Longitudinal sleep patterns of problematic and non-problematic infant sleepers

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A research project submitted in partial fulfilment of the requirements for the degree of Master of Osteopathy, Unitec Institute of Technology, 2014
Declaration

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This Research Project entitled “Longitudinal sleep patterns of problematic and non-problematic infant sleepers” is submitted in partial fulfillment for the requirements for the Unitec degree of Master of Osteopathy.

Candidate’s declaration

I confirm that:

• This Thesis/Dissertation/Research Project represents my own work;
• Research for this work has been conducted in accordance with the Unitec Research Ethics Committee Policy and Procedures, and has fulfilled any requirements set for this project by the Unitec Research Ethics Committee.
  Research Ethics Committee Approval Number: 2012-1074

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Abbreviations

ANOVA Analysis Of Variance
BISQ Brief Infant Sleep Questionnaire
CI Confidence Interval
CMPI Cow's Milk Protein Intolerance
FUI Fussy Unsettled Irritable [infant]
GORD Gastro-Oesophageal Reflux Disorder
ICC Intraclass Correlation Coefficient
IFCIDS Infant Fuss-Cry-Irritability with sleep Disorder Syndrome
IISMO Irritable Infant Syndrome of Musculoskeletal Origin
ISD Infant Sleep Disturbance
LSP Longest Sleep Period
LSRSP Longest Self Regulated Sleep Period
MDC Minimally Detectable Change
REM Rapid Eye Movement [sleep] or active sleep
NREM Non-Rapid Eye Movement [sleep] or quiet sleep
SD Standard Deviation
SE Standard Error
SED Standard Error of Difference
SEM Standard Error of Measurement
STTN Sleeping Through The Night
TST Total Sleep Time
TST24 Total Sleep Time over 24 hours
USA United States of America
WASO Wake After Sleep Onset
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Introduction

Sleep is a reversible period of behavioural quietude, characterised by disengagement and unresponsiveness to the surrounding environment (Carskadon & Dement, 2011; Zee & Hammond, 2007). During this period, essential physiological and behavioural functions occur. As a result, sleep can provide meaningful insight into the development of key regulatory functions such as feeding, crying, emotional development and behaviour maturation (Spruyt et al., 2008). Infants spend a significant portion of the first year asleep so it is concerning that sleeping problems have been estimated to affect approximately 30% of infants up to 2 years of age (France, Blampied, & Henderson, 2003; Gibson, Gander, & Elder, 2012; Sadeh, 2004; Teng, Bartle, Sadeh, & Mindell, 2012). In fact, infant sleep problems, or more commonly sleep deficit, have been associated with long term health problems, encompassing behavioural (Hemmi, Wolke, & Schneider, 2011; Spruyt, et al., 2008), temperamental (Spruyt, et al., 2008), and physical difficulties (Sekine et al., 2002). However, it is often the parents who suffer more from disturbed sleep than the infants themselves, leading to mental health problems (Meltzer & Montgomery-Downs, 2011) and poor physical health for the parents (Bayer, Hiscock, Hampton, & Wake, 2007). Therefore, when an infant is presented to health professionals with reported sleeping difficulties, the degree of objective sleep deficiency in the infants compared to disruption to parents may be difficult to assess.

Currently, research into the differences between problematic and non-problematic infant sleepers in the first 12 months of life is scarce and limited to a few cross-sectional studies. Thus the aims of this thesis are to longitudinally record problematic infant sleep patterns between 3 and 13 months and compare them with their non-problematic counterparts; and to examine the relationships between pregnancy, birth and feeding characteristics with problematic infant sleep.

This thesis consists of three sections: Section 1 is a literature review that provides an overview of sleep physiology, normal infant sleep, problematic infant sleep, and possible treatment options. Section 2 of the thesis is a manuscript presented in accordance with the guidelines for authors for submission to the journal Sleep and Biological Rhythms [see Appendix G]. Section 3 is the appendices, which contains supplementary material.
Section 1: Literature Review
1 Sleep Physiology

