Douglas, Thomas, & Jan, 1992). The EEG records sleep and wake, as well as information regarding sleep stages (Douglas et al., 1992). Sleep is divided into two main stages, rapid-eye movement (REM) sleep and Non-REM (NREM) sleep (Dement & Kleitman, 1957). The sleep cycle generally begins in NREM sleep, with each stage getting progressively deeper and finally entering REM sleep (Dement & Kleitman, 1957). The majority of total sleep time is spent in NREM sleep, which is divided into three alternating stages: NREM-1, NREM-2, which constitute as lighter sleep and NREM-3, which is a deep sleep (Dement & Kleitman, 1957). During the first cycle of the night, the NREM sleep period lasts for about 80 minutes, and is followed by a 10-minute period of REM sleep (M. A. Carskadon & Dement, 2011). During the first half of the night, the amount of NREM-3 sleep tends to be greater, however throughout the night, REM sleep periods lengthen (M. A. Carskadon & Dement, 2011).

PSG is useful in identifying deviations to normal sleep patterns and architecture (Xu et al., 2017). The hallmark feature of narcolepsy on PSG is the presence of sleep onset REM periods (SOREMPs) (Xu et al., 2017). SOREMPs are REM periods beginning within 15 minutes of sleep onset at night or during daytime naps (Plazzi, Serra, & Ferri, 2008). Other PSG features associated with narcolepsy include greater total sleep time, specifically greater time spent in lighter sleep (NREM-1 and NREM-2) (Plazzi et al., 2008) but a reduced time in NREM-3 (Roth et al., 2013). Narcolepsy is also associated with an increase in REM sleep (Kiran Maski & Heroux, 2016). Patients with narcolepsy also fall into REM sleep at any time of the day, while in healthy
individuals, REM sleep only occurs during nocturnal sleep periods (Roth et al., 2013). Patients with narcolepsy also have a shorter sleep latency (less than 10 minutes), which is the time it takes to fall asleep, and a shorter REM latency, which is the time it takes to enter REM sleep (Dement & Kleitman, 1957; Xu et al., 2017). Disturbed nocturnal sleep is visible on the PSG through a reduced sleep efficiency (less than 80%) and increased wake after sleep onset due to increased nocturnal awakenings (Serra et al., 2008).

Data from the PSG can also rule out other sleep disorders that may be the cause of EDS, such as obstructive sleep apnea, REM behaviour disorder and sleep related movement disorders (AASM, 2007). PSG is considered the gold standard for assessing sleep architecture and cardiopulmonary physiology (AASM, 2007). However, PSGs are typically undertaken in designated sleep facilities which limits the ability to provide a realistic representation of a patient’s natural sleeping environment (Sadeh, Lavie, Scher, Tirosh, & Epstein, 1991).

**Figure 3:** Hypnogram (a form of PSG) Comparing a Healthy Individual to a Patient with Narcolepsy. The healthy individual has relatively consolidated sleep between midnight and 8 AM, but the person with narcolepsy has fragmented sleep, a rapid entry into REM sleep (red outline), and numerous naps during the day that include REM sleep. Figure adapted from (School, 2016).
Multiple Sleep Latency Test

A Multiple Sleep Latency Test (MSLT) is another diagnostic test used in narcolepsy, which is a follow-up test to the overnight PSG (Aurora et al., 2012). The MSLT includes five nap opportunities that are twenty minutes in duration given at two hour intervals throughout the day (Littner et al., 2005). For each nap, the sleep latency and SOREMPs are recorded (Littner et al., 2005) (see Figure 4). On the MSLT, the generally accepted diagnostic rules regard an abnormal mean sleep latency to be less than eight minutes (M. A. Carskadon et al., 1986). In both pediatric and adult populations, two or more episodes of SOREMPs are also considered pathological, with the highest number of SOREMPs at disease onset (M. A. Carskadon et al., 1986).

**Figure 4:** MSLT of Patient with Narcolepsy. Figured adapted from Berry et al (Berry RB, 2012)

![MSLT of Patient with Narcolepsy](image-url)

Mean sleep latency of all naps = 0.9 min, SOREMP = 4.
Epworth Sleepiness Scale

The self-report adapted Epworth Sleepiness Scale (Epworth scale) is a measure of EDS for pediatric populations (Johns, 2015). Epworth scale scores range from 0 to 24, with higher scores indicating greater daytime sleepiness (Johns, 2015). Epworth scale scores greater than ten have been reported to be clinically significant (Johns, 2015).

Hypocretin Levels

Hypocretin levels are measured by cerebrospinal fluid but not in the blood or in any other peripheral tissue (Mignot et al., 2002). Hypocretin levels that are lower than 110 pg/ml are strongly predictive of narcolepsy (Mignot et al., 2002).

Human leukocyte antigen typing

HLA typing is non-invasive test (done by obtaining a blood sample) used in diagnosing narcolepsy (Nevsimalova, Mignot, Sonka, & Arrigoni, 1997). Human leukocyte antigens (HLA) are proteins located on the surface of white blood cells and other tissues in the body (Bjorkman et al., 1987) and certain diseases are associated with particular HLA types (Thorsby, 1997). Narcolepsy is associated with the HLA DQB1 0602/DRB1 1501 haplotype, and over 90 percent of narcolepsy patients with cataplexy express this marker (Nevsimalova et al., 1997). However, HLA DQB1 0602/DRB1 1501 is also seen in the general population, and some patients with narcolepsy do not have it, limiting it as a diagnostic tool (Nevsimalova et al., 1997).

Actigraphy

Actigraphy is an objective and non-invasive way of measuring sleep patterns (Meltzer et al., 2016). Actigraphy is a watch-like device worn which has a built-in accelerometer that collects data on gross motor activity and can be done in the natural sleep environment (e.g., the patient’s bedroom at home) (Meltzer et al., 2016). Actigraphy is used in association with a sleep diary to log sleep patterns and behaviour (Sadeh, 2011). The data is translated to periods of wake or sleep using an algorithm specific to the device (Meltzer et al., 2016). Actigraphy is also a valid measure of total sleep time in children (Sadeh, Raviv, & Gruber, 2000; Werner, Molinari, Guyer, & Jenni, 2008). Actigraphy has been shown to accurately discriminate between young adults with narcolepsy and controls (Bruck, Kennedy, Cooper, & Apel, 2005). When comparing actigraphy
to PSG data, patients with narcolepsy have a reduced total sleep time (6.39 vs 7.64 hours), and a reduced sleep efficiency (74.38 vs 85.87 per cent) (A. Alakuijala, Sarkanen, & Partinen, 2015). Sleep onset latency is also reported to be longer in patients with narcolepsy on actigraphy data when compared to PSG data (16.45 vs 5.43 minutes) (A. Alakuijala et al., 2015). The fact that actigraphy does not measure sleep stages may account for the differences seen between actigraphy and PSG data (A. Alakuijala et al., 2015). REM sleep with minor movement activity would be scored as sleep time on PSG data, but not on actigraphy (A. Alakuijala et al., 2015). Additionally, patients with narcolepsy have extensive motor dysregulation during REM sleep (Nightingale et al., 2005), which may further account for decreased total sleep time seen through actigraphy. However, actigraphy may be more useful than PSG data to capture nocturnal sleep fragmentation—a common feature of narcolepsy, because it measures movement activity and not stages of sleep (A. Alakuijala et al., 2015). In summary, actigraphy is a useful objective measure of sleep for clinical and research purposes to provide data on total sleep time and sleep efficiency that is comparable to PSG data (Kushida et al., 2001).

A summary of diagnostic tests for narcolepsy can be found in Table 1.

**Table 1: Diagnostic Tests in Narcolepsy**

<table>
<thead>
<tr>
<th>Test Name</th>
<th>Features Associated with Narcolepsy</th>
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| Polysomnogram                  | • Presence of SOREMPs  
• REM latency ≤ 15 minutes  
• Sleep efficiency < 80%  
• Frequent nocturnal awakenings |
| Multiple Sleep Latency Test    | • Mean sleep latency ≤ 8 minutes  
• ≥ 2 SOREMPs                                                              |
| Hypocretin levels              | • < 110 pg/ml                                                            |
| Human leukocyte antigen typing | • Presence of DQB1:0602/DRB1 1501 haplotype                              |
| Epworth Sleepiness Scale       | • > 10                                                                  |
| Actigraphy                     | • Sleep efficiency <80%  
• Increased wake after sleep onset  
• Frequent nocturnal awakenings |

SOREMP-Sleep onset REM period  
REM-Rapid Eye Movement
### 2.1.3 Pathophysiology

Narcolepsy is caused by a loss of hypothalamic neurons containing hypocretin (Scammell, 2015) (Thannickal et al., 2000). An autopsy study shows that the number of hypocretin neurons are 85 to 95 per cent lower in individuals with a history of narcolepsy compared to healthy controls (Thannickal et al., 2000) (See Figure 5A and 5B). Hypocretin is a neuropeptide that is involved in sleep regulation (Bourgin et al., 2000; K. Maski & Owens, 2016). Hypocretin also stimulates target neurons in different regions of the brain that promote wakefulness (R. Y. Moore, Abrahamson, & Van Den Pol, 2001) (Scammell, 2015). Hypocretin acts on neurons in the cortex and basal forebrain, brain stem and hypothalamus that produce neurotransmitters norepinephrine, serotonin, dopamine, and histamine (Gujar, Yoo, Hu, & Walker, 2011). Hypocretin deficiency causes inconsistencies in the release of these neurotransmitters resulting in EDS, sudden lapses into sleep and the poor regulation of REM sleep seen in narcolepsy (Gujar et al., 2011) (Lu, Sherman, Devor, & Saper, 2006). Hypocretin deficiency reduces activity of the pathway that suppresses REM sleep, enabling elements of REM sleep during wakefulness such as dreamlike hallucinations (Bourgin et al., 2000; Clifford B. Saper, Fuller, Pedersen, Lu, & Scammell, 2010). Lower hypocretin levels have also been associated with sleep fragmentation in patients in narcolepsy (Anniina Alakuijala, Sarkanen, & Partinen, 2016), as hypocretin neurons are stabilizers of the sleep-wake transition (Clifford B. Saper et al., 2010). Cataplexy results when strong emotions experienced by the patient activate neuronal pathways in the medial prefrontal cortex and the amygdala (Bassetti & Aldrich, 1996; Scammell, 2015). The medial prefrontal cortex and amygdala activate circuits in the pons that cause muscle paralysis, resulting in partial or complete cataplexy (Bassetti & Aldrich, 1996; Scammell, 2015) (See Figure 6).

The exact cause of hypocretin deficiency in narcolepsy is unclear (Picchioni, Hope, & Harsh, 2007), but the leading hypothesis is that autoimmune processes destroy hypocretin neurons (Liblau, Vassali, Seifinejad, & Tafti, 2015). The autoimmune hypothesis suggests T cells destroy hypocretin neurons through HLA presentation (Matsuki et al., 1992) (Mahlios, De la Herrán-Arita, & Mignot, 2013). HLA alleles encode subtypes of Major Histocompatibility Complex classes I and II proteins, which are responsible for presenting foreign peptides to T cells during infections (Janeway, Travers, & Walport, 2001; Klein & Figueroa, 1986). However, in individuals with narcolepsy, the immune system may mistaken self-peptides on hypocretin neurons as foreign (Matsuki et al., 1992) (Mahlios et al., 2013) (Janeway et al., 2001; Klein & Figueroa, 1986). The
association between human autoimmune diseases and infections is also evident in narcolepsy, as disease onset is associated with the development of infections such as streptococcus pyogenes, influenza and H1N1 (Nohynek et al., 2012) (M. Partinen et al., 2012) (Aran et al., 2009).

Two major hypotheses that may explain the autoimmune destruction of hypocretin producing cells include the bystander of autoreactive T cells and molecular mimicry (De la Herrán-Arita & García-García, 2014; Mahlios et al., 2013). The bystander of autoreactive T cells hypothesis suggests that T cells stimulated during an infection may directly stimulate surrounding T cells by cytokines (Singal & Blajchman, 1973). The stimulated surrounding T cells (that are not specific to a pathogen) may subsequently damage hypocretin cells (Fontana et al., 2010). The molecular mimicry hypothesis suggests that there are structural similarities between both the antigen of the pathogen and host (Petrie, Livak, Burtrum, & Mazel, 1995). As a result, T cell receptor may bind to structurally related antigens on the host, activating T cells that result in cell death (Petrie et al., 1995).
**Figure 5A:** Distribution of Hypocretin Neurons (Black Spots) in a Normal Brain Compared to Narcolepsy Brain
Figure adapted from Thannickal et al. (Thannickal et al., 2000)

**Figure 5B:** Graph Showing Decreased Hypocretin Neurons in a Narcolepsy Brain Compared to Normal Brain
Figure adapted from Thannickal et al. (Thannickal et al., 2000)
**Figure 6:** Pathways Showing Mechanism of Cataplexy In Narcolepsy

Open white circles are neuron-cell bodies. The green lines resemble excitatory pathways and red lines resemble inhibitory pathways. The dotted lines indicate reduced activity of the pathway. Figure adapted from Scammell et al (Scammell, 2015)
2.1.4 Epidemiology

The prevalence of narcolepsy is approximately between 25 and 50 per 100,000 (Longstreth, Koepsell, Ton, Hendrickson, & van Belle, 2007; Ohayon, 2008) however data on pediatric narcolepsy is unavailable (Nevsimalova, 2014). The prevalence of narcolepsy has increased significantly within the last decade (Rocca et al., 2016). Data from a study in Finland reveals that in 2010, the average incidence of pediatric narcolepsy (patients <17 years of age) was 17 times higher (5.30 diagnoses per 100 000) than the average incidence between 2002 and 2009 (0.31 diagnoses per 100 000) (Markku Partinen et al., 2012). The highest incidence was seen in children ages 11 to 16 years (Markku Partinen et al., 2012). In children less than 11 years of age, there was an alarming a 177-fold increase in new cases of pediatric narcolepsy in 2010 (increase from an average of 0.02 to 3.39 diagnoses per 100 000) (Markku Partinen et al., 2012). No increase was seen in the incidence of adult narcolepsy (patients ≥20 years of age) (Markku Partinen et al., 2012). Preliminary data from the Pediatric Working Group of the Sleep Research Network in the United States shows a two-fold increase in number of pediatric narcolepsy cases from 2010 to 2013 (Simakajornboon et al., 2017).

It is unclear why there has been an increased incidence in pediatric narcolepsy (Rocca et al., 2016). Some have attributed this increase to the use of the Pandemrix vaccine (used for influenza pandemics, such as the H1N1 2009 flu) (Szakacs, Darin, & Hallbook, 2013). In Finland, researchers retrospectively reviewed vaccination data from primary health care data bases from January 2009 to December 2010, on all living children born between January 1991 and December 2005 (Nohynek et al., 2012). All new cases of narcolepsy in this cohort were identified from the patient’s medical record (Nohynek et al., 2012). The incidence of narcolepsy was 9.0 in the vaccinated as compared to 0.7 per 100,000 person years in the unvaccinated individuals (Nohynek et al., 2012). The vaccine-attributable risk of developing narcolepsy was 1:16,000 vaccinated 4 to 19-year-olds (95% confidence interval 1:13,000–1:21,000) (Nohynek et al., 2012).
Similar trends were seen across Europe, where Sweden also observed an increase in pediatric narcolepsy and sixty-seven per cent of children and adolescents received a Pandemrix vaccination (Mereckiene et al., 2012). In the Netherlands, the Pandemrix vaccination was not used in older children and adolescents and the incidence of narcolepsy was stated to be lower than other nations that did (Markku Partinen et al., 2012). The relationship between the Pandemrix vaccination and increased incidence of narcolepsy may be due to the non-specific immune-stimulating effect of the adjuvants squalene and tocopherol in the vaccine and a more specific triggering of the H1N1 antigen working together (Szakacs et al., 2013). However, cross-reactive autoimmunity of hypocretin neurons is unlikely as a computer search for peptide homologies between the H1N1 virus and hypocretin neuron-specific proteins did not reveal any potential molecular mimicry (Fontana et al., 2010). The adjuvants in the Pandemrix vaccine may have induced a bystander activated immune response (Carmona et al., 2010). Further research is needed to identify the specific biological mechanisms of this relationship (Sarkanen, Alakuijala, Dauvilliers, & Partinen, 2018).

Another possible reason for the reported increased incidence of narcolepsy could be attributed to increased awareness (Sarkanen et al., 2018). Previous recognition of narcolepsy has been limited especially amongst primary care health practitioners due to its rarity, however following the H1N1 related cases there has been an increase in media attention of narcolepsy (Sarkanen et al., 2018). Therefore, an increase in awareness of the disease may lead to an increase in number of diagnoses, without an actual rise in incidence (Sarkanen et al., 2018).
2.1.5 Treatment of Pediatric Narcolepsy

2.1.5.1 Pharmaceutical Treatment

Treatment of narcolepsy is aimed at relieving disease symptoms particularly EDS, cataplexy, hallucinations, sleep paralysis and disturbed nocturnal sleep (Bhattarai & Sumerall, 2017). A description of different pharmaceutical treatment available for narcolepsy follows:

Stimulants

EDS is the most commonly treated symptom in narcolepsy, which patients report to be the most problematic on daily function (Wozniak & Quinnell, 2015). EDS is targeted by the use of stimulants such as amphetamines, dextroamphetamine and methylphenidate (Billiard, 2008). Stimulants increase monoaminergic activity by targeting the neurotransmitters dopamine and norepinephrine to promote wakefulness and help alleviate EDS (Thorpy & Dauvilliers, 2015).

There are no studies evaluating the effect of stimulants solely in pediatric patients with narcolepsy (Nevsimalova, 2014). One study on adults with narcolepsy (N=94), which included 13 pediatric patients (ages 9-17 years), showed that using mazindol (non-amphetamine stimulant) for 30 months improved EDS symptoms and cataplexy (Nittur et al., 2013). This study reported Epworth scale scores decreased from 17.7 ± 3.5 to 12.8 ± 5.1, with an average fall of -4.6 ± 4.7 (p<0.0001) and the frequency of cataplexy fell from 4.6 ± 3.1 to 2.0 ± 2.8 episodes per week (Nittur et al., 2013).

A more recent pharmacotherapy called Pitolisant is an alternative stimulant to promote wakefulness in patients with narcolepsy and is currently only approved in Europe (Calik, 2017). Pitolisant works to block histamine H3 auto receptor to increase brain histamine levels and consequently promote wakefulness (Calik, 2017). In one open-label trial in four teenagers with narcolepsy, the use of Pitolisant showed a decrease in EDS measured by Epworth scale scores and a slight decrease in the severity and frequency of episodes of cataplexy (C. Inocente et al., 2012).
Wakefulness-promoting agents

More recently, wakefulness promoting agents—specifically, modafinil and armodafinil have been increasingly used in treating EDS due to the side effects and addictive properties of other stimulants (Thorpy & Dauvilliers, 2015). The mechanism of action of modafinil and armodafinil are not well understood, but they are thought to influence the dopaminergic, adrenergic, and histaminergic systems of the hypothalamus (Thorpy & Dauvilliers, 2015). One pediatric study across nine centres in Europe shared their clinical experience with modafinil (through a retrospective chart review) in treating pediatric patients with narcolepsy (combined n=205; age range 4-18 years) (Lecendreux et al., 2012). Collectively, authors stated that 85 per cent of patients reported improvements in symptoms of EDS (Lecendreux et al., 2012).

Central Nervous System Depressant/ Gamma Hydroxybutyrate

Another drug used in the treatment of narcolepsy is sodium oxybate (Peacock & Benca, 2010). Sodium oxybate works by improving nocturnal sleep quality, allowing patients to feel more rested after awakening and consequently decreasing daytime symptoms (Thorpy & Dauvilliers, 2015). Sodium oxybate is also shown to be more effective than benzodiazepines at improving nocturnal sleep (Black, Pardi, Hornfeldt, & Inhaber, 2010). Sodium oxybate works by increasing deep sleep—which is reduced in narcolepsy, by inhibiting the release of neurotransmitters gamma-aminobutyric acid, glutamate and dopamine (Ahmed & Thorpy, 2010).

A recent clinical trial in pediatric narcolepsy patients shows sodium oxybate improves nocturnal sleep quality and reduces EDS and episodes of cataplexy after one year of treatment in drug-naive children and adolescents (N=24, mean age: 12.20 ± 2.95 years, range: 7.10–17.03) (Filardi et al., 2018). Sodium oxybate treatment showed a decrease in nocturnal awakenings measured by actigraphy (32.88 ± 8.15 16.83 ± 4.08; p<0.01), a decrease in Epworth scale scores (15.71 ± 2.56 to 10.29 ± 3.52; p<0.01) and a reduced frequency of patients reporting daily episodes of cataplexy (83% vs 8.3%; p<0.01) (Filardi et al., 2018). A double-blind, placebo-controlled, randomized-withdrawal, multicenter study was recently conducted to assess the efficacy of sodium oxybate in pediatric patients with narcolepsy (ages 7-16 years) (Plazzi et al., 2017). Preliminary results on 35 patients showed a reduction in weekly cataplexy attacks (Plazzi et al., 2017). Although effective in treating narcolepsy, sodium oxybate can be a challenging treatment to adhere
to as it is typically prescribed in two nightly doses, and its euphoric effects have been linked with abuse and dependence (Peacock & Benca, 2010).