Sleep is a reversible state of behavioural quietude that is achieved through disengagement with the surrounding environment and which decreases motor activity to allow for numerous physiological processes to occur (Carskadon & Dement, 2011; Zee & Hammond, 2007). Intrinsic to human culture is the clear differentiation between sleep and wake states of arousal. The acknowledgement that the sleep state is vital to growth and optimal function is a belief firmly entrenched within our psyche (Owens, 2005). Sleep comprises two distinct states, rapid eye movement (REM) sleep and non-rapid eye movement (NREM), which allows different and relatively incompatible processes to occur. Within an infant population, REM sleep is often referred to as active sleep, and NREM as quiet sleep. Active sleep is associated with rapid bursts of eye movement, increased neurological activity and generalised muscle atonia, although bursts of muscular twitching can also occur periodically. Physiologically, active sleep exhibits increased sympathetic tone, increased blood flow to the brain, increased glucose use, irregular breathing patterns, diminished reflexes and depressed thermoregulation when compared to quiet sleep (Carskadon & Dement, 2011; Sheldon, 2005b; Zee & Hammond, 2007). Quiet sleep, by contrast, displays several stages of sleep depth along a progressive continuum with decreased neurological activity and muscle relaxation from one stage to the next. Physiologically within this sleep state, parasympathetic activity dominates showing a decrease in metabolic rate whilst thermoregulation is unaffected, in contrast to active sleep (Giglio, Lane, Barkoukis, & Dumitru, 2007; Sheldon, 2005b; Zee & Hammond, 2007).

Sleep patterns undergo age-related changes, moving from fragmented frequent sleep bouts in infants, to more distinct sleep stages that eventually consolidate into fewer longer sleep periods in adults. In adults, for example, sleep cycles are approximately 90 to 120 minutes whereas, in infants, it is 50 to 60 minutes in duration. A sleep cycle is the progression from quiet or NREM sleep to the first bout of active or REM sleep (Carskadon & Dement, 2011; Zee & Hammond, 2007). Often, infant sleep cycles show short periods of semi-waking after the active sleep phase, these partially awake periods are often unnoticed by parents (Terman & McMahan, 2012). Complete awakening from sleep states has been shown to have a lower threshold in adults for meaningful stimuli, such as hearing their own name spoken, compared with insignificant verbal cues (Carskadon & Dement, 2011). Although unverified in an infant population, it could be possible that a similar distinction in the waking effect of different sounds would occur in this age group too.

Sleep-wake cycles are regulated through sleep pressure, circadian rhythms and environmental factors. Sleep pressure or sleep homeostasis refers to the need to sleep, which occurs in response to increased wake time, decreased sleep time, increased likelihood of sleep onset and increased sleep time once sleep occurs. The increase in sleep pressure causes
compensatory changes in sleep depth and duration of NREM sleep (Terman & McMahan, 2012; Zee & Hammond, 2007). Circadian rhythms are the inherent biological rhythms that affect sleep, temperature and melatonin secretion. In humans, the circadian rhythm is slightly longer than 24 hours and synchronisation occurs with environmental cues, primarily light exposure (Zee & Hammond, 2007). Physical activity is also shown to have effects on melatonin levels, particularly in the evening periods where it can blunt rising levels in adults but it is still an emerging area within sleep research (Atkinson, Edwards, Reilly, & Waterhouse, 2007; Barger, Wright Jr., Hughes, & Czeisler, 2004). These circadian rhythms progressively develop within an infant’s first 6 months of life, although the sleep cycle is the last to regulate itself (Herman, 2005). The strength of the circadian rhythm increases over the first year to reach adult levels. These rhythms are determined to be in phase if they match up to social norms regarding appropriate sleep-wake times. By approximately 2 months of age, infants start showing regulation to light and social environment, while at 6 months sleep stages typically show similar organisation to adults (Herman, 2005).

1.1 Measuring Sleep

Traditionally, polysomnography has been used to measure sleep and is referred to as the ‘gold standard’ by the American Academy of Sleep Medicine (2005). Polysomnography measures the biophysical changes that occur during sleep through electrocardiogram, electroencephalogram, electrooculogram and respiration usually within a sleep laboratory. Within an infant population, polysomnography is often impractical and invasive so parental sleep diaries are regularly used as the reference standard (Morgenthaler et al., 2007). More recently, the use of actigraphs has increased, in an attempt to capture objective data when polysomnography is unavailable.

An actigraph is an accelerometer that measures magnitude and total volume of movement over a specific duration (epoch), usually of one minute. These points of data are scored via pre-set activity thresholds into sleep-wake patterns via specific algorithms, enabling the quality and quantity of sleep to be estimated (Cliff, Reilly, & Okely, 2009; Littner et al., 2003; Sadeh, 2011). The question of accuracy amongst the numerous models of actigraph available and consistency amongst research studies has raised concerns, particularly as sleep states are frequently over-estimated and wake is underestimated (Cellini, Buman, McDevitt, Ricker, & Mednick, 2013; de Souza et al., 2003; Meltzer, Walsh, Traylor, & Westin, 2012; Sadeh, Mindell, & Owens, 2011). Although the actigraph has systematic errors when measuring sleep states, monitoring participants for a minimum of five days is recommended to allow a more reliable average to be calculated and decrease daily variability (Acebo et al., 1999; Sadeh, 2011).

Sleep diaries are completed by parents or caregivers for their infant and typically involve recording the times that the infant goes to sleep, times the infant wakes up, crying bouts, times of meals and method of feeding as well as any disruption in routine such as illness or a social
event (Morgenthaler, et al., 2007; Sadeh, 2011; So, Adamson, & Horne, 2007). Given that sleep diaries are subjective, there are inherent limitations such as their accuracy and the motivation of the parent to complete the diary. They also need increased time for instruction as well as follow up and processing of information which can vary depending on the detail required for the sleep diary (Thomas & Burr, 2009). However, when completed correctly, sleep diaries provide a good insight into sleep patterns and are better than parents having to recall events where accuracy can be dubious (Richardson, 1994). Sleep diaries can either be in paper or electronic format, which has been found to make no significant difference in variables when compared with actigraph assessment of infant sleep; although parents seemed to be less compliant in completing an electronic diary even though it was the preferred format (Muller, Hemmi, Wilhelm, Barr, & Schneider, 2011).

Questionnaires are another tool commonly used to assess sleep patterns. Critical evaluation of current questionnaire tools was conducted by Spruyt and Gozal (2011) who determined that few were subject to all the methodological steps required. Of those pertaining to infants, only one, the Brief Infant Sleep Questionnaire (BISQ) was designed for use within a younger population, with infants ranging from newborn to 36 months of age. The BISQ was subject to reliability and validity testing through test-retest (two weeks apart), sleep diary and actigraphic measurement agreements (Sadeh, 2004). Although Spruyt and Gozal (2011) have determined that there has been no pilot study, item analysis or structure review on the questionnaire, it has been given a ‘well-established’ evidence-based assessment rating within the Society of Paediatric Psychology Assessment Task Force criteria by Lewandowski, Toliver-Sokol and Palermo (2011). The BISQ questionnaire has subsequently been used in several large internet based studies to ascertain infant sleep patterns (Mindell, Sadeh, Wiegand, How, & Goh, 2010; Sadeh, Mindell, Luedtke, & Wiegand, 2009; Teng, et al., 2012)

1.1.1 Sleep Variables
Numerous sleep variables are used to define and understand sleep-wake patterns. It has been noted that there is variability between the definitions used by different researchers that can create problems when comparing studies, particularly with actigraphy (Meltzer, Montgomery-Downs, Isana, & Walsh, 2011). In an endeavour to combat this, Meltzer, Montgomery-Downs, Isana and Walsh (2011) propose the following definitions for sleep variables: total sleep time (TST), the total amount of sleep within a set period usually daytime, night-time or 24 hours; longest sleep period (LSP), time from sleep onset to waking measured objectively; wake after sleep onset (WASO), amount of time spent awake within a sleep period; night waking, number of wakes (greater than 5 minutes) within the night sleep period. Additionally, Henderson, France, Owens and Blampied (2010) have put forward longest self-regulated sleep period (LSRSP), as a measure of the longest period of sleep, sleep and self-soothe or behavioural quietude that is terminated by signalling such as crying or calling out, as measured via sleep
Sleeping through the night (STTN) is another common variable reported in infant sleep studies due to its social validity. STTN is traditionally defined as sleeping between 2400 – 0500 with no wakes for six of seven nights (Moore & Ucko, 1957) but more recently as 2200 – 0600 with no wakes by Henderson, et al., (2010).
2 Normal Infant Sleep