**Antidepressants**

Antidepressants are also used in the treatment of narcolepsy, particularly for symptoms of cataplexy (Peacock & Benca, 2010). Although their mechanism of action is not understood, one study shows antidepressants inhibit norepinephrine reuptake and are effective in treating cataplexy (Morgenthaler et al., 2007). Anti-depressants have also been used in treating sleep paralysis, hypnagogic hallucinations (Morgenthaler et al., 2007) as they suppress REM sleep (Winokur et al., 2001). In six clinical case reports of children and adolescents with narcolepsy (ages 7-12 years old), patients on Venlafaxine reported reduced episodes of cataplexy and hypnagogic hallucinations (Moller & Ostergaard, 2009).

**Benzodiazepines**

Benzodiazepines have been used to treat disturbed nocturnal sleep, however no studies have assessed their efficacy in the pediatric narcolepsy population (Billiard, 2008). In adults with narcolepsy (ages 18-60 years), a single-blind within-subject crossover study comparing placebo and the benzodiazepine triazolam showed improvements in sleep efficiency (baseline-77.6 ± 8.2 per cent; triazolam-87.1 ± 5.6 per cent; placebo-77.2 ± 9.6 per cent; p<0.005) measured by PSG (Thorpy, Snyder, Aloe, Ledereich, & Starz, 1992). A summary of pharmaceuticals used to treat pediatric narcolepsy symptoms are provided in Table 2.
Table 2: Pharmaceuticals Used in Treating Pediatric Narcolepsy

<table>
<thead>
<tr>
<th>Drug</th>
<th>Drug Class</th>
<th>Target Symptoms to Treat</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methylphenidate (Ritalin)</td>
<td>Stimulants</td>
<td>Excessive Daytime Sleepiness/Sleep attacks</td>
</tr>
<tr>
<td>Amphetatmine Salts (Adderall)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pitolisant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Modafinil (Provigil)</td>
<td>Wakefulness-promoting agents</td>
<td>Excessive Daytime Sleepiness/Sleep attacks</td>
</tr>
<tr>
<td>Armodafinil (Nuvigil)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium Oxybate (Xyrem)</td>
<td>Central Nervous System</td>
<td>Excessive Daytime Sleepiness/Sleep attacks</td>
</tr>
<tr>
<td></td>
<td>Depressants/ Gamma</td>
<td>Disturbed nocturnal sleep</td>
</tr>
<tr>
<td></td>
<td>Hydroxybutyrate</td>
<td>Cataplexy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sleep paralysis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hypnagogic hallucinations</td>
</tr>
<tr>
<td>Clomipramine (Anafranil)</td>
<td>Antidepressants</td>
<td>Disturbed nocturnal sleep</td>
</tr>
<tr>
<td>Venlafaxine (Effexor)</td>
<td></td>
<td>Cataplexy</td>
</tr>
<tr>
<td>Fluoxetine (Prozac)</td>
<td></td>
<td>Sleep paralysis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hypnagogic hallucinations</td>
</tr>
<tr>
<td>Triazolam</td>
<td>Benzodiazepines</td>
<td>Disturbed nocturnal sleep</td>
</tr>
</tbody>
</table>

Unfortunately many patients with narcolepsy continue to experience symptoms and their negative impact despite treatment (Wozniak & Quinnell, 2015). This has been shown in a European study on adults with narcolepsy (n=67) (age range-19 to >71 years (44.8% were aged ≤40 years; 55.2% were aged >40 years)), where all patients were on standard treatment (modafinil (62.7%), methylphenidate (19.4%), venlafaxine (11.9%), clomipramine (11.9%), fluoxetine (7.5%), paroxetine (4.5%), dextroamphetamine (3.0%), sodium oxybate (26.9%)) (Shneerson, Dauvilliers, Plazzi, Myers, & Garcia-Borreguero, 2008). Despite treatment, 84 per cent of patients reported feeling the negative impact of symptoms on a daily basis (Shneerson et al., 2008). Specifically, 70 per cent of patients reported experiencing EDS and 31 per cent reported experiencing daily cataplexy (Shneerson et al., 2008).
2.1.5.2 Non-pharmacological Treatment

There is limited evidence on the efficacy of non-pharmacological treatment to improve symptoms in pediatric narcolepsy (Kacar Bayram et al., 2016). The most common non-pharmacological intervention in narcolepsy is that of practicing good sleep hygiene (e.g., regular sleep–wake schedules and planned naps) and exercise (Nevsimalova, 2014) (Kacar Bayram et al., 2016). Patients with narcolepsy have self-reported improvement in symptoms using non-pharmacological treatments (K. Maski et al., 2017). A cross-sectional survey of 1,699 people (8.5 per cent <17 years old) in the United States with narcolepsy (K. Maski et al., 2017). Thirty-six percent of participants reported good sleep hygiene (e.g., naps, regular schedule) improved their symptoms, while a small number also reported that participating in exercise (14.5%) improved their symptoms (K. Maski et al., 2017).

In addition, scheduled naps and regular nocturnal sleep times has been assessed in a study of 29 adults patients with narcolepsy (mean age of 43.7 ± 13.9 years; all patients were treated with stimulants) (Rogers, Aldrich, & Lin, 2001). Patients were randomly assigned to one of three treatment groups: 1) two 15-minute naps per day; 2) a regular schedule for nocturnal sleep; or 3) a combination of scheduled naps and regular bedtimes (Rogers et al., 2001). Measures of symptom severity and number of unscheduled daytime sleep periods were obtained at baseline and at the end of the two-week treatment period, using the Narcolepsy Symptom Status Questionnaire and 24 hour ambulatory PSG monitoring (Rogers et al., 2001). Only the combination of scheduled naps and regular bedtimes (group 3), significantly reduced both symptom severity and the amount of unscheduled daytime sleep in patients (Rogers et al., 2001).

Patients with narcolepsy are also encouraged to participate in physical activity (PA) due to its stimulating effect, which can promote wakefulness (Nevsimalova, 2014). However, there are currently no studies assessing the association between PA levels and symptoms in narcolepsy in adult or pediatric populations. Although not tested in humans, an animal study examined the effects of PA (spontaneous wheel running activity) on wakefulness in both hypocretin knock-out and wild type mice (Espana, McCormack, Mochizuki, & Scammell, 2007). Both groups of mice spent a significantly greater amount of time awake (approximately 20 per cent more) during the wheel running period (PA period) compared to when the wheel was locked (sedentary period) (Espana et al., 2007).
2.1.6 Comorbidities

A co-morbidity is defined as one or more additional diseases co-occurring with a primary condition (Valderas, Starfield, Sibbald, Salisbury, & Roland, 2009). A common co-morbidities in pediatric narcolepsy is obesity, which is usually the result of excessive weight gain at disease onset (K. Maski et al., 2017). Pediatric patients with narcolepsy have been reported to gain 20 to 40 pounds (9 to 18 kg) at disease onset, contributing to the prevalence of co-existing obesity, which is reported to be as high as 50 per cent (Plazzi et al., 2006; Poli et al., 2013; Scammell, 2015). Excessive weight gain at disease onset in narcolepsy may be explained by decreased secretion of leptin—a hormone involved in inhibiting hunger (Kotagal, Krahn, & Slocumb, 2004). In a case-control study, serum levels of leptin in adults with narcolepsy have been reported to be approximately half of healthy controls (5.9 µg/liter in narcolepsy vs. 11.4 µg/liter; p<0.05) (Kok et al., 2002). Sleep deprivation may also be the cause of weight gain in patients with narcolepsy (Pack & Pien, 2011). In a randomized two-period, two-condition crossover clinical study with adults, sleep deprivation (under controlled laboratory conditions) was associated to an increase in levels of Ghrelin—a hormone that promotes hunger (increase, 28%; p< 0.04), and a decrease in leptin secretion (decrease, 18%; p= 0.04) (Spiegel, Tasali, Penev, & Van Cauter, 2004).

Another common co-morbidity in pediatric narcolepsy is precocious puberty (K. Maski et al., 2017). The symptoms of narcolepsy (e.g., EDS etc.), precocious puberty and obesity tend to occur in close temporal sequence, as they are all related to hypothalamic dysfunction (K. Maski et al., 2017) (Poli et al., 2013). Precocious puberty, affects approximately 41 per cent of pediatric patients with narcolepsy (Poli et al., 2013). This may be linked to the role that hypocretin plays on Gonadotropin-releasing hormone secretion, which is important to pubertal timing determination (Lopez, Nogueiras, Tena-Sempere, & Dieguez, 2010). Hypothalamic dysfunction in narcolepsy may alter and accelerate the timing of puberty (Lopez et al., 2010), by increasing body fat (Walvoord, 2010), which commonly occurs during puberty (Kotagal et al., 2004).

In a cross-sectional survey of over 1000 participants in the United States with a self-reported diagnosis of narcolepsy, 67 per cent of respondents (973/1,450) reported co-morbidities such as obstructive sleep apnea (9%), fibromyalgia (7.4%), and celiac disease (1.4%) (K. Maski et al., 2017). The most common co-morbidities reported by participants were depressive symptoms (24.8%) and anxiety (17.7%) (K. Maski et al., 2017), and are outcomes of interest in this thesis.
2.2 Adolescent Mental Health

Depressive Symptoms in Adolescents

Depression effects five to nine per cent of adolescents (Costello, Mustillo, Erkanli, Keeler, & Angold, 2003; Merikangas et al., 2010; Wiens et al., 2017). Typical onset of depression occurs during adolescence, peaking at the age of 14 years (Kessler et al., 2005). To diagnose major depressive disorder, The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V) states a child must have five of the following nine symptoms: depressed or irritable mood, decreased interest of lack of enjoyment, decreased concentration or indecision, insomnia or hypersomnia, change of appetite or change of weight, excessive fatigue, feelings of worthlessness of excessive guilt, recurrent thoughts of death or suicidal ideation and/or psychomotor agitation or retardation (APA, 2013). Symptoms must occur during the same two week period, with at least one symptom being either depressed or irritable mood or anhedonia (APA, 2013). Symptoms must also indicate a significant change from an individual’s baseline presentation and cause significant functional impairments in school, social settings, and/or family (APA, 2013).

Assessing Depressive Symptoms in Adolescents

Multiple tools may be used in the assessment of depressive symptoms (Kendall, Cantwell, & Kazdin, 1989). During initial contact with a health care professional, screening measures, such as questionnaires, may be used to decide whether a diagnostic assessment is necessary (Timbremont, Braet, & Dreessen, 2004). A diagnostic assessment consists of a semi-structured diagnostic interview by a psychiatrist to assess for presence, severity, and duration of depressive symptoms, as well as interference with daily functioning following the DSM-V (APA, 2013). In the research setting, self-report measures are often used to assess depressive symptoms as they are less costly, easier to use and require less of a time commitment for the participant (Timbremont et al., 2004).

For screening purposes, the Children’s Depression Inventory (CDI) is the most widely used self-report measure to assess depressive symptoms in children and adolescents (Timbremont et al., 2004). Although it cannot yield a diagnosis, the CDI provides information about the presence and severity of depressive symptoms by asking about thoughts, feelings and behavior (Kovacs, 1985). The CDI has been reported to successfully discriminate patients with and without depressive
symptoms, as CDI total scores of depressed and non-depressed youth are significantly different (Carey, Faulstich, Gresham, Ruggiero, & Enyart, 1987; Hodges, 1990). The psychometric characteristics of the CDI-2 in a community-based and clinical sample between 10 and 18 years old show reliability coefficients range, for both samples, from 0.82 (test) to 0.84 (retest) in the community sample, and 0.85 (test, clinical sample); test-retest reliability is 0.81 in the community sample.

The CDI cutoff score of 13, which suggests possible depression in clinical settings, has been found to have a sensitivity of 94.4% and a specificity is 67.7% (Timbremont et al., 2004). At the cut off score of 13, the negative predictive value (the probability that a patient with a negative screening test does not have depressive symptoms) is 97.7% and the positive predictive value (the probability that a patient with a positive screening test has depressive symptoms) is 46.0% (Timbremont et al., 2004). In community samples (not seeking medical care), the cut-off point that best differentiates between depressive and community participants is 19, with a sensitivity of 94.7%, a specificity of 95.6% (Figueras Masip, Amador-Campos, Gomez-Benito, & del Barrio Gandara, 2010). Therefore, there is support for the utility of the CDI as a screening tool for detecting depressive symptoms in children and adolescents (Timbremont et al., 2004). The second edition of the CDI (CDI-2) was established in 2010 and was administered to a new, nationally representative, normative U.S. sample, aged 7–17 years (and their parents) in addition to a separate clinically referred sample (Kovacs, 2015). The CDI-2 has also has excellent psychometric properties (reliability coefficients is 0.91 and test-retest reliability is 0.92) (Kovacs, 2015; Yunhee, 2012).

**Anxiety Disorders in Adolescents**

Anxiety disorders affect approximately ten per cent of adolescents (Costello et al., 2003; Merikangas et al., 2010), and are also an outcome of interest for this thesis. Categories of generalized anxiety, social anxiety, separation anxiety, obsessive-compulsive symptoms, phobias, and panic disorders (APA, 2013). Common symptoms of anxiety disorders include: feeling nervous, unfounded or unrealistic fears, trouble separating from parents, sleep disturbance, obsessive thoughts and/or compulsive behaviors, trembling, sweating, shortness of breath, stomachaches, headaches, and/or muscle tension or other physical symptoms (APA, 2013).
Adolescents with anxiety disorder experience significant distress and reduced level of functioning (APA, 2013).

Assessing Anxiety Disorders in Adolescents

The Screen for Child Anxiety Related Emotional Disorders (SCARED) is a self-report measure that was specifically developed to assess anxiety in pediatric populations, and is not a modified version of a tool previously developed to assess anxiety in adults (Birmaher et al., 1999). The SCARED evaluates symptoms according to DSM-IV diagnostic criteria for specific anxiety disorders (social phobia, generalized anxiety disorder (GAD), separation anxiety disorder, panic disorder) (Birmaher et al., 1999). The SCARED also measures school-related anxiety, which is a prevalent problem in pediatrics (Birmaher et al., 1999).

In a community sample (n=119), using a cut off score of 22, the SCARED significantly differentiated anxious from non-anxious children with a sensitivity of 81.8 per cent and specificity of 52.0 per cent (compared to the gold standard of a diagnosis of anxiety disorder using psychiatric interviews) (Desousa, Salum, Isolan, & Manfro, 2013). Another community based sample study (n=137) used a cut off score of 25 (the current recommendation) (Birmaher et al., 1999), and reported a sensitivity is 75.9 per cent and specificity of 68.5 per cent (compared to the gold standard of a diagnosis of an anxiety disorder using psychiatric interviews) (Canals, Hernandez-Martinez, Cosi, & Domenech, 2012).

Depressive Symptoms and Anxiety in Pediatric Narcolepsy

Adolescents with primary sleep disorders are almost twice as likely than healthy adolescents to develop depressive symptoms and anxiety (Chorney, Detweiler, Morris, & Kuhn, 2008). Limited research in pediatric narcolepsy reveals similar findings: five studies to date have quantified rates of depressive symptoms and anxiety across a wide age range of children and youth (Dorris, Zuberi, Scott, Moffat, & McArthur, 2008; C. O. Inocente et al., 2014; Rocca et al., 2016; Stores, Montgomery, & Wiggs, 2006; Szakacs, Hallbook, Tideman, Darin, & Wentz, 2015).

Only one study has used clinical interviews to assess depression and anxiety in children and adolescents with narcolepsy (Szakacs et al., 2015). Szakács et al reported depression and anxiety to occur in 20 and 10 per cent of pediatric patients with narcolepsy respectively (n=38, ages 5.7-25 years) (Szakacs et al., 2015). Two studies in the pediatric narcolepsy population used the CDI to assess depressive symptoms (C. O. Inocente et al., 2014) (Stores et al., 2006). However
both studies used a cut off score to assess for depressive symptoms for their entire cohort (C. O. Inocente et al., 2014) (Stores et al., 2006). This is a limitation of these studies because cut off scores on the CDI that classify an individual as having either elevated or normal scores vary between sex and age groups (7-12 years vs 13-17 years) (Kovacs, 2015). The other two studies used the parent version of the Child Behavioural Checklist (CBCL) to assess psychosocial functioning (Dorris et al., 2008; Rocca et al., 2016). The CBCL may be a valid screen for children with observable behavioral difficulties, but is limited in detecting internalizing symptoms which include feelings of depression and anxiety (Kolko David & Kazdin Alan, 1993). Additionally, the CBCL is a parent-report tool, and parents are relatively poor informants of children’s internalizing symptoms (Canning & Kelleher, 1994; Kolko David & Kazdin Alan, 1993). There are also no pediatric studies that focus solely on adolescents, who are particularly vulnerable to developing mental health problems as they are undergoing major physical, cognitive and psychosocial changes (D. Taddeo, M. Egedy, & J.-Y. Frappier, 2008). Detailed rates of depressive symptoms and anxiety are found in Table 3.
Table 3: Rates of Depressive Symptoms and Anxiety in Pediatric Patients with Narcolepsy

<table>
<thead>
<tr>
<th>Author &amp; Year</th>
<th>N</th>
<th>Age (years)</th>
<th>Tool</th>
<th>Depressive Symptoms (%)</th>
<th>Anxiety (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rocca 2016 (Rocca et al., 2016)</td>
<td>29 Narcolepsy</td>
<td>7-16</td>
<td>CBCL</td>
<td>27.60*</td>
<td>17.2‡</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>7.70*</td>
<td>0‡</td>
</tr>
<tr>
<td></td>
<td>39 Controls</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Szakács 2015 (Szakacs et al., 2015)</td>
<td>38</td>
<td>15.3 (5.7-25)</td>
<td>DSM IV</td>
<td>20</td>
<td>10</td>
</tr>
<tr>
<td>Inocente 2014 (C. O. Inocente et al., 2014)</td>
<td>88</td>
<td>11.9 ± 3.1 (&lt;18)</td>
<td>CDI (&gt;16)</td>
<td>25</td>
<td>NA</td>
</tr>
<tr>
<td>Dorris 2008 (Dorris et al., 2008)</td>
<td>12</td>
<td>10 (7-16)</td>
<td>CBCL</td>
<td>41.60*</td>
<td>16.60‡</td>
</tr>
<tr>
<td>Stores 2006 Ω (Stores et al., 2006)</td>
<td>42 Narcolepsy</td>
<td>4-18</td>
<td>CDI (&gt;19)</td>
<td>12.30 (8.54)</td>
<td>4.00 (4.00)</td>
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<td>23 Controls</td>
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</table>

CBCL: Child Behavioural Checklist
DSM IV: Diagnostic and Statistical Manual of Mental Disorders, fourth edition
CDI: Children’s Depression Inventory
NR-Not Reported
NA-Not applicable
*Withdrawn/Depressed domain scores on CBCL
‡Anxious/Depressed domain scores on CBCL
Ω did not report depression scores as percentage, mean CDI total scores and standard deviation reported
2.2.1 Consequences of Adolescent Depression

Further understanding on depressive symptoms in narcolepsy is important because of the detrimental consequences of depression that have been reported amongst otherwise healthy adolescents (Glied & Pine, 2002). Depression is correlated with a significant increase in number of missed school days which may negatively impact school performance (e.g., falling behind in classes, getting poor grades) (Glied & Pine, 2002). Poor school performance during adolescence may limit future educational opportunities, which is a determinant of adult employment opportunities and earning potential (Glied & Pine, 2002) (Greenberg, Stiglin, Finkelstein, & Berndt, 1993). The majority of depressed girls and boys (65%) have reported to have participated in at least one of the following risky behaviors: alcohol, drugs, and smoking (Glied & Pine, 2002). Depressed adolescents are also at an increased risk for the development and persistence of obesity during adolescence (Goodman & Whitaker, 2002; Korczak, Lipman, Morrison, & Szatmari, 2013). In a cohort of 9374 adolescents in grades 7 through 12, having a depressed mood at baseline predicted obesity at follow-up (odds ratio: 2.05; 95% confidence interval: 1.18-3.56) after controlling for various factors (obesity status at baseline, age, race, gender, parental obesity, number of parents in the home, family socioeconomic status, adolescents’ report of smoking, self-esteem, delinquent behavior (conduct disorder), and PA levels (Goodman & Whitaker, 2002).

Importantly, depression is considered to be the most significant psychiatric risk factor for suicide amongst adolescents (Groholt, Ekeberg, Wichstrom, & Haldorsen, 2005; Shaffer et al., 1996) (Kessler, Borges, & Walters, 1999). Suicide rates are also higher amongst adolescents with chronic medical conditions (Mazur-Mosiewicz et al., 2015). Additionally, a relationship between suicide and sleep deprivation (reduced nocturnal sleep duration) has been reported amongst healthy adolescents (X. Liu, 2004). A study in over 1000 adolescents (mean age 14.6±3.4 years) reported that that sleeping less than 7 hours at night was significantly associated with increased risk for suicide attempts (Odds Ratio = 2.43, 95% Confidence Interval = 1.76-3.35) after adjustment for depressive symptoms and demographic variables such as age, sex and parental education level) (X. Liu, 2004).
2.2.2 Biological Contributors to Depressive Symptoms in Narcolepsy

Decreased hypocretin levels are seen in the pathogenesis of both depression and narcolepsy (Gujar et al., 2011; Kiran Maski & Heroux, 2016) (Tsuneki, Wada, & Sasaoka, 2017). One study evaluated hypocretin levels in both depressed (n=15) and non-depressed (n=14) adults and reported daily hypocretin concentrations were reduced in depressed patients compared to non-depressed controls (Salomon et al., 2003). However, nighttime values of hypocretin were higher in the depressed group (Salomon et al., 2003). Post-mortem evaluation in a group adults who died from suicide (n=66) revealed the patients with major depressive disorder had significantly lower levels of hypocretin compared patients with dysthymia or an adjustment disorder (Brundin, Bjorkqvist, Petersen, & Traskman-Bendz, 2007). However, this is inconsistent with findings from Schmidt et al, who reported no difference in mean hypocretin levels in 17 adults in-patients with major depressive disorder (mean Hamilton Depression Rating Scale 13.9± 7.4) (hypocretin levels-74.3± 17.8 pg/ml) in comparison to ten healthy controls (hypocretin levels-82.8 ± 22.1 pg/ml) (Schmidt et al., 2011).

The mechanism explaining the interaction between hypocretin levels and depression remains unclear due to its complexity and limited research (Tsuneki et al., 2017). Hypocretin deficiency may affect mood states due to the cholinergic monoaminergic imbalance caused by dysfunction in signaling pathways (Janowsky, el-Yousef, Davis, & Sekerke, 1972). Hypocretin and dopamine (a neurotransmitter that plays a role in the pathophysiology of depression (Brown & Gershon, 1993)) have overlapping circuits, particularly in the basal forebrain, thalamic paraventricular nucleus, and prefrontal cortex (Deutch & Bubser, 2007). There are also overlapping circuits for hypocretin and other monoamines, such as serotonin and norepinephrine, which also play a role in the pathophysiology of depression (Brown & Gershon, 1993). Hypocretin has been shown to have direct excitatory effects on serotonergic neurons (a neurotransmitter that is decreased in patients with depression (Maes, Leonard, Myint, Kubera, & Verkerk, 2011)) so its deficiency may contribute to low mood (R. J. Liu, van den Pol, & Aghajanian, 2002). However, this hypothesis has only been tested in mice models, and is only speculative in humans (Scott et al., 2011). Further research exploring how hypocretin levels are associated with depression is needed.
Sleep architecture in patients with narcolepsy may also be associated with depression (Kiran Maski & Heroux, 2016). This is relevant as the sleep architecture in patients with major depressive disorder include SOREMPs, reduced time in NREM-3 sleep and sleep fragmentation (Medina, Lechuga, Escandon, & Moctezuma, 2014), which are similar findings reported in patients with narcolepsy (Xu et al., 2017) (Plazzi et al., 2008). The increase in REM sleep seen in narcolepsy may be associated with depression, as REM sleep plays a role in affective reactivity and emotional information processing which includes emotional memory (Kiran Maski & Heroux, 2016). It is speculated that if patients with narcolepsy spend greater time in REM sleep, they may also spend more time consolidating negative emotional memories predisposing them to depressive symptoms (Kiran Maski & Heroux, 2016). The amount of time spent in REM sleep and its association with depressive symptoms has never been studied in both adult and pediatric narcolepsy populations.
2.2.3 Factors Associated with Depressive Symptoms in Narcolepsy

The factors associated with depressive symptoms amongst adolescents with narcolepsy remain largely unknown. A stronger understanding of factors that are associated with depressive symptoms is important in setting the groundwork for longitudinal studies and future quasi-experimental studies which can help in developing interventions that can be tested in a rigorous manner.

Limited research suggests associations between depressive symptoms and health-related quality of life (HRQOL) (Rocca et al., 2016). Rocca et al. found mental health (anxiety/depression and withdrawn/depressed) scores as measured by the CBCL correlated with HRQOL, particularly in the domains of physical ($R^2 = -0.40$, $p<0.05$), emotional ($R^2 = -0.62$, $p<0.001$) and social ($R^2 = -0.46$, $p<0.05$) functioning (Rocca et al., 2016). Disease-specific symptoms (e.g., EDS, cataplexy, sleep paralysis and hypnagogic/hypnopompic hallucinations) may also be associated with depressive symptoms in pediatric narcolepsy (Stores et al., 2006). Stores et al. suggested the psychosocial profile of pediatric patients with narcolepsy was similar to pediatric patients with idiopathic hypersomnolence in their study (Stores et al., 2006). Similarly, Inocente et al. found depressive symptoms measured by the CDI to be significantly correlated with EDS (Epworth Scale scores) ($R^2 = 0.24$, $p<0.01$) (C. O. Inocente et al., 2014). Inocente et al. also reported patients with elevated CDI scores had a higher prevalence of sleep paralysis ($16 \pm 72.2$ vs $21 \pm 31.8$ per cent; $p<0.01$) and hypnagogic/hypnopompic hallucinations ($14 \pm 63.4$ vs $11 \pm 16.7$ per cent; $p<0.01$) compared to patients without elevated CDI scores (C. O. Inocente et al., 2014). However, a greater prevalence of cataplexy was not present in patients with elevated CDI scores ($20 \pm 90.8$ vs $51 \pm 77.3$ per cent; $p=0.16$) (C. O. Inocente et al., 2014).

Other factors that may be associated with depressive symptoms in adolescents with narcolepsy include total sleep duration, sleep quality, and physical activity (PA) levels. Sleep patterns and PA levels are relevant factors, as they are reported to be associated with depressive symptoms in otherwise healthy adolescents (Biddle & Asare, 2011; Roberts & Duong, 2014). Current knowledge on the relationship between sleep patterns, PA levels and depressive symptoms and anxiety will be discussed in the next section.
2.3 Sleep, Physical Activity and Mental Health

Sleep and Mental Health

Decreased sleep duration and depressive symptoms and anxiety have been reported amongst healthy adolescents in many studies (Ojio, Nishida, Shimodera, Togo, & Sasaki, 2016) (Baum et al., 2014) (Roberts & Duong, 2014) (Roberts & Duong, 2017). In a study of 15,637 healthy adolescents (ages 12-18 years), sleeping less than 7.5 hours at night was associated with greater self-reported depressive symptoms and anxiety (Ojio et al., 2016). One experimental study, randomized healthy adolescents (n=50; ages 14-17 years) into two groups, the sleep deprived group (in bed for 6.5 hours per night for 5 nights) and a healthy sleep duration group (in bed for 10 hours per night for 5 nights) (Baum et al., 2014). The sleep deprived group reported poorer emotional regulation and being more anxious compared to adolescents in the healthy sleep duration group (Baum et al., 2014). In a large study on 4,175 healthy adolescents (ages 11-17 years), sleep deprivation (≤6 hours a night) was associated with depression and anxiety, that was diagnosed by clinical interviews (Roberts & Duong, 2014) (Roberts & Duong, 2017).

Poor sleep quality is also associated with mental health outcomes, such as depressive symptoms and anxiety amongst healthy adolescents (Tanaka et al., 2002). One study surveying 805 junior high school students, showed better self-reported nocturnal sleep (e.g., less difficulty in maintaining nocturnal sleep) was associated with better mental health outcomes (measured by the General Health Questionnaire) (0.33, p<0.01) (Tanaka et al., 2002). Another study in 5399 students (in grade 8-10) showed self-reported sleep quality categorized as good (as opposed to poor) was associated with positive mental health (assessed using the self-report Mental Health Continuum) (Odds Ratio 1.89; 95% Confidence Interval 1.61–2.21) (Guo, Tomson, Keller, & Söderqvist, 2018).

A potential hypothesis explaining the relationship between sleep deprivation and depressive symptoms amongst healthy adolescents includes spending time online in bed before sleep, which is associated with both with sleep disturbance and depressive symptoms (Lemola, Perkinson-Gloor, Brand, Dewald-Kaufmann, & Grob, 2015). Over 95 per cent of adolescents in the United States of America have at least one electronic media device (e.g., television, computer, mobile phone, video game console) in their bedroom (Foundation, 2006). Due to an increase in electronic media use before bed, adolescents report having later sleep times, worse sleep quality
and increased daytime sleepiness (Cain & Gradisar, 2010). Possible reasons for this include the device’s screen light increases alertness and may be associated with melatonin suppression, a hormone involved in regulating sleep and wake cycles (Wood, Rea, Plitnick, & Figueiro, 2013). Disturbed nocturnal sleep associated with increased electronic media usage before bed are also associated with depressive symptoms and anxiety (Lemola et al., 2015). This may be because of the vast amount of time adolescents spend on social media sites (e.g., Instagram and Facebook), which consist of psychologically arousing content (Lemola et al., 2015). The social interaction and anxiety associated with social media may induce negative feelings interfering with the ability to fall asleep (Lemola et al., 2015). It is also important to note that the a bidirectional relationship between sleep deprivation (short sleep duration and/or poor sleep quality) and depression may exist, as a high percentage of adolescents presenting to pediatric psychiatric clinics, display sleep disturbance (Chorney et al., 2008). Poor sleep quality as well as increased or decreased sleep duration, are also important components of diagnostic criteria for major depression (APA, 2013; Lofthouse et al., 2009) and are amongst the most prevalent symptoms of depression after depressed mood itself (Chorney et al., 2008). Recent longitudinal research in a cohort of almost 5000 children (preschool to early adolescence) reported sleep problems (e.g., difficulty falling asleep, nocturnal awakenings, restless sleep) to be significantly associated with later internalizing difficulties (e.g., low mood, anxiety), but not the reverse (Quach, Nguyen, Williams, & Sciberras, 2018). Similar findings were seen in over 4000 typically developing youth (ages 11-17 years), where sleep deprivation (≤6 hours only on weeknights and ≤ 6 hours on both weeknights and weekend night) was associated with depression and anxiety (diagnosed by psychiatric interviews), but the reverse association was not seen (Roberts & Duong, 2014) (Roberts & Duong, 2017).

Furthermore, sleep deprivation in adults has been associated with increased amygdala activation (Yoo, Gujar, Hu, Jolesz, & Walker, 2007). A neuroimaging (functional magnetic resonance imaging) in 26 healthy adults (ages 18–30 years (mean 24.1 ± 2.3) were assigned to either a sleep-deprivation group (accumulating approximately 35 hours without sleep in an experimental laboratory) (n=14; 7 males) or sleep-control group (sleeping normally at home) (n=12; 6 males) (Yoo et al., 2007). Amygdala activation was used as an outcome measure because of the role the amygdala plays in processing emotionally significant information, particularly aversive stimuli (Davidson, 2002). Both groups expressed significant amygdala activation when shown increasingly negative picture stimuli, however adults in the sleep-deprivation group showed
a +60 per cent greater magnitude of amygdala activation, relative to adults in the control group (Yoo et al., 2007). There was also a three-fold increase in the extent of amygdala volume that was activated in the sleep-deprivation group (Yoo et al., 2007). The greater magnitude of amygdala activation suggests that sleep-deprived individuals may experience negative affect states (e.g., depressed mood) to a greater degree than those who are not sleep deprived (Yoo et al., 2007). The neural circuits that play a role in both emotional regulation and sleep regulation have been shown to interact in a bidirectional fashion (C. B. Saper, Cano, & Scammell, 2005), however the exact mechanism that explain these effects remain under investigation (Clarke & Harvey, 2012).

**Physical Activity Levels and Mental Health**

In typically developing adolescents, higher PA levels are associated with depressive symptoms (Biddle & Asare, 2011). In a study of over 8000 adolescents, authors report an inverse relationship between self-reported PA levels and self-reported depressive symptoms (depression scores) (Kremer et al., 2014). Similar results were seen by Wiles et al with objective PA levels—measured by an accelerometer (Wiles, Haase, Lawlor, Ness, & Lewis, 2012). Wiles et al reported the amount of time spent participating in PA is inversely associated with depression scores in 2,951 adolescents, rather than the intensity (e.g., light, moderate or vigorous) when controlling for age, gender, maternal education, obesity and substance abuse (Wiles et al., 2012). Wiles et al categorized depression scores in tertiles (Mood and Feelings questionnaire scores: 0–2; 3–5; ≥6). Total PA time was also defined in tertiles (≤270 minutes; >270–326.6 minutes; ≥326.7 minutes), and total PA time at different intensities was based on accelerometer counts per minute at 200–3,599 (light), 3,600–6,199 (moderate) and ≥6,200 (vigorous) (Wiles et al., 2012). A greater total amount of time spent participating in PA was associated with a reduced odds of being depressed (Odds Ratio<sub>adj</sub> total PA (tertiles): medium 0.82 (95% Confidence Interval: 0.70, 0.98); high 0.70 (95% Confidence Interval: 0.58, 0.85) (Wiles et al., 2012). However, increasing the percentage of time spent in moderate-vigorous PA was not independently associated with a reduction in the odds of being depressed [Odds Ratio<sub>adj</sub> Moderate-Vigorous PA (tertiles) medium 1.05 (95% Confidence Interval: 0.88, 1.24), high 0.91 (95% Confidence Interval: 0.77, 1.09)] (Wiles et al., 2012). A recent systematic review and meta-analysis of 50 independent samples involving 89,894 participants also found that a greater PA level was associated with fewer depressive symptoms (but not a decreased diagnoses of major depressive disorder) (Korczak,
It is important to note that this association was stronger for cross-sectional studies (k=36, r= −0.17; 95% Confidence Interval = −0.23 to −0.10) than for longitudinal studies (k=14, r= −0.07; 95% Confidence Interval = −0.10 to −0.04) where the mean effect size was weak but still significant (Korczak et al., 2017). Cross-sectional studies are limited as they cannot examine causality and the direction of the association cannot be evaluated. It is possible that the cross-sectional studies in this meta-analyses are actually indicative of the reverse association of PA and depression where children with increased depressive symptoms are less likely to participate in PA possibly due to lack of motivation and anhedonia (Korczak et al., 2017). This systematic review and meta-analysis also found that increased frequency and intensity of PA was more strongly associated with fewer depressive symptoms compared with increased intensity of alone (Korczak et al., 2017).

It is speculated that participating in PA may improve depression scores because PA may provide a distraction from negative thoughts or constant rumination in depression (Rood, Roelofs, Bogels, Nolen-Hoeksema, & Schouten, 2009). Additionally, PA provides opportunities for social interaction (e.g., being a part of a sports team) resulting in feelings of increased support and connectedness with others through being a part of the activity (Wiles et al., 2012). The relationship between PA and depressive symptoms may be bidirectional, as adolescents who are depressed may be less inclined to participate in PA, leading to social isolation and elevated depression scores (Kremer et al., 2014). Additionally, participation in PA may release of endorphins, which can produce feelings of euphoria (Dishman & O'Connor, 2009; Lubans et al., 2016). Euphoric feelings after participating in PA may be due to changes in one or more brain monoamines, with the strongest evidence available for dopamine, noradrenaline, and serotonin.(Lin & Kuo, 2013; Lubans et al., 2016). However, there is little empirical evidence to support this assertion in pediatric populations (Bouix et al., 1994; Lubans et al., 2016).

The association between PA level and depression scores has not been assessed in adolescents with narcolepsy, and will be evaluated in this master’s thesis. Currently, there is no data on PA levels in pediatric narcolepsy. However, research on adults suggests PA levels are lower in patients with narcolepsy compared to age and gender matched controls (Matoulek, Tuka, Fialova, Nevsimalova, & Sonka, 2017). Adults with narcolepsy have a reduced average daily step
count of 6346 ± 2026 (Matoulek et al., 2017), which is lower than the recommended 10 000 steps per day for healthy adults (Tudor-Locke & Bassett, 2004). Adults with narcolepsy also reported more problems in performing recreational activities and playing sports compared to healthy controls (Broughton et al., 1983) (Daniels, King, Smith, & Shneerson, 2001; Teixeira, Faccenda, & Douglas, 2004).

Physical Activity and Sleep

Amongst healthy adolescents, participating in regular PA has been associated with better nocturnal sleep duration and quality (Lang et al., 2016). A systematic review of 21 studies including a total of 16 549 participants (14-24 years old) concluded that adolescents and young adults with higher levels of PA are more likely to experience longer sleep duration and better sleep quality (Lang et al., 2016). A positive relationship between PA levels and sleep quality, measured subjectively using questionnaires and diaries was reported, but only two of the 21 studies used objective measures to assess sleep quality and PA (Lang et al., 2013) (Gerber et al., 2014). In both of these studies, sleep quality was quantified as sleep efficiency (measured using a portable EEG) and PA was measured with an accelerometer (Lang et al., 2016). Both studies revealed increased PA levels were associated with longer sleep duration and better sleep quality (higher sleep efficiency) (Lang et al., 2013) (Gerber et al., 2014). Lang et al assessed 37 adolescents, and reported participants in the high PA level group (≥30 minutes of moderate-intensity physical activity) had a significantly greater total sleep time and sleep efficiency when controlling for gender (Lang et al., 2013). In a group of active adolescents and young adults (≥150 min/week of moderate PA) (n= 22), Gerber et al assessed how PA intensity affected objective sleep parameters (Gerber et al., 2014). Participants who undertook vigorous PA (≥3 × 20 min/week) vs moderate PA alone, had a significantly greater total sleep time (414.6 ± 35.9 vs 371.2 ± 34.9 minutes; p<0.01), but not significantly better sleep quality measured by sleep efficiency percentage (Gerber et al., 2014).

There are two main hypotheses on the mechanism by which increased levels of PA are associated with better sleep (Lang et al., 2013). The first is that participating in PA contributes to circadian alignment, which is the synchronization of behavioral and physiological rhythm (Westerterp-Plantenga, 2016). PA stabilizes the circadian clock (the suprachiasmatic nucleus of the hypothalamus) which consequently improves nocturnal sleep quality by stabilizing the
circadian rhythm (Westerterp-Plantenga, 2016) (Chennaoui, Arnal, Sauvet, & Leger, 2015). The second is that participating in PA is beneficial by decreasing depressive symptoms, anxiety and stress and consequently improving sleep (Biddle & Asare, 2011).
2.4 Family Functioning in Pediatric Narcolepsy

Pediatric conditions adversely affect the well-being of the entire family, particularly the affected patient’s parents or immediate caregivers (Kazak, 1989). Various factors of the child’s illness such as the demanding treatment regimens, an increase in responsibilities (e.g., attending medical appointments) or shifts in parenting roles (e.g., less time at work and more at home with sick child) may negatively impact family functioning (Cousino & Hazen, 2013). Poor family functioning is also associated with depressive symptoms in pediatric patients with chronic conditions (Kemp, Langer, & Tompson, 2016) (Whittemore et al., 2002). For instance, one study in adolescents with type-1 diabetes (n=117; mean age-14.3±2.0 years) assessed the relationship between family functioning (measured by the Family Adaptability and Cohesion Scale) and depression scores (measured by (Whittemore et al., 2002). This study showed that 35 per cent of adolescents with depressive symptoms reported their families to have poorer functioning (to be rigid and disengaged) compared with 16 per cent without depressive symptoms (Whittemore et al., 2002). In contrast, 37 per cent of adolescents with type-1 diabetes without depressive symptoms reported higher family functioning (to be balanced, flexible and connected) compared with 19 per cent with depressive symptoms (Whittemore et al., 2002). Poor family functioning is also associated with suboptimal adherence to treatment regimens (Smith, Mara, & Modi, 2018). For example, in 48 adolescents with epilepsy (aged 13–17 years), lower family conflict (measured by the Parental Environment Questionnaire) was associated with better treatment adherence (b= −0.19, p=0.05) (Smith et al., 2018).