2.1 Total sleep time

Infants require a considerable amount of sleep. This is reported to be between 14 to 15 hours per day over the first year of life (Terman & McMahan, 2012). Similarly, Galland, et al. (2012) indicate that infants have an average of 14.6 hours of total sleep per day (TST24) between newborn and 2 months, decreasing to 12.9 hours per day at 12 months of life within a sizable range of 8.8 – 20.0 hours (95% confidence interval (CI)). Although mean values of TST24 at 6 months and 12 months stay the same at 12.9 hours per day, the data variability decreases from 8.8 – 17.0 hours at 6 months to 10.1 – 15.8 hours at 12 months. These reference values from Galland, et al. (2012) are derived from a systematic review and meta-analysis of 21 infants studies (both cross sectional and longitudinal) performed between 1990 and 2010 involving sleep diaries and questionnaires. The quality of these articles was assessed using a modified Downs and Black quality index. Statistics were calculated using weighted inverse variance, mean, standard deviation and standard error; additionally 95% CI were calculated to provide overall age range conclusions. The review also plotted TST24 against age, with a regression line that showed a decrease of 10.5 minutes per month for infants newborn to 6 months of age, which altered to a decrease of 5.4 minutes per month from 7 to 12 months of age (Galland, et al., 2012). These figures should be interpreted with caution, as large CI’s demonstrate the data was highly variable. Some of this variability may be attributed to the amalgamation of multiple cross sectional studies rather than longitudinal studies, hence changes in the same infant are unclear and differences with age may have been affected by the integration of studies.

Higher averages and larger ranges were reported for TST24 from longitudinal study conducted in Switzerland by Iglowstein, Jenni, Molinari, and Largo (2003). A cohort of 493 participants completed sleep-related questionnaires through structured interviews at 1, 3, 6, 9, 12, 18, and 24 months of age, then annually until 16 years. Higher TST24 averages were found for 6, 9, and 12 months (14.2 hours, 13.9 hours, 13.9 hours respectively) when compared with the reference values proposed by Galland, et al., (2012) in addition to smaller ranges of variability (95% CI ranges: 12.3 – 16.1 hours at 6 months; 12.2 – 15.6 hours at 9 months; 12.7 – 15.1, hours at 12 months) (Iglowstein, et al., 2003). Data were unavailable for the 1 month and 3 month age groups. The authors report that the data fitted a normal distribution, although the variability over the first 12 months was high. Unfortunately, reliability of this data collection method is not currently available. Interestingly, the authors reported a cohort effect whereby the babies in the earlier cohort (1974) demonstrated longer sleep times than those in the later cohort (1986) (Iglowstein, et al., 2003). The authors observed that this occurred due to the later sleep onset reported in the later cohort but similar wake times in both groups.
Several large web-based studies have been conducted in the United States of America (USA) and Canada (Sadeh, et al., 2009), among predominantly Asian countries (Mindell, et al., 2010) and in Australia and New Zealand (Teng, et al., 2012). Using an expanded version of the BISQ, each study has sought to characterise the sleep patterns of infants from newborn to 36 months of age. Questionnaires were predominantly displayed to participants via a popup window when visiting a popular baby website, with sample numbers as follows: 5006 participants for Sadeh, et al. (2009), over 29,000 for Mindell, et al. (2010) and 2154 recruited for Teng, et al. (2012). All studies found respondents were skewed toward those with higher education qualifications and higher socioeconomic status, limiting external validity and thus generalisability of the findings to the population at large. The results from the USA show TST24 decreases with age from 13.3 ± 2.0 (mean ± SD) hours for infants between 3 to 5 months of age to 12.8 ± 1.7 hours for infants between 9 to 11 months of age (Sadeh, et al., 2009). In comparison, the infants from Australia and New Zealand showed higher averages for TST24, with 13.8 ± 1.95 hours at 3 to 5 months, and 13.3 ±1.6 at 9 to 11 months of age (Teng, et al., 2012).

In the larger Internet survey conducted by Mindell, et al. (2010), the data collected was used to compare sleep characteristics of infants from predominantly Asian countries, such as Japan, China, Thailand, Korea, and Malaysia with predominantly Caucasian countries such as Australia, New Zealand, United Kingdom and USA. Considerable differences were shown between the populations. The infants from Asian countries had less total sleep than their Caucasian counterparts; TST24 averages ranged from 11.6 hours (Japan) to 13.3 hours (New Zealand) over all countries (Mindell, et al., 2010). The authors suspect this difference in TST24 to be related to the later bed times that are also reported for infants in Asian countries (19:27 for New Zealand compared to 22:17 for Hong Kong). This claim is supported by McDonald, Wardle, Llewellyn, van Jaarsveld and Fischer (2014) who also reported ethnic minorities have later bedtimes than Caucasian infants.