Research on family functioning in the pediatric narcolepsy population is scarce. Only one mixed-methods study (n=58) has briefly explored the impact of pediatric narcolepsy on the family (Kippola-Paakkonen, Harkapaa, Valkonen, Tuulio-Henriksson, & Autti-Ramo, 2016). This study was primarily assessing the parents’ perceived support from a psychosocial intervention for family’s with a child with narcolepsy, and identifying parent’s personal concerns regarding their child’s diagnoses was a secondary aim (Kippola-Paakkonen et al., 2016). Parents personal concerns about having a child with narcolepsy (e.g., child’s coping, parents coping, job stress etc.) were assed with questionnaires (Kippola-Paakkonen et al., 2016). Questionnaires also included open ended questions so families could provide more details on their experience with their child’s diagnosis (Kippola-Paakkonen et al., 2016). Families shared that they were very worried about
the entire family's ability to cope with the illness (e.g., parents, the affected child and the affected child’s siblings) (Kippola-Paakkonen et al., 2016). Parents also discussed life adjustments as a result of the diagnosis such as not having enough time with their spouse, or having to quit their job or work part-time as their child needed more supervision at home than before (Kippola-Paakkonen et al., 2016).

It is unclear how family functioning in pediatric narcolepsy compares to 1) families with healthy children (not seeking ongoing medical care) and 2) families with other pediatric conditions. This is important as it can contextualize level of impairment a family is experiencing as a result of the illness or lack thereof (Herzer et al., 2010; McClellan & Cohen, 2007) (See Figure 7). The relationship between family functioning and depressive symptoms in pediatric narcolepsy is also unknown. As such, investigation of family functioning is pertinent to understanding outcomes in pediatric narcolepsy.
Figure 7: A comparison of family functioning across multiple pediatric chronic conditions using published data (de Kloet et al., 2015; Jastrowski Mano, Khan, Ladwig, & Weisman, 2011; Matziou et al., 2016; Panepinto, Hoffmann, & Pajewski, 2009)

Family functioning was assessed using The PedsQL Family Impact Module total score, which measures the disease impact on the family through questions about parent HRQOL, family communication, levels of worry, daily activities and relationships (Varni, Sherman, Burwinkle, Dickinson, & Dixon, 2004). Lower scores suggest a more negative disease impact on the family (Varni et al., 2004).
2.5 Summary of Gaps in the Literature

This literature review highlights the current knowledge on depressive symptoms in pediatric narcolepsy. Limited research has shown adolescents with narcolepsy have co-existing depressive symptoms, however the associated factors remain unclear. To address this gap, this thesis will evaluate sleep (duration and quality) and PA levels in adolescents with narcolepsy, as potential factors that are associated with depression scores. Finally, it is unclear how family functioning in adolescents with narcolepsy compares with that of healthy adolescents (not seeking medical care) and adolescents with other medical conditions. The association between family functioning and depression scores and anxiety scores in adolescents with narcolepsy is also unknown. To address this gap, this thesis will evaluate family functioning in adolescents with narcolepsy compared otherwise healthy adolescents and adolescents with other medical conditions, as well as assess the relationship between family functioning and depression scores and anxiety scores. Thus, the data from this thesis will provide new and relevant knowledge to the clinical community involved in caring for adolescents with narcolepsy.
Chapter Three: Rationale, Objectives and Hypotheses

3.1. Rationale

Narcolepsy is a life-long sleep disorder with no cure that commonly manifests during adolescence (Viorritto et al., 2012). Limited research shows pediatric patients with narcolepsy have co-existing depressive symptoms (Dorris et al., 2008; C. O. Inocente et al., 2014; Rocca et al., 2016; Stores et al., 2006; Szakacs et al., 2015), but data in adolescents is limited. Mental illness peaks during adolescence (Kessler et al., 2005), and has detrimental consequences such as poor school performance, substance abuse and suicide (Carotenuto et al., 2012; Glied & Pine, 2002). Moreover, factors associated with depressive symptoms in adolescents with narcolepsy remain largely unknown. Sleep patterns (duration and quality) and PA levels are factors that may be associated with depression scores amongst adolescents with narcolepsy. This is relevant as this association has been seen amongst otherwise healthy adolescents (Smagula et al., 2016) (Biddle & Asare, 2011).

In addition to the affected patient, pediatric conditions can affect the well-being of the entire family (Giallo et al., 2014). Poor family functioning is also associated with depressive symptoms in children and adolescents (Kemp et al., 2016). Family Functioning in pediatric narcolepsy has been scarcely studied. Further research on family functioning as well as knowledge regarding the relationship between family functioning and depression scores are important for clinical teams providing family-centered care patients with narcolepsy.
3.2. Objectives and Hypotheses

**Objective 1:** Examine if sleep patterns (duration and quality), excessive daytime sleepiness and physical activity levels are associated with depression scores as the primary outcome and anxiety scores as the secondary outcome in adolescents with narcolepsy compared with controls

**Hypothesis:** Poor nocturnal sleep quality, excessive daytime sleepiness and lower levels of physical activity will be associated with depression scores and anxiety scores in adolescents with narcolepsy and controls

**Objective 2:** To describe family functioning in adolescents with narcolepsy, in comparison to otherwise healthy adolescents (not seeking medical care) and other pediatric conditions

**Hypothesis:** Family functioning will be impaired in adolescents with narcolepsy in comparison to healthy adolescents but similar to adolescents with other pediatric conditions

**Objective 3:** Examine the association between family functioning and depression and anxiety scores in adolescents with narcolepsy

**Hypothesis:** Family functioning will be associated with depression and anxiety scores
Chapter Four: Methodology

4.1. Overview and Study Design

This was a prospective, observational, cross-sectional research study evaluating if sleep patterns (duration and quality), EDS and PA levels are associated with depression scores as the primary outcome and anxiety scores as the secondary outcome in adolescents with narcolepsy compared with controls. This study also evaluates family functioning amongst adolescents with narcolepsy in comparison to otherwise healthy adolescents (not seeking medical care) and adolescents with chronic conditions. This study also evaluates the association between family functioning and depression scores and anxiety scores amongst adolescents with narcolepsy.

Depression scores were assessed using the Children’s Depression Inventory-2nd edition and anxiety scores were assessed using the Screen for Childhood Anxiety Related Emotional Disorders (SCARED). Sleep duration and quality which were assessed objectively using actigraphy. Self-reported sleep quality was assessed using The Pittsburgh Sleep Quality Index and EDS was assessed using the modified Epworth sleepiness scale (Epworth scale). PA levels were measured objectively using a pedometer. Self-report PA levels were measured using the Godin Leisure-Time Exercise Questionnaire (Godin). Family functioning was assessed using the PedsQL Family Impact Module. Demographic, anthropometric and clinical variables were also collected.

4.1.1. Ethics

The study protocol was approved by the research ethics board at the Hospital for Sick Children in Toronto Ontario in March 2017 (REB #1000055883).

4.2. Study Population

The study population consisted of two groups of adolescents, the narcolepsy group and a control group. The narcolepsy group included pediatric patients followed clinically at The Hospital for Sick Children. The Hospital for Sick Children is the largest pediatric tertiary care center in Canada and follows one of the largest pediatric narcolepsy population in the country. The narcolepsy group was recruited from the dedicated pediatric narcolepsy clinic. The control group was recruited from the greater Toronto area community via flyers in the hospital and/or through friends and family members of the study team and participants.
4.3. Eligibility Criteria

Eligibility to participate in the study was determined using the following inclusion and exclusion criteria:

4.3.1. Inclusion Criteria

**Narcolepsy Group:**

Participants were required to be in the age range (10-18 years). This age range was selected as it encompasses the World Health Organization definition of an adolescence (WHO, 2014). Participants had a confirmed diagnosis of narcolepsy made by the sleep medicine team at the Hospital for Sick Children, which was verified by a study team member.

**Diagnosis of Narcolepsy**

Patients with narcolepsy were referred to the Hospital for Sick Children Sleep Medicine team from community pediatricians or general practitioners. Symptoms were self-reported by parents and/or patients themselves. The adapted Epworth sleepiness scale which is used in pediatrics (Johns, 2015) was administered to all patients and their families to assess EDS at first clinical presentation, when patients were not receiving treatment. A diagnosis of EDS was made for any individual who scored 10 or higher on the Epworth sleepiness scale (the maximum score was 24). All patients underwent a full clinical examination, including a neurological examination. As per standard of clinical care, all patients with suspected narcolepsy had an overnight PSG (with sleep EEG) to rule out other sleep disorders followed by a daytime MSLT with five 20-minute nap periods. Human leukocyte antigen typing was also done. For a diagnosis of narcolepsy, patients had to meet the following criteria which was adapted from the International Classification of Sleep Disorders Diagnostic and Coding Manual (3rd edition) (AASM, 2014):

a. History consistent with narcolepsy (EDS (Epworth Sleepiness Scale Score >10), irresistible urge to sleep, falling asleep unexpectedly)

b. MSLT consistent with narcolepsy; defined as two or more SOREMPs and a mean sleep latency < 8 minutes

c. Symptoms not explained by another sleep disorder, medical and/or neurological disorder.
Hypocretin Levels were not assessed as they are available as a clinical or research test in Canada.

**Control Group:**

Participants were recruited from the Toronto area community setting and were required to be in the age range of 10-18 years. This age range was selected as it encompasses the World Health Organization definition of an adolescence (WHO, 2014). Participants were recruited consecutively with the goal to match for age and sex which was dependent on the availability of healthy participants willing to participate in this study.

**4.3.2. Exclusion Criteria**

**Narcolepsy Group:**

Participants unable to speak read or write English were not eligible to participate. To avoid potential confounding variables, patients with known global developmental delay, sleep disorder other than narcolepsy, for example, Obstructive Sleep Apnea were excluded from the study. All PSGs performed in children narcolepsy were re-reviewed to ensure that they did not have Obstructive Sleep Apnea.

**Control Group:**

Participants unable to speak read or write English were not eligible to participate. To avoid potential confounding variables, patients with known global developmental delay, sleep disorders or a known chronic condition that required ongoing medical care, were excluded from the study.

There was no clinical indication for an overnight PSG in the control group so participants were screened for sleep disordered breathing using the Pediatric Sleep Questionnaire (PSQ) (Chervin, Hedger, Dillon, & Pituch, 2000). Additionally, the incidence of sleep disordered breathing in otherwise healthy adolescents is less than one per cent (Petry, Pereira, Pitrez, Jones, & Stein, 2008). The PSQ is a valid and reliable tool used in children ages 2-18 years, the PSQ has a sensitivity of 85% and specificity 87% compared to a PSG for the diagnosis of Obstructive Sleep Apnea (Chervin et al., 2000). **Study Procedures**
Following informed consent, participants in either group (narcolepsy or control) were asked to complete the questionnaires independently at the research visit (see Table 4 for questionnaires). The Pediatric Sleep Questionnaire was only completed by the control group and was completed by the participant’s caregiver. The PedsQL Family Impact Module was only completed by the narcolepsy group and was completed by the participant’s caregiver. Anthropometric measures (height and weight) were obtained at the research visit for both groups as well.

**Table 4: Questionnaires Completed at Research Visit**

<table>
<thead>
<tr>
<th>Questionnaire Name</th>
<th>Questionnaire Description</th>
<th>Questionnaire Completed by:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children’s Depression Inventory-2nd Edition</td>
<td>Evaluates the presence and severity of depressive symptoms</td>
<td>Participant</td>
</tr>
<tr>
<td>The Screen for Childhood Anxiety Related</td>
<td>Evaluates the presence of anxiety</td>
<td>Participant</td>
</tr>
<tr>
<td>Emotional Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pittsburgh Sleep Quality Index</td>
<td>Measure of self-reported sleep quality/sleep disturbance</td>
<td>Participant</td>
</tr>
<tr>
<td>Adapted Epworth Sleepiness Scale</td>
<td>Measure of daytime sleepiness</td>
<td>Participant</td>
</tr>
<tr>
<td>Godin Leisure-Time Exercise Questionnaire</td>
<td>Measure of self-reported physical activity levels</td>
<td>Participant</td>
</tr>
<tr>
<td>Child Family and Demographic Questionnaire</td>
<td>Measure of family socioeconomics</td>
<td>Participant/Participant/Participant</td>
</tr>
<tr>
<td>PedsQL Family Impact Module</td>
<td>Measure of the disease impact on the family by asking questions regarding the family’s overall functioning, communication, worry, daily activities and relationships.</td>
<td>Participant Caregiver (Narcolepsy Group Only)</td>
</tr>
<tr>
<td>Pediatric Sleep Questionnaire</td>
<td>Evaluates for probable sleep disordered breathing</td>
<td>Participant Caregiver (Control Group Only)</td>
</tr>
</tbody>
</table>
Participants were also given an actigraph to measure sleep and a pedometer to measure PA levels at the research visit. Participants were asked to wear the actigraph for 24 hours per day for 7 continuous days (removed only during aquatic activities) and the pedometer for 7 continuous days during hours they are awake. Participants were also asked to complete logs/diaries at home to track sleep patterns and pedometer usage (see Table 5). Participants mailed completed questionnaires, pedometers and actiwatches approximately one week later in the prepaid envelope provided.

**Table 5: Log/Diary Completed at Home**

<table>
<thead>
<tr>
<th>Log/Diary to be completed at home</th>
<th>Log/Diary Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep Diary</td>
<td>Tracks sleep and wake hours and awakenings during sleep</td>
</tr>
<tr>
<td>Pedometer Log</td>
<td>Tracks when pedometer was put on and taken off</td>
</tr>
</tbody>
</table>
4.4. Study Measures

4.4.1. Outcomes

Primary Outcome

**Depression Scores:** The primary outcome of interest in this study were depression scores, which were measured by the Children’s Depression Inventory-2nd edition (CDI-2) total score. The CDI-2 is a 28-item self-report assessment that yields a total score, two scale scores (Emotional Problems and Functional Problems), and four subscale scores (negative mood/physical symptoms, negative self-esteem, ineffectiveness and interpersonal problems) used in children ages 7 to 17 years. The item response “I want to kill myself” was used to indicate suicidal ideation with intent. This question was assessed immediately, and if a participant selected the option “I want to kill myself” as the option, the principal investigator/staff physician was called immediately who intervened as per standard clinical care (e.g., assessing patient, taken to emergency department). Scores in the elevated range vary by gender and age group (Kovacs, 1985, 2015). The psychometric characteristics of the CDI-2 in a community-based sample (recruited from the school setting) and a clinical sample (recruited from pediatric mental health clinics) (ages 10 and 17 years old) show reliability coefficients range, for both samples, from .82 (test) to .84 (retest) in the community sample, and .85 (test) in the clinical sample (Figueras Masip et al., 2010). For this study, the cut-off point that was used in females was 14 (ages 7-12 years) and 20 (ages 13-17 years), and the cut-off point that was used in males was 17 (ages 7-12 years) and 16 (ages 13-17 years), as recommended by the CDI-2 scoring guidelines as an elevated score (Kovacs, 1985, 2015). Different cut-off points are used to account for age and gender differences in depression scores, particularly the increase in depressive symptoms with age and the greater prevalence of depressive symptoms in females (Saluja et al., 2004).

Secondary Outcomes

**Anxiety scores:** The secondary outcome of interest in this study were anxiety scores, which were assessed by The Screen for Childhood Anxiety Related Emotional Disorders (SCARED). The SCARED has both child and parent versions, with 41 items and 5 factors (panic disorder or significant somatic symptoms, generalized anxiety disorder, separation anxiety, social anxiety disorder, significant school avoidance) that parallel the DSM-IV classification of anxiety
disorders. The SCARED has sound psychometric properties and is designed for children aged 8 to 18 years of age. For the total score and each of the five factors, the SCARED demonstrated good internal consistency (alpha = 0.90), test-retest reliability (intraclass correlation coefficients = 0.70 to 0.90), discriminative validity (both between anxiety and other disorders and within anxiety disorders). Total score ≥25 may indicate the presence of an anxiety disorder. A cut off of a total score of 25 has a sensitivity of 71% and specificity of 67% (Birmaher et al., 1999).

**Family Functioning:** Another outcome of interest in this study was family functioning, which was assessed by The PedsQL family impact module total scores. The PedsQL family impact module is a valid and reliable 36-item parent-report questionnaire that was used to measures how having a child with a medical condition impacts overall family functioning. Total scores encompass scores from the following domains: parent health related quality of life (encompassing physical, emotional, social, and cognitive functioning), communication, worry, daily activities and relationships. A family summary score is also generated which encompasses scores from the also domains of daily activities and overall relationships. Higher scores on the module indicate better family functioning and less of a negative family impact from the child’s health. PedsQL family impact module total scores were used to determine family functioning in this study as they encompass scores from all domains (Varni et al., 2004).
4.4.2. Exposures

Sleep Patterns
Sleep patterns were assessed objectively for 7 days using actigraphy which are described in detail in section 4.5.4. Sleep duration was assessed as total sleep time in a 24 hour period for an average of 7 days. Sleep quality was assessed objectively using sleep efficiency percentage in a 24 hour period for an average of 7 days. Table 6 provides a summary of sleep patterns of interest.

Self-Reported Sleep Quality: The Pittsburgh Sleep Quality Index provides information on sleep quality by providing an overall sleep disturbance score (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989) (Carpenter & Andrykowski, 1998). The Pittsburgh Sleep Quality Index is a 19-item self-rated questionnaire that assesses sleep quality and sleep disturbances in adolescents and adults. Individuals rate the frequency of several sleep-related problems. The individual questions from seven components ask about subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medications and daytime dysfunction. For example, question 5 asks about the frequency of issues (e.g., nighttime awakenings, bad dreams, uncomfortable room/body temperature) that may have contributed to trouble sleeping in the past month. Responses range from 0 for “not during the past month” to 3 for “three or more times a week”. The sum of the scores for the seven components yields one global score. In adolescents and young adults (ages 14-24 years old), the Pittsburgh Sleep Quality Index demonstrates a one-factor model with a moderate reliability (Cronbach's alpha =0.72) (de la Vega et al., 2015). Higher scores indicate greater sleep disturbances, where a global score greater than 5 suggests poor sleep quality (Carpenter & Andrykowski, 1998).

Excessive Daytime Sleepiness
Daytime sleepiness was measured using adapted version of the Epworth sleepiness scale (Epworth scale) used in pediatrics (Johns, 2015). The Epworth scale is an 8 items questionnaire that assesses excessive daytime sleepiness at first clinical presentation. Individuals indicate how likely they are to fall asleep in each situation (0=would never doze or sleep, 1=slight chance of dozing or sleeping, 2=moderate chance of dozing or sleeping, 3=high chance of dozing or sleeping). A diagnosis of excessive daytime sleepiness was made for any individual who scored greater than 10 on this scale.
(Johns, 2015). In adolescents (ages 12-18 years) the Epworth scale demonstrates a moderate internal reliability (Cronbach's alpha= 0.73) (Janssen, Phillipson, O'Connor, & Johns, 2017).

**Physical Activity Levels**

PA levels were assessed objectively with a pedometer that calculates total daily step count. The daily step count of an average of 7 days was used. Pedometer details are described in section 4.5.5. Below are details on the questionnaire used to assess self-reported PA levels:

**Self-reported physical activity (PA) levels:** The Godin Leisure-Time Exercise Questionnaire (Godin) provides a general estimation of weekend and weekday activity levels (Godin & Shephard, 1985). The Godin has been found to be reliable and valid for use in the pediatric population (Sallis, Buono, Roby, Micale, & Nelson, 1993) and has also been used in other pediatric neurological conditions (Kinnett-Hopkins, Grover, Yeh, & Motl, 2016). Individuals are asked to report the frequency (number of days) of strenuous (i.e., running or jogging), moderate (i.e., fast walking), and mild (i.e., easy, leisurely walking) PA performed for periods of 15 minutes or more during leisure time over a usual week. The Godin health contribution score was calculated by using metabolic equivalents (METS) using the following formula: (number of days of strenuous PA X 9 METs) + (number of days of moderate PA X 5 METs).