There are several limitations to conclusions drawn from these Internet based samples. Researchers are unable to control who the responder is and the degree of selection bias between regions is difficult to assess. Similarly, responders may complete the survey more than once. It is not clear in these studies whether infants have any medical conditions that may affect sleep. Similarly, the infants who were classified as problematic sleepers were not excluded from the data set, quite possibly leading to a higher range of variability than otherwise expected. For surveys in which problematic sleeping was specifically addressed, the variability of definitions for problematic sleep may have differed markedly between countries or cultures. With these limitations, the information collected has helped to provide reference norms for infants’ sleep from newborn to 36 months of age. This is important information as few studies have contributed to sleep data for infants between 7 and 11 months old (Galland, et al., 2012).
2.2 Age-Related Changes

As infants age, several changes are noted in their sleep patterns. In particular, daytime sleep decreases in conjunction with daytime naps while night-time sleep increases as a result of circadian rhythm development (Terman & McMahan, 2012). Reference values proposed by Galland, et al. (2012), are amalgamated from five studies, reporting 3.1 naps per day for infants newborn to 5 months which decreases to 2.2 naps per day between 6 and 11 months of age. The range (95% CI) of daytime naps was quite large at 1.2 – 5.0 naps per day for the younger infants but narrowed to 0.9 – 3.5 naps per day for the older infants. The limited number of studies and the wide age bands that contributed to these figures indicate they should be interpreted with caution. In contrast, Iglowstein, et al. (2003) did not report the frequency of daily naps but instead reported the percentage of the participants who still undertook naps. All infants reported daytime naps over the first year, which slowly decreased to 50% of participants at 3 years of age, and terminated at 5 years old. This finding agrees with Galland, et al. (2012), who reported that most infants ceased daytime naps between 3 to 5 years old. Iglowstein, et al. (2003) also reported that daytime sleep reduced from of 3.4 ± 1.5 (mean ± SD) hours per day at 6 months to 2.4 ± 1.1 hours per day at 12 months. Reference values for daytime sleep were not reported by Galland, et al. (2012).

Many studies have used the expanded BISQ questionnaire to characterise infant sleep patterns, which show consistent patterns regarding age related changes. Decreases in daytime sleep are noted across all of the studies, with similar results across age groups. For example, Sadeh, et al. (2009) reported averages of daytime sleep as 3.8 ± 1.6 (mean ± SD) hours for infants 3 to 5 months, 3.0 ± 1.2 hours for infants 6 to 8 months and 2.8 ± 1.0 hours for infants 9 to 11 months in the USA and Canada. Comparatively, Teng, et al. (2012) reported very similar daytime sleep durations of 3.8 ± 1.6 hours for infants 3 to 5 months, 3.1 ± 1.1 hours for infants 6 to 8 months and 2.7 ± 1.0 hours for infants 9 to 11 months in a population of Australian and New Zealand infants. The average number of daytime naps decreased from 3.09 naps per day to 2.04 between 3 and 11 months for Australian and New Zealand infants (Teng, et al., 2012), similar to American and Canadian infants who reported 2.93 naps per day reduced to 2.02 for the same period (Sadeh, et al., 2009). Mindell, et al. (2010) reported minimal differences when comparing daytime sleep and daytime naps between Asian and Caucasian countries. The consistent decrease in infant daytime naps between countries, has led researchers to speculate that there is a strong biological component to daytime sleep and the cultural variations and differences in sleep ecology (bed location, position, routine) do not make a difference (Mindell, et al., 2010).

2.3 Sleep Consolidation
Sleep consolidation is the term used to describe the progress infants make from short frequent bouts of sleep to longer sleep periods with fewer night wakes. Sleep consolidation is based on three measures: the duration of the longest sleep period, the duration of night wakefulness and the number of night wakes (Sadeh, 2004). Most authors consider sleep consolidation to occur in the first 4 months, with a period of relative stability from 5 to 9 months (Henderson, France, & Blampied, 2011; Henderson, et al., 2010). Although others suggest it occurs as young as 2 months (Moore & Ucko, 1957) and as old as 6 months particularly if infants are still requiring feeding (France & Hudson, 1993). Sleep consolidation is a change related to circadian development, but focused more specifically on elongation of night-time sleep periods which align with parental and social norms (Terman & McMahan, 2012).