Health contribution scores are classified as follows: <14 indicate the individual is insufficiently active, scores 14-23 indicate the individual is moderately active and scores ≥24 indicate the individual is active (Godin & Shephard, 1985).
4.4.3. Covariates

**Participant Demographics and Medical History:**

Demographic data was collected from participants using a standardized case report form. For the narcolepsy group this data was collected from participants/parents and medical records at the Hospital for Sick Children at the time of the clinic visit. For the control group, this data was collected from participants/parents at the time of their research visit. For the narcolepsy group, patients/caregivers were asked to self-report disease symptoms (EDS, cataplexy, sleep paralysis, hallucinations) and report their current medications (if any). The following variables were identified as potential covariates because of the current literature reporting an association between the respective covariate and depressive symptoms:

1. Obesity (yes or no) (Melnyk et al., 2006), which was calculated using the Body mass index (BMI) Z-score. BMI Z score was calculated using measured height and weight according to age and sex specific growth curves (https://zscore.research.chop.edu) Obesity was defined as a BMI Z-score $\geq 2.0$ (de Onis et al., 2007).
2. Age (years) (Saluja et al., 2004)
3. Sex (male or female) (Saluja et al., 2004)

Obesity, age and sex are associated with the exposure/independent variables of interest:

1) Sleep (Mary A. Carskadon, 2011; Chaput & Dutil, 2016; Marczyk Organek et al., 2015)
2) PA levels (Anderson et al., 2017; Cairney, Veldhuizen, Kwan, Hay, & Faught, 2014)
4.4.4. Actigraphy Monitoring of Sleep

PSG is the gold standard for the diagnosis of sleep-related disorders but it only measures sleep cycles for one night and may not be a reflection of the natural sleep environment. Therefore, actigraphy was chosen as a tool for this study to allow for longer monitoring of the sleep patterns. Actigraphy was obtained using the Mini-Mitter Actiwatch-2 (Philips Respironics Bend, OR). The Actiwatch-2 is a portable device worn on the wrist that detects gross motor activity through an internal sensor. Epoch intervals are used to assess gross motor activity. Data from epoch intervals are then stored in the device’s internal memory. The Actiwatch-2 utilizes wake sensitivity thresholds to discriminate between sleep and wakefulness during gross motor activity. A medium threshold defines wakefulness as an epoch with 40+ activity counts. A low threshold is defined as an epoch with 20+ activity counts and high as 80+ activity counts (Meltzer, Walsh, Traylor, & Westin, 2012). The raw actigraphy data is translated to sleep measures using the actigraph scoring analysis software (Philips Actiware Version 6.0.9). Participants in this study wore the Actiwatch-2 on their wrist for 7 days for 24 hours, and removed it only during aquatic activities (e.g., showering). Data collection with actigraphy for at least five nights ensures reliable estimates (≥ 0.70) for sleep measures including sleep efficiency and wake after sleep onset (Acebo et al., 1999).

A sleep diary was used in conjugation with actigraphy to derive contextual information about sleep. The sleep diary is a record of the patient’s bedtime and wake time each day, the start and end times of any daytime naps as well as descriptive explanations of any sleep interruptions. Sleep diaries were used to set scoring parameters for actigraphy data. Discrepancies between the actigraph data and the sleep diary were identified and the actigraph record annotated for periods when the device was off.

Actigraphy demonstrates feasibility and practicality in pediatric population for both clinical and research purposes (Sadeh, 2011; Sadeh et al., 2000; Werner et al., 2008). Actigraphy is an objective, non-invasive and cost-effective method for estimating sleep-wake patterns using activity-based monitoring (Sadeh, 2011) (See Appendix 1). Actigraphy demonstrates good sensitivity to detect sleep from limb activity (89-97%) (Meltzer et al., 2012) compared to PSG. Additionally, actigraphy has been shown to be useful for can provide objective data regarding the efficacy of the intervention (Sadeh, 2011) and has been used in pediatric narcolepsy populations (Filardi et al., 2018).
However, actigraphy has limitations that should be considered. Actigraphy demonstrates poor specificity (the ability to detect wakefulness following sleep onset) compared to polysomnography (54% to 77%) (Meltzer et al., 2012). Data loss is another limitation with actigraphy that can occur due to a failure to wear the actigraph and technical issues with the actigraph (Sadeh, 2011). Using a sleep diary in conjunction with actigraphy is important to derive contextual information about sleep and to help reduce uncertainties associated with actigraphy (e.g., sleep and wake times) (Werner et al., 2008).

### 4.4.4.1. Scoring and Data Analysis

Data was collected in 30-second epochs, using a medium wake sensitivity (each epoch with 40+ activity counts was classified as being awake). The medium threshold is considered as the most accurate in estimating sleep patterns in the pediatric population (Meltzer et al., 2012). Sleep onset latency was scored following 10 consecutive minutes of immobility (Meltzer, Walsh, & Peightal, 2015).

An actogram, which is graphical representation of the sleep-wake cycle that is generated by the actigraphic scoring analysis software, is shown in Figure 8. Bedtime and wake time were scored using event markers in conjugation with the self-report sleep diary. In the case where a discrepancy was found between the event markers and the diary, precedence was given to the sleep diary, as patients often forgot to press the button on the actiwatch indicating they were trying to fall asleep. Any periods during which the watch was removed were excluded. Definitions for actigraph sleep measures are shown in Table 6.
**Figure 8:** Scored Actogram of One Day for Control (17 year old female)
Specific sleep measures are obtained from the actogram as shown below

![Actogram Image]

**Table 6: Actigraph Sleep Parameter and Definitions**

<table>
<thead>
<tr>
<th>Sleep Parameter</th>
<th>Scoring Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Sleep Time (over 24 hour period)*</td>
<td>Minutes scored as sleep between sleep onset and final awakening</td>
</tr>
<tr>
<td>Sleep Efficiencyϕ</td>
<td>Percentage of time spent asleep during a defined interval (total sleep time divided by time in bed)</td>
</tr>
<tr>
<td>Sleep Onset Latency</td>
<td>Duration between bedtime and sleep onset</td>
</tr>
<tr>
<td>Wake After Sleep Onset</td>
<td>Minutes scored as wake during sleep duration period</td>
</tr>
</tbody>
</table>

*Used as an objective measure of sleep duration
ϕUsed as an objective measure of sleep quality
4.4.4.2. Transition Probabilities

An advanced algorithm for analyzing actigraphy data involves the application of a state-transition approach to assess local temporal dynamics of rest-activity patterns (Lim et al., 2011). This algorithm was designed by Lim and colleagues and provides a detailed means of quantifying sleep fragmentation based on rest-activity data that is generated by actigraphy and provides an index of fragmentation (Lim et al., 2011). The transitions probabilities algorithm has also been used in pediatric populations (S. Selvadurai et al., 2018).

MATLAB was used to implement the algorithm. Using the algorithm, each 30-second epoch of the actigraphic record was categorized as either rest or activity based on the number of activity counts. An epoch with a number of counts of 0 was classified as rest, and an epoch with a number of counts greater than 0 was classified as activity. The probability that an individual will transition to rest after being in an active state is defined as $p_{AR}(t)$ (Lim et al., 2011). Likewise, the probability that an individual will transition to an active state after being in a rest state is defined as $p_{RA}(t)$ (Lim et al., 2011). Figure 9 illustrates the estimated transition probabilities $p_{RA}(t)$ and $p_{AR}(t)$ plotted against the duration of time that is spent in rest or activity (Lim et al., 2011).

A locally weighted scatterplot smoothing regression was performed with the $p_{RA}(t)$ and $p_{AR}(t)$ plots. The plot is divided into 3 regions: a falling region, a constant non-zero probability region and a rising region (Lim et al., 2011). A weighted average of data within the constant non-zero probability region on each plot to calculate an index of fragmentation (Lim et al., 2011). Data from the $p_{RA}(t)$ plot produces a $k_{RA}$ value which indicates the degree of fragmentation during rest. Therefore higher $k_{RA}$ values indicate greater fragmentation during sleep (Lim et al., 2011). Data from the $p_{AR}(t)$ plot produces a $k_{AR}$ value which indicates the degree of fragmentation during activity. Higher $k_{AR}$ values indicate greater fragmentation during activity (wake hours) (Lim et al., 2011).
**Figure 9:** Plot of pRA(t) and pAR(t) (A) and (B) show the plot for pRA(t) and pAR(t), respectively. Observed values are indicated as blue dots. The solid line represents the fitted LOWESS curve, and the dashed line represents estimates for $k_{RA}$ and $k_{AR}$. Figure Adapted from Selvadurai 2017 (Sarah. Selvadurai, 2017).
4.4.5. Pedometers: An Objective Measure of Physical Activity

Pedometers are widely used instruments to obtain an objective measure of free living PA by calculating the number of steps taken per day (Colley, Janssen, & Tremblay, 2012). Pedometers use different mechanic or electronic motion sensors to quantify the amount of PA by accumulating steps (Butte, Ekelund, & Westerterp, 2012). Pedometers are cost-effective, easy to use and their data is easy to analyze, making them one of the most widely used objective PA measures across all age groups (Clemes & Biddle, 2013). Some disadvantages of using pedometers to measure PA is that they cannot measure water-based activities (e.g., swimming) or cycling (Clemes & Biddle, 2013). It is also not possible to measure the PA intensity, so a distinction between light PA and moderate PA cannot be made (Clemes & Biddle, 2013).

In this study, all participants were asked to wear the Omron HJ-720ITCCAN pocket pedometer (See Appendix 2) daily for seven days during wake hours, but not during sleep and aquatic activities (e.g., swimming). An average daily step count was obtained based on seven days of data. The Omron HJ-720ITCCAN pedometer provides a reliable and valid estimate of steps taken, when compared to manually counted steps on a treadmill (±1.1% of manually counted steps) (Lee, Williams, Brown, & Laurson, 2015). In a pediatric sample (N=41; mean age 5.43±0.63 years) the Omron HJ-720ITCCAN pocket pedometer step counts had a moderately high correlation to accelerometer activity counts (r = 0.64, p < 0.001) (De Craemer et al., 2015).

4.5. Sample Size Calculation

The primary outcome of interest in this study were depression scores, which were measured by the Children’s Depression Inventory-2nd edition (CDI-2) total score. The comparison of Children’s Depression Inventory-2nd edition (CDI-2) scores between narcolepsy and control group was conducted using two sample t-test assuming unequal variances (i.e. Satterthwaite t test). Therefore, given a power of 0.8 and a type-1 error (alpha) of 0.05, assuming the mean ± standard deviation of CDI-2 depression scores for narcolepsy and control group are 13±9 and 7±7 respectively (Stores et al., 2006), a total of 60 participants (i.e. 30 for each group) were needed to achieve a power of 80 per cent.
4.6. Statistical Analyses

Descriptive statistics (means, standard deviations, and frequencies) were applied to evaluate demographics, depression scores, anxiety scores, sleep patterns and PA levels in both adolescents with narcolepsy and controls. The Shapiro-Wilk Test was used to examine normalcy of distribution. Between-group comparisons were performed with independent sample t-tests and chi-square tests as appropriate. To help decide what exposure variables should be entered in to the regression models, pearson or spearman correlation analyses were done as appropriate, to evaluate the association between sleep patterns, PA levels and depression scores. Exposure variables that were associated with CDI-2 total scores at the ≤0.05 significance level were considered potential factors associated with depression scores and were entered into the multiple linear regression models.

Hierarchical multiple linear regression models were used to examine the relationship between the primary outcome of depression scores (CDI-2 total scores) and self-reported sleep quality, EDS and PA levels while controlling for various covariates (e.g., co-existing obesity). For each analyses, group status (narcolepsy or control) was forced into the first block on step 1. Co-existing obesity (yes or no) was entered on step 2 and age and sex were entered on step 3 and self-reported sleep quality (Pittsburgh sleep quality index scores >5 yes or no) was entered on step 4. A stepwise entry method was used from step 2 to 4. Two additional analyses were run with the exception of self-reported PA levels (Godin health contribution score) and EDS (Epworth scale scores) on step 4. Self-reported sleep quality, EDS and PA levels could not be run in the same model as they were significantly correlated.

Secondary data analyses was used to compare PedsQL Family Impact Module total scores in the narcolepsy group to published data of a community sample (not seeking medical care) (Medrano, Berlin, & Hobart Davies, 2013) and other pediatric disease groups (de Kloet et al., 2015) (Jastrowski Mano et al., 2011) (Matziou et al., 2016). These studies were selected because they: 1) Examined family functioning in youth or adolescents using the PedsQL Family Impact Module and 2) Reported the mean and standard deviation (SD) of PedsQL Family Impact Module total and domain scores. One-way analysis of variance and Tukey Honestly Significant Difference Post Hoc Tests which accounted for multiple comparisons, using an interactive statistics webpage (http://statpages.info/anova1sm.html) was performed. The association between depressive
symptoms and family functioning was evaluated using correlation analysis, however multiple regression analysis (stepwise entry method) could not be performed because no significant correlations (p≤0.05) were identified. All other analyses were performed using SPSS version 23.0.

**Figure 10: Conceptual Framework for Primary Objective**

<table>
<thead>
<tr>
<th>EXPOSURES</th>
<th>PRIMARY OUTCOME</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep quality and duration</td>
<td>Depression Scores*</td>
</tr>
<tr>
<td>Excessive Daytime Sleepiness</td>
<td></td>
</tr>
<tr>
<td>Physical Activity Levels</td>
<td></td>
</tr>
</tbody>
</table>

**COVARIATES**

Obesity, age, sex,

*A bidirectional relationship between exposures and primary outcome has been reported in the literature (Chorney et al., 2008) (Korczak et al., 2017) but directionality will not be assessed by this master’s thesis*
Chapter Five: Results

5.1. Demographics

From March 2017 to March 2018, a total of 35 adolescents with narcolepsy were eligible for this study based on the inclusion/exclusion criteria. See Figure 11.

Figure 11: Participant Flow for the Narcolepsy Group
The control group consisted of 30 participants. Pedometer data was lost on three participants due to a malfunctioning pedometer that did not collect data. Participants refused to wear the pedometer again.

Detailed participant demographics can be found in table 7. The narcolepsy group was significantly younger than the control group (mean age=13.8 ± 2.2 vs 14.9 ± 1.5 years; p=0.03). The narcolepsy group also had a significantly higher BMI Z-score, a greater percentage of individuals with co-existing obesity, and differences in distribution of race compared with the control group.
Table 7: Participant Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Narcolepsy N=30</th>
<th>Control N=30</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>13.8 ± 2.2</td>
<td>14.9 ± 1.5</td>
<td>0.03</td>
</tr>
<tr>
<td>Sex (% Male)</td>
<td>76.7</td>
<td>56.7</td>
<td>NS</td>
</tr>
<tr>
<td>Race (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Caucasian</td>
<td>46.7</td>
<td>70.0</td>
<td>0.01*</td>
</tr>
<tr>
<td>• Black</td>
<td>13.3</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td>• Mixed</td>
<td>33.3</td>
<td>10.0</td>
<td></td>
</tr>
<tr>
<td>• Other♦</td>
<td>6.7</td>
<td>20.0</td>
<td></td>
</tr>
<tr>
<td>BMI Z Score</td>
<td>1.4 ± 0.8</td>
<td>0.3 ± 0.9</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Co-existing Obesity (% Yes)</td>
<td>30</td>
<td>3.3</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Narcolepsy Group Only

<table>
<thead>
<tr>
<th>Narcolepsy Symptoms (%)*</th>
<th>100</th>
</tr>
</thead>
<tbody>
<tr>
<td>• EDS</td>
<td>75.9</td>
</tr>
<tr>
<td>• Cataplexy</td>
<td>17.2</td>
</tr>
<tr>
<td>• Sleep paralysis</td>
<td>10.3</td>
</tr>
</tbody>
</table>

Medication (% Using)

<table>
<thead>
<tr>
<th></th>
<th>33.3</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Modafinil</td>
<td></td>
</tr>
<tr>
<td>• Ritalin</td>
<td>26.7</td>
</tr>
<tr>
<td>• Dexedrine</td>
<td>6.7</td>
</tr>
<tr>
<td>• Strattera</td>
<td>3.3</td>
</tr>
<tr>
<td>• Clomipramine</td>
<td>3.3</td>
</tr>
</tbody>
</table>

| Not taking any medication | 26.7 |

Obstructive Apnea Hypopnea Index

| 0.7 ± 0.7 |

Values reported as mean and ± standard deviation unless otherwise specified

NS-Not Significant

EDS-Excessive Daytime Sleepiness

♦Other races include Arab/West Asian, Chinese, Korean, South Asian

*symptoms reported by patients and caregivers

*assesses significant difference between distributions of races between groups
5.2. Mental Health Outcomes: Depression Scores and Anxiety Scores

Depression scores (CDI-2 total scores) were significantly higher in the narcolepsy group than the control group (p=0.01). A significantly greater proportion of patients in the narcolepsy group also had depression scores in the elevated range (p=0.02). More patients in the narcolepsy group (10%) reported suicidal ideation than the control group (3.3%), however this difference was not statistically significant. Anxiety scores (SCARED total scores) were not significantly different between groups. SCARED separation anxiety disorder (p=0.03) and social anxiety disorder (p<0.01) subscale scores were significantly higher in the narcolepsy group compared to the control group.

In this study, there were no significant associations between depression scores, sex, the presence of obesity and age (data not shown). Details of all scores can be found in Table 8.
Table 8: Depression Scores and Anxiety Scores in Adolescents with Narcolepsy and Controls

<table>
<thead>
<tr>
<th></th>
<th>Narcolepsy N=30</th>
<th>Control N=30</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Depression Scores</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CDI-2 Total Score</td>
<td>10.9 ± 6.8</td>
<td>6.7 ± 5.5</td>
<td>0.01</td>
</tr>
<tr>
<td>CDI-2 Total Elevated (%Yes)*</td>
<td>23.3</td>
<td>3.3</td>
<td>0.02</td>
</tr>
<tr>
<td>CDI-2 Suicidal ideation (%Yes)</td>
<td>“I think about killing myself but would not do it”</td>
<td>10.0</td>
<td>3.3</td>
</tr>
<tr>
<td><strong>Anxiety Scores</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SCARED Total Score</td>
<td>20.5 ± 11.8</td>
<td>16.1 ± 10.9</td>
<td>NS</td>
</tr>
<tr>
<td>• Panic Disorder or Significant Somatic Symptoms</td>
<td>3.1 ± 2.8</td>
<td>3.6 ± 3.4</td>
<td>NS</td>
</tr>
<tr>
<td>• Generalized Anxiety Disorder</td>
<td>6.7 ± 5.2</td>
<td>6.1 ± 4.5</td>
<td>NS</td>
</tr>
<tr>
<td>• Separation Anxiety Disorder</td>
<td>3.2 ± 2.7</td>
<td>1.8 ± 1.7</td>
<td>0.03</td>
</tr>
<tr>
<td>• Social Anxiety Disorder</td>
<td>6.2 ± 4.3</td>
<td>3.5 ± 2.8</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>• Significant School Avoidance</td>
<td>1.3 ± 1.4</td>
<td>0.9 ± 1.1</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values reported as mean and ± standard deviation unless otherwise specified.

CDI-2-Children’s Depression Inventory 2nd edition
SCARED-The Screen for Childhood Anxiety Related Emotional Disorders
NS-Not significant

*CDI-2 total elevated cut-off points: [Females: ages 7-12 years-(14)/ages 13-17 years-(20)] [males: ages 7-12 years-(17)/ages 13-17 years-(16)]
5.3. Sleep Patterns

Actigraphy data revealed the narcolepsy group had a significantly shorter total sleep time (p=0.03) and lower sleep efficiency (p<0.01). The narcolepsy group also had a significantly greater wake after sleep onset and number of awakenings (p<0.01). Sleep diary data revealed that the narcolepsy group also had significantly greater self-reported nocturnal awakenings per night (p<0.01). Pittsburgh Sleep Quality Index scores were also significantly higher in the narcolepsy group, with a mean score of 5.7 ± 4.1 which is in the poor sleep quality range (≥5) (p<0.01). More patients were in the poor sleep-quality range in the narcolepsy group compared to the control group and a trend towards significance was seen (50 vs 26.6 per cent; p=0.06). The narcolepsy group also had a significantly higher Epworth scale scores (p<0.01). There were no significant differences in transition probabilities between the narcolepsy and control groups. Details on sleep patterns can be found in Table 9.
Table 9: Sleep Patterns in Adolescents with Narcolepsy and Controls

<table>
<thead>
<tr>
<th>Actigraphy Data</th>
<th>Narcolepsy N=30*</th>
<th>Control N=30</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Sleep Time (hours)</td>
<td>6.5 ± 1.5</td>
<td>7.2 ± 0.8</td>
<td>0.03</td>
</tr>
<tr>
<td>Sleep Efficiency (%)</td>
<td>63.7 ± 13.2</td>
<td>80.5 ± 11.8</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Wake After Sleep Onset (min)</td>
<td>88.1 ± 36.4</td>
<td>37.9 ± 12.6</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Awakenings (number)</td>
<td>52.1 ± 14.9</td>
<td>34.4 ± 7.7</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>$k_{AR}$ (Wake Fragmentation)</td>
<td>0.03 ± 0.01</td>
<td>0.03 ± 0.02</td>
<td>NS</td>
</tr>
<tr>
<td>$k_{RA}$ (Sleep Fragmentation)</td>
<td>0.03 ± 0.01</td>
<td>0.03 ± 0.01</td>
<td>NS</td>
</tr>
<tr>
<td>Self-Reported Nocturnal Awakenings (number per night)</td>
<td>2.6 ± 2.2</td>
<td>0.6 ± 0.9</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Pittsburgh Sleep Quality Index Score</td>
<td>5.7 ± 4.0</td>
<td>3.6 ± 2.3</td>
<td>0.02</td>
</tr>
<tr>
<td>Patients in Poor Sleep Quality Range (% with Pittsburgh Sleep Quality Index &gt;5)</td>
<td>50</td>
<td>26.6</td>
<td>0.06</td>
</tr>
<tr>
<td>Epworth Sleepiness Scale Score</td>
<td>13.1 ± 4.5</td>
<td>4.8 ± 3.5</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

NS-Not significant
$k_{AR}$ - probability of transition from active state to rest (Fragmentation during wake)
$k_{RA}$ - probability of transition from rest to active state (Nocturnal Sleep Fragmentation)
*N=29 for actigraphy data in narcolepsy group
5.4. Physical Activity Levels

Objective PA levels (pedometer step counts) were less than 10,000 steps daily in both groups. However, self-reported PA levels in both groups were in the active range (Godin health contribution score ≥24). The control group had a significantly greater percentage of patients with Godin health contribution scores in the active range (93.3 vs 73.3 per cent; p=0.04). The Godin health contribution score and pedometer step count (daily average) were not significantly correlated (r=0.04; p=0.807). Detailed PA data is found in Table 10.

Table 10: Physical Activity Data in Adolescents with Narcolepsy and Controls

<table>
<thead>
<tr>
<th></th>
<th>Narcolepsy N=30*</th>
<th>Control N=30*</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pedometer step count (daily average)</td>
<td>7808.7 ± 3089.5</td>
<td>6939.3 ± 2205.6</td>
<td>NS</td>
</tr>
<tr>
<td>Godin Health Contribution Score</td>
<td>47.3 ± 31.7</td>
<td>59.3 ± 25.8</td>
<td>NS</td>
</tr>
<tr>
<td>Godin Health Contribution Score in Active Range (% ≥24)</td>
<td>73.3</td>
<td>93.3</td>
<td>0.04</td>
</tr>
<tr>
<td>Strenuous Activity (days per week)</td>
<td>3.2 ± 2.5</td>
<td>4.3 ± 2.5</td>
<td>NS</td>
</tr>
<tr>
<td>Moderate Activity (days per week)</td>
<td>3.7 ± 3.7</td>
<td>4.5 ± 2.3</td>
<td>NS</td>
</tr>
<tr>
<td>Mild (days per week)</td>
<td>2.5 ± 3.4</td>
<td>3.4 ± 3.4</td>
<td>NS</td>
</tr>
</tbody>
</table>

NS-Not Significant
*N=22 and 27 for pedometer data in narcolepsy and control group respectively
5.5. The Association between Mental Health and Sleep Patterns

**Spearman's Rank-Order Correlation Analysis**

In analyses using both groups, greater depression scores (CDI-2 total scores) were associated with worse self-reported sleep quality (Pittsburgh sleep quality index scores) ($r=0.586; p<0.01$) (See Figure 11) and greater EDS (Epworth scale scores) ($r=0.463; p<0.01$). Greater anxiety scores (SCARED total scores) were also associated with poorer self-reported sleep quality ($r=0.632; p<0.01$) and greater EDS ($r=0.320; p=0.01$).

In the narcolepsy group, greater depression scores ($r=0.427; p=0.02$) and anxiety scores ($r=0.603; p<0.01$) were associated with worse self-reported sleep quality. In the control group, greater depression scores were associated with worse self-reported sleep quality ($r=0.521; p<0.01$) and greater EDS ($r=0.420; p=0.02$). In the control group, greater anxiety scores were also associated with worse self-reported sleep quality ($r=0.580; p<0.01$) and greater EDS ($r=0.511; p<0.01$). See Table 11 for details on associations.
Table 11: Associations between Sleep Patterns, Depression Scores and Anxiety Scores

<table>
<thead>
<tr>
<th></th>
<th>CDI-2 Total Score (Depression Scores)</th>
<th>SCARED Total Score (Anxiety Scores)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Narcolepsy Group (N=30)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Excessive Daytime Sleepiness</td>
<td>r</td>
<td>0.360</td>
</tr>
<tr>
<td>(Epworth Sleepiness Scale)</td>
<td>p</td>
<td>0.051</td>
</tr>
<tr>
<td>Self-Reported Sleep Quality</td>
<td>r</td>
<td>0.427*</td>
</tr>
<tr>
<td>(Pittsburgh Sleep Quality Index)</td>
<td>p</td>
<td>0.02</td>
</tr>
<tr>
<td>Total Sleep Time (hours)</td>
<td>r</td>
<td>0.045</td>
</tr>
<tr>
<td>(Actigraphy)</td>
<td>p</td>
<td>0.817</td>
</tr>
<tr>
<td>Sleep Efficiency (%)</td>
<td>r</td>
<td>0.166</td>
</tr>
<tr>
<td>(Actigraphy)</td>
<td>p</td>
<td>0.391</td>
</tr>
<tr>
<td><strong>Control Group (N=30)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Excessive Daytime Sleepiness</td>
<td>r</td>
<td>0.420*</td>
</tr>
<tr>
<td>(Epworth Sleepiness Scale)</td>
<td>p</td>
<td>0.02</td>
</tr>
<tr>
<td>Self-Reported Sleep Quality</td>
<td>r</td>
<td>0.521**</td>
</tr>
<tr>
<td>(Pittsburgh Sleep Quality Index)</td>
<td>p</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Total Sleep Time (hours)</td>
<td>r</td>
<td>-0.293</td>
</tr>
<tr>
<td>(Actigraphy)</td>
<td>p</td>
<td>0.117</td>
</tr>
<tr>
<td>Sleep Efficiency (%)</td>
<td>r</td>
<td>0.193</td>
</tr>
<tr>
<td>(Actigraphy)</td>
<td>p</td>
<td>0.306</td>
</tr>
<tr>
<td><strong>Both Groups (N=60)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Excessive Daytime Sleepiness</td>
<td>r</td>
<td>0.463**</td>
</tr>
<tr>
<td>(Epworth Sleepiness Scale)</td>
<td>p</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Self-Reported Sleep Quality</td>
<td>r</td>
<td>0.586**</td>
</tr>
<tr>
<td>(Pittsburgh Sleep Quality Index)</td>
<td>p</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Total Sleep Time (hours)</td>
<td>r</td>
<td>-0.183</td>
</tr>
<tr>
<td>(Actigraphy)</td>
<td>p</td>
<td>1.65</td>
</tr>
<tr>
<td>Sleep Efficiency (%)</td>
<td>r</td>
<td>-0.142</td>
</tr>
<tr>
<td>(Actigraphy)</td>
<td>p</td>
<td>0.285</td>
</tr>
</tbody>
</table>

CDI-2-Children’s Depression Inventory 2nd edition
SCARED-The Screen for Childhood Anxiety Related Emotional Disorders
*p<0.05
**p<0.01
r-Correlation Coefficient
N=29 for actigraphy data in narcolepsy group
**Figure 12:** Correlation Analysis between CDI-2 Total Scores and Pittsburgh Sleep Quality Index Scores (Total N=60; N=30 for both adolescents with narcolepsy and controls)

This graph shows a positive association between depression scores (CDI-2 Total Scores) and Pittsburgh Sleep Quality Index Scores in both adolescents with narcolepsy and controls.
Multiple Linear Regression Models

Data from the hierarchical multiple linear regression models with depression scores (CDI-2 total scores) as the dependent variable are shown in Tables 12, 13 and 18. Because of the limited sample size, only variables that were significantly associated with depression scores in the correlation analyses as well as covariates: age, sex and presence of obesity were included in the regression model using a stepwise entry method. Because depression scores differed significantly between groups, group was forced into the model at step 1 explaining 10% of the variance in depression scores. Age was included in the model at step 2, which explained an additional 7% of the variance. The following covariates: presence of obesity (yes or no) and sex (male or female) were not selected to be included in the final models of the stepwise regression.

The addition of the variables self-reported sleep quality (Pittsburgh Sleep Quality Index scores >5 (yes or no)) at step 3 explained 18% of the variance. The unstandardized β coefficients indicate that participants with a Pittsburgh Sleep Quality Index scores greater than 5 (indicating poor self-reported sleep quality) have depression scores that are 6.1 units higher than participants with Pittsburgh Sleep Quality Index scores less than 5 (See Table 14).

Epworth scale scores were included in a separate regression model because of the significant correlation between Pittsburgh Sleep Quality Index and Epworth scale scores (r=0.337; p<0.01). The inclusion of Epworth scale scores at step 3 explained 15% of the variance in depression scores. The unstandardized β coefficients indicate that for every unit increase in Epworth scale scores (indicating greater EDS), there is a 0.7 unit increase in depression scores. Age was also significantly associated with CDI-2 total scores in this model (β=1.10; p=0.01) (See Table 15).

In summary, self-reported sleep quality, EDS and age predict depression scores amongst adolescents with narcolepsy and controls.
Table 12: Multiple Regression Analysis Results: Sleep Quality and Depression Scores

<table>
<thead>
<tr>
<th>Model</th>
<th>Unstandardized Coefficients</th>
<th>p</th>
<th>95% Confidence Interval for β</th>
<th>R² change</th>
<th>Overall p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(Constant)</td>
<td>14.9</td>
<td>2.6</td>
<td>0.10</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>Group</td>
<td>-4.2</td>
<td>1.7</td>
<td>0.02</td>
<td>-7.6 -0.9</td>
</tr>
<tr>
<td>2</td>
<td>(Constant)</td>
<td>3.1</td>
<td>6.1</td>
<td>0.18</td>
<td>0.07</td>
</tr>
<tr>
<td></td>
<td>Group</td>
<td>-5.2</td>
<td>1.7</td>
<td>&lt;0.01</td>
<td>-8.6 -1.8</td>
</tr>
<tr>
<td></td>
<td>Age</td>
<td>0.9</td>
<td>0.4</td>
<td>0.04</td>
<td>0.1 1.8</td>
</tr>
<tr>
<td>3</td>
<td>(Constant)</td>
<td>3.5</td>
<td>5.4</td>
<td>0.36</td>
<td>0.18</td>
</tr>
<tr>
<td></td>
<td>Group</td>
<td>-3.5</td>
<td>1.6</td>
<td>0.03</td>
<td>-6.6 -0.3</td>
</tr>
<tr>
<td></td>
<td>Age</td>
<td>0.6</td>
<td>0.4</td>
<td>0.16</td>
<td>-0.2 1.3</td>
</tr>
<tr>
<td></td>
<td>Pittsburgh Sleep</td>
<td>6.1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Quality Index Score &gt;5</td>
<td>1.6</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Dependent Variable: CDI-2 Total Scores
Pittsburgh Sleep Quality Index Score >5 (Yes or No)-Yes indicates poor self-reported sleep quality
The unstandardized regression coefficient (β), standard error (SE) of the coefficient, p value of the coefficient, R², R² change and overall p value for the model are shown for the primary outcome (CDI-2 total scores)
The unstandardized regression coefficient (β) reflects the change in the outcome per unit change in the predictor variable.
Table 13: Multiple Regression Analysis Results: Excessive Daytime Sleepiness and Depression Scores

<table>
<thead>
<tr>
<th>Model</th>
<th>Unstandardized Coefficients</th>
<th>( p )</th>
<th>95% Confidence Interval for ( \beta )</th>
<th>( R^2 )</th>
<th>( R^2 ) change</th>
<th>Overall p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( \beta )</td>
<td>SE</td>
<td>Lower Bound</td>
<td>Upper Bound</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>(Constant)</td>
<td>14.9</td>
<td>2.6</td>
<td>&lt;0.01</td>
<td>9.7</td>
<td>20.3</td>
</tr>
<tr>
<td></td>
<td>Group</td>
<td>-4.2</td>
<td>1.7</td>
<td>0.02</td>
<td>-7.6</td>
<td>-0.9</td>
</tr>
<tr>
<td>2</td>
<td>(Constant)</td>
<td>3.1</td>
<td>6.1</td>
<td>0.61</td>
<td>-9.1</td>
<td>15.3</td>
</tr>
<tr>
<td></td>
<td>Group</td>
<td>-5.2</td>
<td>1.7</td>
<td>&lt;0.01</td>
<td>-8.6</td>
<td>-1.8</td>
</tr>
<tr>
<td></td>
<td>Age</td>
<td>0.9</td>
<td>0.4</td>
<td>0.04</td>
<td>0.1</td>
<td>1.8</td>
</tr>
<tr>
<td>3</td>
<td>(Constant)</td>
<td>-13.0</td>
<td>7.3</td>
<td>0.08</td>
<td>-27.7</td>
<td>1.7</td>
</tr>
<tr>
<td></td>
<td>Group</td>
<td>0.1</td>
<td>2.2</td>
<td>0.97</td>
<td>-4.4</td>
<td>4.5</td>
</tr>
<tr>
<td></td>
<td>Age</td>
<td>1.1</td>
<td>0.4</td>
<td>0.01</td>
<td>0.3</td>
<td>1.9</td>
</tr>
<tr>
<td></td>
<td>Epworth Sleepiness Scale</td>
<td>0.7</td>
<td>0.2</td>
<td>&lt;0.01</td>
<td>0.3</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Dependent Variable: CDI-2 Total Scores
Epworth Sleepiness Scale is a measure of excessive daytime sleepiness
The unstandardized regression coefficient (\( \beta \)), standard error (SE) of the coefficient, \( p \) value of the coefficient, \( R^2 \), \( R^2 \) change and overall \( p \) value for the model are shown for the primary outcome (CDI-2 total scores)
The unstandardized regression coefficient (\( \beta \)) reflects the change in the outcome per unit change in the predictor variable.
5.6. The Association between Mental Health, Sleep Patterns and Physical Activity

Spearman's Rank-Order Correlation Analysis

In analyses using both groups, greater depression scores were associated with lower self-reported PA levels (Godin Health Contribution score) \((r=-0.434; p<0.01)\). Greater anxiety total scores were also associated lower self-reported PA levels \((r=-0.274; p=0.03)\). Greater self-reported PA levels were also associated with better self-reported sleep quality \((r=-0.288; p=0.03)\). See Table 14 for details on associations.

When evaluating the narcolepsy group, greater depression scores were associated with lower self-reported PA levels \((r=-0.512; p<0.01)\). Greater self-reported PA levels were associated with better self-reported sleep quality (Pittsburgh sleep quality index) \((r=-0.427; p=0.02)\). No significant associations were seen in the control group. See Table 15 for details on associations.
Table 14: Association between Physical Activity Levels, Sleep Patterns and Depression/Anxiety Scores in Both Groups (N=60)

<table>
<thead>
<tr>
<th></th>
<th>Godin Health Contribution Score</th>
<th>Pedometer Average # of Daily Steps</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDI-2 Total Score (Depression Scores)</td>
<td>r -0.434**</td>
<td>-0.004</td>
</tr>
<tr>
<td></td>
<td>p &lt;0.01</td>
<td>0.979</td>
</tr>
<tr>
<td>SCARED Total Score (Anxiety Scores)</td>
<td>r -0.274*</td>
<td>-0.113</td>
</tr>
<tr>
<td></td>
<td>p 0.03</td>
<td>0.441</td>
</tr>
<tr>
<td>Epworth Scale</td>
<td>r -0.117</td>
<td>0.086</td>
</tr>
<tr>
<td></td>
<td>p 0.375</td>
<td>0.556</td>
</tr>
<tr>
<td>Pittsburgh Sleep Quality Index</td>
<td>r -0.288*</td>
<td>0.093</td>
</tr>
<tr>
<td></td>
<td>p 0.03</td>
<td>0.527</td>
</tr>
<tr>
<td>Total Sleep Time (Actigraphy)</td>
<td>r 0.230</td>
<td>-0.150</td>
</tr>
<tr>
<td></td>
<td>p 0.08</td>
<td>0.304</td>
</tr>
<tr>
<td>Sleep Efficiency % (Actigraphy)</td>
<td>r 0.152</td>
<td>-0.268</td>
</tr>
<tr>
<td></td>
<td>p 0.249</td>
<td>0.060</td>
</tr>
</tbody>
</table>

Pedometer Average Daily Steps N=49
CDI-2-Children’s Depression Inventory 2nd edition
SCARED-The Screen for Childhood Anxiety Related Emotional Disorders
*p<0.05
**p<0.01
Table 15: Association between Physical Activity Levels, Sleep Patterns and Depression/Anxiety Scores in the Narcolepsy and Control Group

<table>
<thead>
<tr>
<th></th>
<th>Narcolepsy Group (N=30)</th>
<th>Control Group (N=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Godin Health Contribution Score</td>
<td>Pedometer Average Daily Steps</td>
</tr>
<tr>
<td>CDI-2 Total Score (Depression Scores)</td>
<td>r</td>
<td>-0.512**</td>
</tr>
<tr>
<td></td>
<td>p</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>SCARED Total Score (Anxiety Scores)</td>
<td>r</td>
<td>-0.271</td>
</tr>
<tr>
<td></td>
<td>p</td>
<td>0.148</td>
</tr>
<tr>
<td>Epworth Scale</td>
<td>r</td>
<td>0.024</td>
</tr>
<tr>
<td></td>
<td>p</td>
<td>0.901</td>
</tr>
<tr>
<td>Pittsburgh Sleep Quality Index</td>
<td>r</td>
<td>-0.427*</td>
</tr>
<tr>
<td></td>
<td>p</td>
<td>0.02</td>
</tr>
<tr>
<td>Total Sleep Time (Actigraphy)</td>
<td>r</td>
<td>0.158</td>
</tr>
<tr>
<td></td>
<td>p</td>
<td>0.412</td>
</tr>
<tr>
<td>Sleep Efficiency % (Actigraphy)</td>
<td>r</td>
<td>0.085</td>
</tr>
<tr>
<td></td>
<td>p</td>
<td>0.661</td>
</tr>
</tbody>
</table>

Pedometer Average Daily Steps N=22 for Narcolepsy group and N=27 for Control Group
CDI-2-Children’s Depression Inventory 2nd edition
SCARED-The Screen for Childhood Anxiety Related Emotional Disorders
*p<0.05
**p<0.01
Multiple Linear Regression Models

The first two steps of the regression analyses are identical to table 12 and 13. The inclusion of Godin Health Contribution scores at step 3 explained 9% of the variance. The unstandardized β coefficients indicate that for every unit increase in Godin Health Contribution scores (indicating greater self-reported PA), the CDI-2 total scores decrease by 0.10 (See Table 16).

In summary, self-reported physical activity levels depression scores amongst adolescents with narcolepsy and controls

Table 16: Multiple Regression Analysis Results: Self-Reported Physical Activity and Depression Scores

<table>
<thead>
<tr>
<th>Model</th>
<th>Unstandardized Coefficients</th>
<th>p</th>
<th>95% Confidence Interval for β</th>
<th>R²</th>
<th>R² change</th>
<th>Overall p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β</td>
<td>SE</td>
<td>Lower Bound</td>
<td>Upper Bound</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>(Constant)</td>
<td>14.9</td>
<td>2.6</td>
<td>&lt;0.01</td>
<td>9.7</td>
<td>20.3</td>
</tr>
<tr>
<td></td>
<td>Group</td>
<td>-4.2</td>
<td>1.7</td>
<td>0.02</td>
<td>-7.6</td>
<td>-0.9</td>
</tr>
<tr>
<td>2</td>
<td>(Constant)</td>
<td>3.1</td>
<td>6.1</td>
<td>0.61</td>
<td>-9.1</td>
<td>15.3</td>
</tr>
<tr>
<td></td>
<td>Group</td>
<td>-5.2</td>
<td>1.7</td>
<td>&lt;0.01</td>
<td>-8.6</td>
<td>-1.8</td>
</tr>
<tr>
<td></td>
<td>Age</td>
<td>0.9</td>
<td>0.4</td>
<td>0.04</td>
<td>0.1</td>
<td>1.8</td>
</tr>
<tr>
<td>3</td>
<td>(Constant)</td>
<td>13.4</td>
<td>7.2</td>
<td>0.07</td>
<td>-0.9</td>
<td>27.8</td>
</tr>
<tr>
<td></td>
<td>Group</td>
<td>-3.6</td>
<td>1.7</td>
<td>0.04</td>
<td>-7.1</td>
<td>-0.1</td>
</tr>
<tr>
<td></td>
<td>Age</td>
<td>0.3</td>
<td>0.5</td>
<td>0.48</td>
<td>-0.6</td>
<td>1.3</td>
</tr>
<tr>
<td></td>
<td>Godin Health Contribution Score</td>
<td>-0.1</td>
<td>0.0</td>
<td>0.02</td>
<td>-0.1</td>
<td>-0.01</td>
</tr>
</tbody>
</table>

Dependent Variable: CDI-2 Total Scores
Godin Health Contribution Score-measure of self-reported PA level
The unstandardized regression coefficient (β), standard error (SE) of the coefficient, p value of the coefficient, R², R² change and overall p value for the model are shown for the primary outcome
The unstandardized regression coefficient (β) reflects the change in the outcome per unit change in the predictor variable.
5.7. Family Functioning in Pediatric Narcolepsy

Family functioning was assessed in the narcolepsy group using the PedsQL Family Impact Module. PedsQL Family Impact Module total, communication and worry scores were significantly lower than published scores of a community sample that were not seeking medical care (Medrano et al., 2013). See Table 17 for details on scores.