Traditionally, the longest sleep period (LSP) has been used to determine how the infant’s circadian rhythm is maturing. It is a common measure in infant sleep research but can only be measured accurately through polysomnography, videosomnography or actigraphy (Henderson, et al., 2011). Once sleep consolidation is achieved, it becomes a redundant variable. Galland, et al. (2012), found only four studies that complied with the modified Downs & Black index for quality regarding assessment of LSP. The results of these amalgamated studies report an average of 5.7 hours of sleep for younger infants (newborn to 5 months) compared to 8.3 hours for the older infants (6 to 24 months). These studies used subjective measures (sleep diary and questionnaires), which may be less reliable as parents are not always aware of night wakefulness if the infant does not cry or call out compared to objective measures.

Reference standards pertaining to sleep consolidation measures were evaluated in a review by Henderson, et al. (2011). Articles were not limited by publication age, but were required to include typically developing infants up to 12 months old with sleep variables recorded in time units to enable comparisons. Twenty-six studies were identified, although only seven were used to calculate LSP reference values; a mixture of cross sectional (with multiple age bands) and longitudinal designs. The greatest period of change occurred in the first 3 months of age, with sleep periods increasing from an average of 3.6 ± 1.2 (mean ± SD) hours at 1 month to 5.5 ± 1.5 hours at 3 months. Between 3 to 12 months of age, sleep periods displayed a marginal increase from 5.5 ± 1.5 hours to 5.7 ± 1.98 hours respectively, indicating a considerable period of plateau in LSP development (Henderson, et al., 2011).

Recently, the longest self-regulated sleep period (LSRSP) has been proposed by Henderson, et al. (2010) to address the issue of parental perception accuracy. The LSRSP is the longest sleep period with nocturnal waking where the infant self-soothes and reinitiates sleep. The LSRSP is measured through videosomnography, sleep diaries and questionnaires. The term LSRSP is a much better descriptor for behavioural development and more relevant to parents and health professionals who interact with infants. While there certainly is some variability within the age
bands, LSRSP follows the same developmental trajectory as LSP. Reference values for LSRSP proposed by Henderson, et al. (2011) showed the greatest increase between 1 and 4 months from 7.0 ± 2.0 hours to 9.1 ± 2.1 hours. Between 4 and 9 months data plateaus, with infants receiving between 10.0 ± 1.8 hours to 9.8 ± 2.2 hours of sleep, which then demonstrates an increase to 10.3 ± 1.9 hours at 12 months. It is difficult to accurately ascertain how sleep progresses in older infants, as many of the monthly averages have limited data.

Another variable that helps to assess sleep consolidation, and is important to familial dynamics is 'sleeping through the night' (STTN). Sleeping through the night has been variously defined as behavioural quietude from 24:00 – 05:00 (Moore & Ucko, 1957) or extended to 22:00 – 06:00 (Henderson, et al., 2010) to comply with familial social expectations around sleep. A higher observance of sleeping through the night using the 24:00 – 05:00 definition has been reported to be attained by 67 to 81% of infants at 4 months, and 44 to 87% at 12 months (Moore & Ucko, 1957). Similar rates of adherence have been reported by Henderson, et al. (2010) over the 22:00 – 06:00 period, with 47% of infants sleeping over the longer period at 4 months and 73% at 12 months.
3 Problematic Infant Sleep

Defining problematic sleep can be difficult, as there is a broad range of sleep behaviours. There is no clear consensus as to how best define problematic sleep, thus this section endeavours to look at objective definitions, subjective definitions and regulatory problems. Objective definitions have set criteria, often with age specific reference ranges; subjective definitions allow parents to determine whether their infant’s sleep is problematic; while regulatory syndromes often encompass sleep problems in conjunction with other issues. Feeding methods are also discussed briefly, as they have been reported to be associated with problematic infant sleeping patterns.