**Pearson Correlation Analysis**

No significant associations were seen between family functioning scores and patient depression scores or anxiety scores. See Supplementary table 1 for details on associations.

**Table 17: PedsQL Family Impact Module Scores**

<table>
<thead>
<tr>
<th></th>
<th>Narcolepsy n=30</th>
<th>Community Sample n=726-901* (Medrano et al., 2013)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family Impact Total Score</td>
<td>64.0 ± 19.8</td>
<td>70.8 ± 14.5</td>
<td>0.01</td>
</tr>
<tr>
<td>• Parent HRQOL Total Score</td>
<td>69.4 ± 19.8</td>
<td>69.4 ± 15.5</td>
<td>NS</td>
</tr>
<tr>
<td>o Parent Physical Functioning Score</td>
<td>68.1 ± 22.8</td>
<td>64.9 ± 17.4</td>
<td>NS</td>
</tr>
<tr>
<td>o Parent Emotional Functioning Score</td>
<td>61.7 ± 21.2</td>
<td>67.6 ± 17.9</td>
<td>NS</td>
</tr>
<tr>
<td>o Parent Social Functioning Score</td>
<td>77.1 ± 24.3</td>
<td>74.4 ± 19.1</td>
<td>NS</td>
</tr>
<tr>
<td>o Parent Cognitive Functioning Score</td>
<td>74.5 ± 23.2</td>
<td>73.3 ± 18.6</td>
<td>NS</td>
</tr>
<tr>
<td>• Communication</td>
<td>70.4 ± 24.2</td>
<td>81.9 ± 17.7</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>• Worry</td>
<td>42.3 ± 21.8</td>
<td>78.1 ± 20.1</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>• Family Summary Score</td>
<td>64.4 ± 26.0</td>
<td>65.5 ± 18.5</td>
<td>NS</td>
</tr>
<tr>
<td>o Daily Activities</td>
<td>59.4 ± 32.6</td>
<td>63.2 ± 22.5</td>
<td>NS</td>
</tr>
<tr>
<td>o Family Relationships</td>
<td>66.7 ± 24.8</td>
<td>67.0 ± 19.4</td>
<td>NS</td>
</tr>
</tbody>
</table>

NS=Not Significant

*Sample size is a range because scores were only calculated on completed scales.
PedsQL Family Impact Module total, parent HRQOL, family summary worry and communication scores in the narcolepsy group were significantly lower than the traumatic brain injury group (e.g., skull/brain trauma, concussions). All scores in the narcolepsy group were similar to adolescents with chronic pain.

Lowest Scores on the PedsQL Family Impact Module were seen in the worry domain, which asks about worries related to medical treatments efficacy, treatment side-effects, others reaction to their child’s illness, illness affecting other family members and the child’s overall future (Varni et al., 2004). Scores in the worry domain were similar to adolescents with chronic pain and significantly lower than pediatric patients with non-traumatic (e.g., stroke) and traumatic brain injuries. See Table 18 for details on all scores and Figure 12 for graphical comparison of PedsQL Family Impact Module total and worry scores. See Supplementary table 2 on details on the characteristics of the studies that were used in the secondary data analysis.
Table 18: Family Functioning in Pediatric Narcolepsy Compared to Other Disease Groups

<table>
<thead>
<tr>
<th>Relevant Group Differences</th>
<th>Narcolepsy (A)</th>
<th>Chronic Pain (Jastrowski Mano et al., 2011) (B)</th>
<th>Cancer (Maizou et al., 2016) (C)</th>
<th>Non-Traumatic Brain Injury (de Kloet et al., 2015) (D)</th>
<th>Traumatic Brain Injury (de Kloet et al., 2015) (E)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample Size</td>
<td>30</td>
<td>458</td>
<td>92</td>
<td>27</td>
<td>81</td>
</tr>
<tr>
<td>Age (years)</td>
<td>13.8 ± 2.2</td>
<td>13.7 ± 2.7</td>
<td>9.1 ± 4.1</td>
<td>13.0 (range: 5.0-22.0)</td>
<td>A&gt;C*</td>
</tr>
<tr>
<td>Family Impact Module Total Score</td>
<td>64.0 ± 19.8</td>
<td>64.7 ± 19.5</td>
<td>53.5 ± 17.4</td>
<td>70.8 ±19.6</td>
<td>83.6 ±16.1</td>
</tr>
<tr>
<td>Parent HRQOL Score</td>
<td>69.4 ± 19.8</td>
<td>67.4 ± 20.7</td>
<td>54.6 ± 19.9</td>
<td>72.6 ±19.7</td>
<td>85.1±17.0</td>
</tr>
<tr>
<td>Family Summary Score*</td>
<td>64.4 ± 26.0</td>
<td>66.1 ± 23.4</td>
<td>58.1 ± 21.8</td>
<td>72.3 ± 21.4</td>
<td>80.8 ± 18.3</td>
</tr>
<tr>
<td>Worry</td>
<td>42.3 ± 21.8</td>
<td>46.8 ± 22.6</td>
<td>NR</td>
<td>60.7 ± 28.0</td>
<td>83.2 ± 21.6</td>
</tr>
<tr>
<td>Communication</td>
<td>70.4 ± 24.2</td>
<td>74.3 ± 23.9</td>
<td>NR</td>
<td>69.4 ± 24.7</td>
<td>90 ± 17.1</td>
</tr>
</tbody>
</table>

Only significant differences with the narcolepsy group reported
All values reported as mean and standard deviation unless otherwise specified
*p<0.01
*Family Summary Scores comprised of daily activities and family relationships scale scores
NR=Not reported
HRQOL=Health Related Quality of Life
**Figure 13:** Family Functioning Scores in Pediatric Narcolepsy Compared to a Community Sample and other Pediatric Conditions

![Bar chart showing family functioning scores for different conditions](chart.png)

- **Pediatric Condition:** Narcolepsy, Chronic Pain, Cancer, Non-Traumatic Brain Injury, Traumatic Brain Injury, Community Sample
- **Scores:**
  - **Family Impact Total Scores**
    - Narcolepsy: 64.4
    - Chronic Pain: 64.7
    - Cancer: 53.5
    - Non-Traumatic Brain Injury: 70.8
    - Traumatic Brain Injury: 83.6
    - Community Sample: 78.1
  - **Worry Subscale Scores**
    - Narcolepsy: 42.3
    - Chronic Pain: 46.8
    - Cancer: 60.7
    - Non-Traumatic Brain Injury: 63.2
    - Traumatic Brain Injury: 70.8
Chapter Six: Conclusions and General Discussion

6.1 Main Conclusions

This thesis examined the relationship between sleep patterns, PA levels and mental health outcomes (depression scores and anxiety scores) amongst adolescents with narcolepsy. The primary objective of this thesis was to examine if sleep patterns (duration and quality), EDS and PA levels are associated with depression scores as the primary outcome and anxiety scores as the secondary outcome in adolescents with narcolepsy compared with healthy adolescents. The hypothesis that poor nocturnal sleep quality, EDS and lower levels of PA would be associated with greater depression scores amongst adolescents with narcolepsy and controls was supported.

The second objective of this thesis was to describe family functioning in adolescents with narcolepsy, in comparison to otherwise healthy adolescents (not seeking medical care) and adolescents with other pediatric conditions. The hypothesis that family functioning would be impaired in adolescents with narcolepsy in comparison to healthy adolescents but similar to adolescents with other pediatric conditions was supported. The third objective of this thesis was to examine the association between family functioning and depression scores and anxiety scores in adolescents with narcolepsy. The hypothesis that family functioning would be associated with depression scores and anxiety scores was not supported.
6.2 Specific Findings

6.2.1 Mental Health in Pediatric Narcolepsy

**Depression Scores**

The findings from this cohort of adolescents with narcolepsy are that a greater percentage of adolescents with narcolepsy report elevated depression scores compared to controls (23.3 vs 3.3 per cent; p=0.02). Similarly, Inocente et al reported depression scores to be elevated in 25 per cent of children and youth with narcolepsy that were less than 18 years of age (n=88) (C. O. Inocente et al., 2014). Similar findings were also reported by Rocca et al (n=29), who used the CBCL and reported 27.6 per cent of patients to have elevated scores in the withdrawn and depressive domain, compared to only 7.7 per cent of controls (n=39) (Rocca et al., 2016). In a cohort of pediatric patients with narcolepsy aged 4 to 18 years (n=42), Stores et al reported mean CDI-2 total scores to be 12.30 ± 8.54 (Stores et al., 2006), which are comparable to this cohort where mean CDI-2 total scores were 10.9 ± 6.8.

**Suicidal Ideation**

This was the first study to report on suicidal ideation in the pediatric narcolepsy population. Ten per cent of patients in the narcolepsy cohort selected the option “I think about killing myself but would not do it” compared to 3.3 per cent of controls. This difference was not statistically significant, which may be attributed to the small sample size. The percentage of patients reporting suicidal ideation in this cohort of adolescents with narcolepsy are similar to other pediatric neurological conditions such as traumatic brain injury and hydrocephalus and stroke where rates were 11.1, 12.5 and 17.7 per cent respectively (Mazur-Mosiewicz et al., 2015). No patients in the narcolepsy group reported suicidal ideation with intent (“I want to kill myself”), in contrast to the 3 and 1.9 per cent of pediatric patients with epilepsy and traumatic brain injury respectively (Mazur-Mosiewicz et al., 2015).
Anxiety Scores

SCARED social anxiety disorder scores were significantly higher in the narcolepsy group than the control group (5.9 ± 4.1 vs 3.5 ± 2.8; p<0.01). Social anxiety disorders, such as panic attacks and social phobias, are reported to occur in 53 per cent of adults with narcolepsy (Fortuyn et al., 2010), which typically onset after the diagnoses of narcolepsy (Ohayon et al., 2014). It has been suggested that social anxiety in patients with narcolepsy may be associated with experiencing disease symptoms (e.g., EDS, cataplexy) unexpectedly, causing embarrassment in social settings (Morse & Sanjeev, 2018; Stores et al., 2006). This may be especially challenging for adolescents, who like to conform to their peers in social settings (D. Taddeo, M. Egedy, & J. Y. Frappier, 2008).

SCARED separation anxiety disorder scores were also significantly higher in the narcolepsy group than the controls (3.2 ± 2.7 vs 1.8 ± 1.7; p=0.02). Separation anxiety is the excessive fear about being separated from home or an attachment figure (e.g., parent) (APA, 2013). Separation anxiety is more common among adolescents with chronic conditions than otherwise healthy adolescents (Chavira, Garland, Daley, & Hough, 2008). This may be because there is anxiety about needing medical attention while being away from caregivers who know the child and the condition well (e.g., dealing with a cataplexy episode, falling asleep in a public place) (Chavira et al., 2008).

In summary, findings from this thesis underscore the prevalence of co-morbid depressive symptoms and anxiety in adolescents with narcolepsy. Alarmingly, almost one fourth of the adolescents with narcolepsy had elevated depression scores in this cohort and ten per cent reported suicidal ideation. This suggests health care teams should prioritize screening for co-existing depressive symptoms at routine clinical visits. Early identification of depressive symptoms in patients can allow for early intervention. Interventions include referrals to an adolescent medicine specialist and/or child psychiatrist who can further assess the patient and provide them with appropriate treatment (e.g., antidepressant medication, cognitive behavioral therapy) to improve patient mental health.
6.2.2 The Association between Sleep Patterns and Depression Scores

This thesis evaluated factors associated with depression scores amongst adolescents with narcolepsy and controls. In the narcolepsy group, poor self-reported sleep quality was associated with greater depression scores. In the control group, poor self-reported sleep quality and greater EDS were associated with greater depression scores. Associations may have been present in the control group because sleep-related problems such as poor sleep quality (Gradisar, Gardner, & Dohnt, 2011), EDS (J. A. Owens, Dearth-Wesley, Lewin, Gioia, & Whitaker, 2016) and EDS as a result of chronic sleep loss (Ojio et al., 2016) are commonly experienced by otherwise healthy adolescents. Sleep-related problems in healthy adolescents may occur for reasons such as excessive use of electronic media before bed, early school start times, as well as increased extracurricular and academic demands leading to less opportunities for sleep (M. Moore & Meltzer, 2008; J. Owens, 2014; J. A. Owens et al., 2016). A discussion of the association between depression scores and sleep patterns in both the narcolepsy and control group will follow:

Sleep Quality

The association between sleep quality and depression scores has not been previously assessed amongst adolescents with narcolepsy however has been reported in adults with narcolepsy. Dauvilliers et al reported adult narcolepsy patients (mean age 42.8±16.7 years) with moderate to severe depressive symptoms had significantly worse self-reported sleep quality (measured by Pittsburgh sleep quality index score) than patients with mild or no depressive symptoms (8.3 ± 3.7 vs 5.9 ± 3.0; p<0.01) (Dauvilliers et al., 2009). The association seen in the control group has been reported in a study of 889 adolescents (mean age 15.71±1.57 years) where depression scores (evaluated with the Center for Epidemiologic Studies – Depression scale) were positively associated with Pittsburgh Sleep Quality Index scores (r=0.58; p<0.01) (Raniti, Waloszek, Schwartz, Allen, & Trinder, 2018).

Although there were significant associations in both the narcolepsy and control group, it is important to note that self-reported nocturnal sleep quality was significantly worse in the narcolepsy group compared to the controls, with a mean score of 5.7 ± 4.1, which is in the poor sleep quality range (>5). Additionally, 50 per cent adolescents in the narcolepsy cohort were in the poor sleep quality range as opposed to 26.6 per cent of controls, and this difference trended
towards statistical significance (p=0.06). Poor nocturnal sleep quality is a common feature in narcolepsy, and has also been reported in adults with narcolepsy (Rovere, Rossini, & Reimao, 2008). In adults with narcolepsy, 45 per cent report being unsatisfied with their nocturnal sleep quality compared to only 10 per cent of healthy controls (p<0.01) (Rovere et al., 2008). Disturbed nocturnal sleep may be due to the use of stimulant medication—the standard treatment in narcolepsy (Corkum, Panton, Ironside, Macpherson, & Williams, 2008). Over 75 per cent of the sample was taking stimulant medication, which has been associated with sleep problems in the pediatric attention deficit hyperactivity disorder (ADHD) population (Storebo et al., 2015). Children with ADHD on Ritalin (methylphenidate) have a 60 per cent greater risk of having sleep problems (Relative Risk 1.60, 95% Confidence Interval 1.15-2.23; 13 trials, 2416 participants) (Storebo et al., 2015). However, no studies have directly compared the presence of disturbed nocturnal sleep in patients with narcolepsy (adult or pediatric) who are on and off stimulants (Roth et al., 2013).

**Excessive Daytime Sleepiness**

The relationship between EDS and depression scores seen in this study, has been previously reported in both adults and adolescents with narcolepsy (Dauvilliers et al., 2009). Dauvilliers et al also reported patients with moderate to severe depressive symptoms had significantly higher Epworth scores than patients with mild or no depressive symptoms (14.9 ± 5.1 vs 12.5 ± 4.9; p<0.01) (Dauvilliers et al., 2009). Inocente et al also reported Epworth scale scores to be significantly higher in adolescents with narcolepsy who had elevated CDI total scores (18 (6–23) vs 15.5 (4–22); p=0.05) (C. O. Inocente et al., 2014). In a longitudinal study on healthy adolescents (n=2787), EDS (Epworth scale scores >10) was reported to be associated with depressive symptoms measured by the Beck Depression Inventory (Luo, Zhang, Chen, Lu, & Pan, 2018). The presence of EDS at baseline also predicted depressive symptoms at one year follow-up amongst otherwise healthy adolescents (Adjusted Odds Ratio 2.26 (95% Confidence Interval 1.47–3.49)) (Luo et al., 2018).
**Sleep Duration**

The relationship between short sleep duration and depression scores has been reported in many studies (Ojio et al., 2016) (Baum et al., 2014) (Roberts & Duong, 2014) (Roberts & Duong, 2017). It is unclear why this association was not seen this study, but it may be due to the small sample size.

Adolescents in the narcolepsy group had a significantly shorter total sleep time than controls (measured by actigraphy). Disturbed nocturnal sleep may explain why adolescents with narcolepsy have a shorter total sleep time than controls. Disturbed nocturnal sleep is a common feature of narcolepsy and is characterized by frequent nightly awakenings resulting in sleep fragmentation (Roth et al., 2013). In the adult narcolepsy population, patients with disturbed nocturnal sleep report a significantly shorter total sleep time than patients without disturbed nocturnal sleep (6 hours vs 7 hours; p<0.01) (Rosenthal et al., 1990). Other features of disturbed nocturnal sleep seen in the narcolepsy group include greater self-reported nocturnal awakenings (2.6 ± 2.2 vs 0.6 ± 0.9 awakenings per night; p<0.01) and lower sleep efficiency (63.7 ± 13.02 vs 80.5 ± 11.8 per cent; p<0.01), which may contribute to shorter total sleep duration. The poor sleep efficiency seen in this cohort at 63.7 ± 13.02 per cent confirms findings by Alakuijala et al who reported a low sleep efficiency percentage in adolescents with narcolepsy at 74.38 ± 9.39 per cent (A. Alakuijala et al., 2015). A healthy sleep efficiency should be greater than or equal to 80 per cent, and anything lower suggests poor sleep quality (Anniina Alakuijala et al., 2016).

It is important to note that actigraphy is sensitive to movement activity and may underestimate total sleep time and sleep efficiency and overestimate the number of awakenings an individual experiences (A. Alakuijala et al., 2015; Rupp & Balkin, 2011). Sleep time with minor movement that would be scored as wake using actigraphy, would be sleep when recorded by PSG (A. Alakuijala et al., 2015; Rupp & Balkin, 2011). Actigraphy data from this study is similar to another study who assessed sleep patterns using actigraphy amongst adolescents with narcolepsy (mean age 15.5 ± 6.5 years) (A. Alakuijala et al., 2015). Alakuijala et al reported an average total sleep time of 6.4 ±1.1 hours in their cohort (n=56) (A. Alakuijala et al., 2015), which is similar to the 6.5 ± 1.5 hours seen in the narcolepsy group in this study. Actigraphy may also underestimate sleep efficiency percentage due to the high sensitivity to minor movements (A. Alakuijala et al., 2015). However, motor disturbances during sleep are common in patients with narcolepsy and can...
contribute to disturbed nocturnal sleep (A. Alakuijala et al., 2015). PSG data on adults with narcolepsy shows the mean motor activity index (defined as movement episodes per hour of sleep excluding electromyographic-related muscle activity in the chin or tibialis anterior channels) is significantly higher than controls (59.9 vs 15.4 per hour of sleep; p<0.01) (Frauscher et al., 2011).

**Possible Mechanisms Explaining the Association between Sleep and Depression Scores**

Sleep deprivation, which includes short total sleep duration and/or poor sleep quality (Paruthi et al., 2016) was seen in both the narcolepsy and control group. The association between sleep deprivation and depression and anxiety scores was seen in both groups. The mechanisms that explain the relationship between sleep deprivation and depression and anxiety scores is largely unknown (Palmer, Oosterhoff, Bower, Kaplow, & Alfano, 2018). Some evidence suggests that sleep deprivation increases vulnerability for depressive symptoms via emotional processes (Gregory & Sadeh, 2016). Specifically, sleep deprivation leads to disrupted emotional regulation (the ability to control and modulate emotions) (Gross, 1998; Palmer & Alfano, 2017). Limited research from correlational and experimental studies amongst adolescents suggests sleep deprivation leads to poorer emotional regulation and increased reactivity to negative emotional stimuli (Baum et al., 2014; McMakin et al., 2016; Vriend et al., 2013). EDS, as a result of sleep deprivation is also associated with poor-emotional self-regulation in typically developing adolescents (J. A. Owens et al., 2016).

The relationship between sleep deprivation and disrupted emotional regulation has also been reported in adults (Palmer & Alfano, 2017). Sleep deprived adults report experiencing heightened reactivity to negative emotional experiences (Palmer & Alfano, 2017). A study using functional magnetic resonance imaging in sleep deprived adults showed, greater activation of the amygdala in response to negative stimuli compared to adults who were not sleep deprived (Yoo et al., 2007). This study also showed decreased connectivity between the medial prefrontal cortex and the ventral anterior cingulate cortex in sleep deprived adults, which can weaken emotional control (Yoo et al., 2007).

Interestingly, preliminary data suggests that adolescents may be even more susceptible to the emotional effects of sleep deprivation than adults (McGlinchey et al., 2011) because they are
still developing emotional regulation skills (J. A. Owens et al., 2016). Regions of the brain that govern emotional regulation (the prefrontal cortex, amygdala and ventral anterior cingulate cortex) are still undergoing developmental changes during adolescence (Casey, 2015), and sleep deprivation may adversely affect their normal function (Holm et al., 2009; Telzer, Fuligni, Lieberman, & Galvan, 2013).
6.2.3 Physical Activity in Pediatric Narcolepsy

This thesis was the first to evaluate PA levels in the pediatric narcolepsy population. Daily step count between the narcolepsy and control group were not significantly different. However, both groups had lower PA levels than the recommended daily 10 000 to 15 000 steps for adolescents (Tudor-Locke & Bassett, 2004). This is consistent with results from the 2012 to 2013 Canadian Health Measures Survey showing that over 90 per cent of children and adolescents (ages 5–17 years) do not meet Canada’s recommended guideline of 60 minutes of moderate-to-vigorous PA daily (Canada, 2015). The lack of PA seen in both groups of adolescents may be due to competing demands (e.g., school work, extracurricular commitments) taking time away from PA (Bauer, Yang, & Austin, 2004).

Objective PA levels in this group of adolescents with narcolepsy are similar to findings from the adult narcolepsy population (Matoulek et al., 2017). One study on adults with narcolepsy (n=42, mean age 34.9 ± 10.0) reported patients had a low average daily step count of 6346 ± 2026 (Matoulek et al., 2017) which is similar to this cohort of adolescents with narcolepsy. Lower PA levels in narcolepsy may also be associated with low cardiopulmonary fitness, which has been reported in the adult narcolepsy population (Matoulek et al., 2017). PA levels may also be lower in adolescents with narcolepsy because of decreased spontaneous activity levels (Bruck et al., 2005). Decreased spontaneous activity has been reported in adults with narcolepsy, even when treated with stimulants (Bruck et al., 2005).

Even though adolescents in both groups had low objective PA levels, the vast majority of participants self-reported PA levels to be in the ‘active’ range (Godin health contribution score ≥24). This discrepancy between objective and self-report data may be due to bias seen with self-report measures (e.g., over estimating PA levels) (Prince et al., 2008). Additionally, some adolescents may have taken off the pedometer during certain types of aquatic PA (e.g., swimming), or simply did not wear the device whilst partaking in PA. Although both groups of adolescents self-reported high PA levels, a significantly lower percentage of adolescents in the narcolepsy group were in the active range compared to the control group (73.3 vs 93.3 per cent; p=0.04). It can be speculated that adolescents in the narcolepsy group self-reported lower PA levels, because they feel that the symptoms of their condition (e.g., EDS, cataplexy) make it more difficult for
them to participate in PA. Godin health contribution scores in adolescents with narcolepsy (47.3 ± 31.7) are similar to other adolescents with neurological disorders such as monophasic acquired demyelinating syndrome (54.0 ± 49.0) and multiple sclerosis (40.0 ± 46.0), who report symptoms of fatigue from lack of sleep, as well as depression (Grover et al., 2015)
6.2.4 The Association between Physical Activity, Sleep Patterns and Depressive Symptoms

This thesis also evaluated the association between depression scores and PA levels in adolescents with narcolepsy and controls. In adolescents with narcolepsy, self-reported and objective PA levels were associated with depression scores. However, this association was not seen in the control group, which is in contrast to larger studies in healthy adolescents where an inverse association between PA levels and depression scores have been reported (Biddle & Asare, 2011) (Kremer et al., 2014; Wiles et al., 2012). This association may have not been seen in control group of this study due to the small sample size (n=30).

The association between increased PA levels and lower depression scores may be explained through a biological mechanism, specifically how participating in PA releases endorphins, which are associated with feelings of euphoria (Dishman & O'Connor, 2009; Lubans et al., 2016). Euphoric feelings after participating in PA may be due to changes in one or more brain monoamines, with the strongest evidence available for dopamine, noradrenaline, and serotonin (Lin & Kuo, 2013; Lubans et al., 2016). However, further research is needed to support this assertion in pediatric populations (Bouix et al., 1994; Lubans et al., 2016).

The association between increased PA levels and lower depression scores may also be explained through psychosocial pathways. Participating in PA in group settings may provide adolescents with opportunities for social interaction and peer-conformity, and consequently improve mood (Wiles et al., 2012). The relationship between PA and depression scores may also be bidirectional (Korczak et al., 2017). It can be speculated that adolescents with narcolepsy may not be interested in participating in PA because of co-existing depressive symptoms, which encompass low mood and self-esteem. It can also be speculated that adolescents with narcolepsy may avoid participating in PA such as team sports, because of the symptoms of their condition (e.g., episodes of cataplexy), which occur unexpectedly and may be embarrassing (Matoulek et al., 2017).

In the narcolepsy group, greater self-reported PA levels were also associated with and better self-reported sleep quality. The association between PA and improved sleep quality has been
reported amongst adolescents with obesity (n=20; mean age: 14.5 ± 1.5 years; body mass index: 34.0 ± 4.7 kg/m²) who participated in a 12-week exercise-training program (3 hours of exercise/week) (Mendelson et al., 2016). In this study, PSG data showed an increase in sleep efficiency from baseline (+7.6 per cent; effect size: 0.76; p = 0.028) (Mendelson et al., 2016).

The relationship between PA and sleep quality may be attributed to the increase in deep sleep (NREM-3) that has been associated with participating in regular PA (Driver & Taylor, 2000). One study reports that healthy adolescents who participate in PA for 3.5 hours per week spend a greater percentage of total sleep time in NREM-3 sleep compared to adolescents who engage in PA for less than 3.5 hours per week (37.4 ± 6.4 vs 29.3 ± 4.3 per cent of total sleep time; p<0.001) and have a greater sleep efficiency (95.19 ± 3.68 vs 94.72 ± 3.91 per cent; p<0.05) (Brand et al., 2010). Additionally, an experimental study in healthy adult males (mean age 27.1 ±1.3 years) has shown that sleep deprivation reduces free-living PA (Schmid et al., 2009), so it can be speculated that feeling more rested (from having better sleep quality) may allow adolescents to have more energy to participate in PA.

Surprisingly, there was no association between EDS and PA levels (both objective and self-reported) in adolescents with narcolepsy, for reasons that are unclear. Although of PA has been recommended for patients with narcolepsy to improve wakefulness due to its stimulating effect (K. Maski & Owens, 2016), evidence for this statement is lacking. There were also no associations seen between total sleep duration (measured by actigraphy) and PA levels. This may be because of pedometers were used as an objective measure of PA, which are unable to assess PA intensity. In the two studies assessing objective PA and sleep amongst healthy adolescents, an accelerometer was used to assess PA (Lang et al., 2013) (Gerber et al., 2014). Both studies reported that greater PA intensity is associated with longer sleep duration (Lang et al., 2013) (Gerber et al., 2014).
6.2.5 Family Functioning in Pediatric with Narcolepsy

PedsQL family impact module total, communication and worry subscale scores in this cohort of adolescents with narcolepsy were significantly lower than a community sample not seeking ongoing care for a medical condition (Medrano et al., 2013). PedsQL family impact module total scores may be significantly lower in the narcolepsy group compared to a community sample because of the greater burden associated with caring for a child with a medical condition, leaving less time for enjoyable activities (McClellan & Cohen, 2007).

PedsQL family impact module total, parent HRQOL, family summary worry and communication scores in the narcolepsy group were significantly lower than the traumatic brain injury group (e.g., skull/brain trauma, concussions) (de Kloet et al., 2015). PedsQL family impact module total scores may be significantly lower in the narcolepsy group compared to children and adolescents with traumatic brain injuries for various reasons. Firstly, pediatric narcolepsy is more rare than pediatric traumatic brain injury, and rare diseases receive less public awareness and support from health care teams as information on disease progression is limited (Dharssi, Wong-Rieger, Harold, & Terry, 2017). Lack of support and disease awareness may cause patients their families to feel misunderstood and isolated, which negatively impacts overall family functioning (Kippola-Paakkonen et al., 2016). Parents of pediatric patients with narcolepsy have reported relying on support from close family and friends, and that support from health care professionals is less common (Kippola-Paakkonen et al., 2016). Secondly, the disease course of narcolepsy varies greatly from traumatic brain injury. Narcolepsy is a chronic condition with no cure, unpredictable symptoms and limited treatment options (Kiran Maski et al., 2017). In contrast, a traumatic brain injury is the result of an acute adverse event, where the patient is recovering to a point where they may eventually lead the life of a healthy child (de Kloet et al., 2015). PedsQL Family Impact Module total scores in the narcolepsy group are similar to a pediatric chronic pain population, who experience a similar disease course of no cure, unpredictable symptoms and limited treatment options (Jastrowski Mano et al., 2011).

Scores in the worry domain of the PedsQL Family Impact Module were the lowest of all domains, and significantly lower than families with a traumatic and non-traumatic brain injury (de Kloet et al., 2015). The worry domain asks caregivers questions regarding anxiety about medical treatments efficacy, treatment side-effects, others reacting to their child’s illness, illness affecting
other family members and their child’s overall future (Varni et al., 2004). The low scores in the worry domain may be because caregivers of children with non-curative chronic conditions often experience a profound uncertainty with respect to their child’s future (Bally et al., 2018). Caregivers of children with chronic conditions have described feeling fearful, alone and powerless about their child’s diagnosis and ambiguity about their future health or overall future (Bally et al., 2018). It can be speculated that families with narcolepsy may worry about daily symptoms (e.g., EDS and cataplexy) interfering with productivity in the school setting, which would limit future educational opportunities (e.g., going to university) and further employment prospects. Parents of pediatric patients with narcolepsy have also reported worrying about the lack of resources available to help their child and their family in coping with the illness (Kippola-Paakkonen et al., 2016).

Family summary scores, which assess how daily activities and family relationships are affected by an illness (Varni et al., 2004), were also significantly lower than families with a traumatic brain injury (de Kloet et al., 2015). Caring for a child with a chronic condition may also put greater demands on a caregiver like taking time off work to take their child to routine clinic appointments, administering medication to their child which may impede daily routines (Herzer et al., 2010). Added stress and workload may also cause tension between family members, as one caregiver may feel a greater burden if responsibilities are not evenly distributed between parents (Herzer et al., 2010). Daily activities may require more effort and flexibility in families caring for a child with a chronic condition (Herzer et al., 2010). For example, in narcolepsy, caregivers may find it more challenging to get their child up and ready for school, due to sleep fragmentation and subsequent early morning fatigue.

These findings highlights how important it is for health care professionals to provide family-centered care to patients with narcolepsy. This can be also done in collaboration with services that offer support to the family (e.g., social work, child life specialists) who need to understand specific needs of the family and connect them to the appropriate resources (e.g., community centers with activities for the entire family).
6.3 Strengths and Limitations

This is the first study to evaluate and describe the relationship between sleep patterns, PA levels and depression and anxiety scores amongst adolescents with narcolepsy. This study also provides preliminary findings regarding the predictors of depression scores amongst adolescents with narcolepsy. Furthermore, this study uses both objective and self-report measures to assess sleep patterns and PA levels. Lastly, a control group was a part of the study to assess how having a diagnosis of narcolepsy affects sleep patterns, PA levels and depression scores.

However, this study has several limitations that require consideration. The sample size of the study population was small, and further large scale studies are needed to confirm these results. Also this study was powered to evaluate and compare the differences in depression scores (CDI-2 total scores) between adolescents with narcolepsy and controls, and not powered to evaluate if sleep patterns, EDS and PA levels are associated with depression scores.

The participants in this study were predominately male, so gender-specific effects of sleep patterns, PA levels and depression and anxiety scores could not be evaluated. Additionally, females typically report higher depression scores than males, so it is possible that depressive symptoms were under-represented in this cohort. We also did not match the control group for age and sex due to limited availability of participants. There was also a statistically significant difference between ages between the control group and the narcolepsy group where the control group was approximately one year older (14.9±1.5 vs 13.8±2.2 years; p=0.03) and being of older age has been reported to be associated with higher depression scores (Saluja et al., 2004). However the mean age of both groups were within a year of each other and limited to the early teen years. Also, the observational nature of this study may introduce a potential for bias, as variables such as sex, age and the presence of co-existing obesity have been reported to be associated with the exposure variables (sleep patterns and PA levels) as well as the primary outcome (depression scores). Additionally, it is likely that there are bidirectional relationships between the exposure and outcome variables in this thesis, which could not be assessed because data was only collected at one time point. Furthermore, it is unclear if patients had depressive symptoms/anxiety prior to their narcolepsy diagnosis as this data was not available. Additionally, depressive symptoms and anxiety were assessed by patient-report measures in this study and not through clinical interviews by a child and adolescent psychiatrist. Clinical interviews are necessary to identify external factors
(e.g., bullying, parents divorcing) that may contribute to depressive symptoms. The patient-report measures have been validated in pediatric populations, but not in patients with narcolepsy.

Moreover, actigraphy estimates sleep-wake cycles based on gross motor activity, but cannot differentiate sleep stages which can only be done using PSG. However, PSG can be burdensome for adolescents and their families, which could potentially influence recruitment bias. Also, PSG only provides information about sleep patterns on one night and are not performed in an adolescent’s natural sleeping environment. Another limitation was the use of pedometers for assessment of PA levels. Pedometers only provide a step count and do not describe the level of intensity PA was performed at. Future research on PA levels amongst adolescents with narcolepsy should consider the use of an accelerometer, to assess PA intensity. Also there may have been reporting bias in the pedometer tracking log, where the participant stated they wore the device throughout the day when they actually did not. Moreover, the use of self-report measures for PA may introduce recall and response bias, as patient may over/under estimate how much PA they participate in for reasons such as inaccurate memory and social desirability (Prince et al., 2008). Finally, using secondary data analyses for the comparison between family functioning scores is also a limitation, as group differences could only be evaluated in the studies that reported mean and standard deviation values of scores.
6.4 Future Directions for Research

Future research is needed to confirm and build on the findings of this study. Longitudinal studies assessing depressive symptoms from the time of disease onset throughout adolescence and adulthood is important to understand when depressive symptoms and anxiety begin and how they change over time. Longitudinal studies may also be useful in assessing the direction of the association (e.g., bidirectional) between sleep patterns, PA levels and depressive symptoms. It is also important to assess other factors that may be associated with depressive symptoms, such as pathophysiological features of narcolepsy (e.g., amount of time spent in REM sleep, hypocretin levels). Future studies should also include a qualitative component with structured interviews where adolescents with narcolepsy discuss how the condition impacts their mental health and psychosocial functioning, and the type of support they would like to receive from their caregivers and health care teams. Qualitative research can also be useful in understanding barriers adolescents with narcolepsy face to participating in PA. Finally, this thesis identified many patients with elevated depression and anxiety scores, so patients were referred on to services from adolescent medicine and child psychiatry for additional support. It would be interesting to assess what affect these services had on depressive symptoms and anxiety amongst adolescents with narcolepsy, and what strategies (e.g., pharmaceuticals, behavioural intervention) were most beneficial to patients.
References


AASM. (2014). *The American Academy of Sleep Medicine-International Classification of Sleep Disorders, Diagnostic and Coding Manual* (3 ed.).


Bauer, K. W., Yang, Y. W., & Austin, S. B. (2004). "How can we stay healthy when you're throwing all of this in front of us?" Findings from focus groups and interviews in middle schools on environmental influences on nutrition and physical activity. *Health Educ Behav*, 31(1), 34-46. doi:10.1177/1090198103255372


doi:10.1016/j.smrv.2015.07.004


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The Actiwatch-2 is a portable device, similar to a watch and is worn on the non-dominant wrist by a subject to measure gross motor activity over extended periods of time. With an internal sensor, the Actiwatch-2 can detect movement and translate this information to internal memory. Also with the light sensor and event marker, it has the ability to record events of significance (i.e. lights-out time). With these features, the Actiwatch-2 can provide objective measures of wake-sleep cycles in the natural home environment including sleep duration and sleep efficiency, providing an overall measure of potential sleep disturbance.
2. Omron HJ-720ITCCAN pocket pedometer

**Main Unit**

- **Display**
  - Displays the number of steps, number of aerobic steps, calorie, and distance.
  - Displays the time and the duration of aerobic walk.

- **RESET Button**
  - Press this button for more than 2 seconds to reset the data of today to 0.
  - Use this button to reset time, weight, and stride distance to the initial values when setting the unit.

- **MODE Button**
  - Use this button to repeat the display in the order of number of steps, number of aerobic steps, calorie, and distance.

**MEMORY/△ Button**

- Use this button to call up the data of seven days.
- Use this button to change time, weight, and stride distance when setting the unit.

**SET Button**

- Press this button for more than 2 seconds so that the screen will change to the setting display.
- Use this button to set time, weight, and stride distance.

- **Holder**
- **Strap**
- **Clip**
Contributions

A number of investigators contributed to the research work presented in this thesis. Dr. Shelly Weiss (pediatric neurologist), Allison Zweerink (sleep medicine nurse practitioner) were staff with expertise in pediatric sleep medicine who assisted in screening and recruiting eligible patients. Dr. Alene Toulany a staff pediatrician specializing in adolescent medicine who provides mental health support and resources to narcolepsy patients. Dr. Brian Murray was the adult neurologist who specializes in narcolepsy. Zihang Lu was the biostatistician that provided assistance with the statistical analysis for this thesis. Funding for this study was provided by the SickKids Research and Training Centre through the Restracomp Graduate Scholarship and Wake up Narcolepsy. Additional funding sources for Arpita Parmar included the travel grant from the SickKids Research and Training Centre.
## Supplementary Data

### Supplementary Table 1: Associations between Family Functioning and Mental Health in Adolescents with Narcolepsy

<table>
<thead>
<tr>
<th></th>
<th>PedsQL Family Impact Module Domains</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total Score</td>
<td>Family Summary Score</td>
<td>Parent Health-related Quality of Life Score</td>
<td>Worry</td>
<td>Communication</td>
<td></td>
</tr>
<tr>
<td>CDI-2 Total (Depressive Symptoms)</td>
<td>r</td>
<td>-0.140</td>
<td>-0.221</td>
<td>-0.064</td>
<td>-0.134</td>
<td>-0.069</td>
</tr>
<tr>
<td></td>
<td>p</td>
<td>0.461</td>
<td>0.242</td>
<td>0.36</td>
<td>0.479</td>
<td>0.718</td>
</tr>
<tr>
<td>SCARED Total Score (Anxiety)</td>
<td>r</td>
<td>-0.265</td>
<td>-0.270</td>
<td>-0.258</td>
<td>-0.212</td>
<td>-0.223</td>
</tr>
<tr>
<td></td>
<td>p</td>
<td>0.157</td>
<td>0.149</td>
<td>0.168</td>
<td>0.260</td>
<td>0.237</td>
</tr>
</tbody>
</table>

CDI-2: Children’s Depression Inventory 2nd edition  
SCARED: The Screen for Childhood Anxiety Related Emotional Disorders  
*p<0.05  
**p<0.01
Supplementary Table 2: Characteristics of Studies used in Secondary Data Analysis

<table>
<thead>
<tr>
<th>Author, Year of study and country</th>
<th>Population and Sample Size</th>
<th>Age (y)</th>
<th>Race (%White)</th>
<th>&gt;Post-Secondary Education (%Yes)</th>
</tr>
</thead>
</table>
| Medrano 2013 USA (Medrano et al., 2013) | Community  
N=726-901  
-Patients not seeking medical care recruited from community)  
*Sample size is a range because scores were only calculated on completed scales | 8.8±3.9  
37.4* | 82.9 | 60 |
| de Kloet 2015 Netherlands (de Kloet et al., 2015) | Traumatic Brain Injury*  
N=81  
-Skull/brain trauma  
-Concussion  
-Contusion cerebri  
-Neurological trauma | 13  
(range 5–22) | NR | 47 |
| | Non- Traumatic Brain Injury*  
N=27  
-Brain tumor  
-Meningitis/encephalitis  
-Stroke  
-Acute disseminated encephalomyelitis  
-Multiple sclerosis  
-Central nervous system demyelinating disease  
-Hypoxia-ischemia | | | |
<table>
<thead>
<tr>
<th>Study</th>
<th>Disease</th>
<th>N</th>
<th>Mean ± SD</th>
<th>Median</th>
<th>Patients recruited from hospitals not rehabilitation/treatment center</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jastrowski Mano 2011 USA (Jastrowski Mano et al., 2011)</td>
<td>Chronic Pain N=458</td>
<td></td>
<td>13.7±2.7</td>
<td>78</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>- Headache (34%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Musculoskeletal pain (26%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Abdominal pain (23%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Complex Regional Pain Syndrome (3%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Other (14%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(generalized pain, pain secondary to trauma, unclear pain diagnosis)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Patients were experiencing pain for at least 3 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vasiliki Matziou 2016 Greece (Matziou et al., 2016)</td>
<td>Cancer N=92</td>
<td></td>
<td>9.1 ± 4.1</td>
<td>15.2*</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>- Leukemia–lymphoma (18%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Solid tumors (7.3%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Others (8.2%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- On treatment (80.2%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Relapse (8.1%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Remission (11.6%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

All values reported as mean and standard deviation unless otherwise specified
NR-Not Reported
*% of patients in adolescent age range (10-18 years)
†Patients recruited from hospitals not rehabilitation/treatment center