3.1 Objective or Clinical Sleep Disorders

Objective or clinical sleep disorders are identified through a set of structured diagnostic criteria. Disorders can be primary, where the main problem is a specific sleep disorder, or secondary, which is a result of another medical condition such as a respiratory disorder or treatment (Thorpy, 2011). There are two classification systems, the International Classification of Sleep Disorders (American Academy of Sleep Medicine, 2005) and the Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association, 2013). Both classification schemes broadly categorise disorders into insomnia (or dyssomnia), hypersomnia, and abnormal sleep behaviours. A specific classification scheme for toddlers has been developed by Gaylor, Burnham, Goodlin-Jones and Anders (2005) in conjunction with the Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association, 2013).

Insomnia is recurrent difficulty with sleep onset and maintenance in conjunction with increased night wakefulness. It is often associated with behavioural problems or psychiatric disorders and may be a side effect of various medications. Within an infant population, circadian rhythm disorders create persistent misalignment to parental sleeping patterns, which are often perceived as infant insomnia by parents (Kryger, 2005; Thorpy, 2011). Insomnia can also be classified as a disorder of initiating and maintaining sleep in a childhood population (Sheldon, 2005a).

In contrast, hypersomnia is excessive sleepiness during the daytime that is often noticed as infant (or child) irritability or hyperactivity by parents. Hypersomnias cause daytime sleepiness without disturbance of night-time sleep or circadian rhythm. Sleep apnoea is a sleep-related breathing disorder that is associated with REM suppression and causes hypersomnia (Kryger, 2005; Thorpy, 2011).
Abnormal sleep behaviours primarily encompass movement disorders (such as restless leg syndrome) and parasomnias (unwanted physical or experiential events that accompany sleep). Broadly speaking, this type of sleep behavior can affect movements, behaviours, emotions, perceptions or nervous system functioning during the sleep period (Kryger, 2005; Thorpy, 2011).

Another definition proposed for infants suffering sleep problems between 6 and 24 months is Infant Sleep Disturbance (ISD) (Blunden, Thompson, & Dawson, 2011; France, et al., 2003; France & Hudson, 1993). This diagnosis is proposed by psychologists and encompasses many symptoms of problematic sleep such as frequent night waking with crying or signalling, delayed or difficult sleep onset and night-time co-sleeping that is unwanted by parents. Unfortunately, ISD is not a common diagnostic term within the literature.

Regardless of diagnosis, as sleep patterns become altered the type of sleep (active or quiet sleep), sleep length and frequency of night wakes alter (Thorpy, 2011). The most common disorder to affect infants is a form of insomnia, labelled protodysonmia that can affect both sleep initiation and maintenance during the night-time period. Generally, these disorders are not diagnosed until the infant is 12 months or older, so that it is clear that it is not a transient sleep problem or delayed maturation of circadian rhythm (Anders & Eiben, 1997; Gaylor, et al., 2005). A study by Gaylor, et al. (2005) consisted of 83 infants, and followed the relationship between non self-soothing infant behaviour at 6, 9, and 12 months monitored by videosomnography, with follow up phone interviews at 2, 3, and 4 years of age. Infants described as non self-soothing (problematic) at 6 months of age, were shown to have continued sleep problems, with the incidence of protodysonmia ($p=0.05$) and co-sleeping ($p= 0.001$) continuing to be significant at 2 years of age (Gaylor, et al., 2005).

### 3.2 Regulatory Syndromes (with sleep involvement)

Regulatory problems often occur in infancy with the maturation of the central nervous system, encompassing sleeping problems as well as crying and feeding problems or regulation of these functions (Ednick et al., 2009). One of the most commonly known regulatory problems is colic. As both Viedma-Dodd (2006) and Miller (2007) point out, colic is a widely encompassing term that is often a diagnosis of convenience with overlapping symptoms. In response to the vague nature of the term colic, many other health professionals have developed alternative terms to describe the varied collection of signs and symptoms infants may present with or experience in the first year of life. These include such terms as fussy unsettled irritable (FUI), irritable infant syndrome of musculoskeletal origin (IISMO) infants, and gastro-oesophageal reflux disorder (GORD).
The classic definition of colic is known as the “rule of threes” describing episodes of irritability, fussing or crying lasting for more than 3 hours per day, occurring more than 3 days per week, for more than 3 weeks in a healthy infant (Wessel, Cobb, Jackson, Harris Jr, & Detwiler, 1954). Onset is usually in the second or third week post partum, with bouts of crying most common in the evening, that disappear for about 50% of infants at 2 months of age and for the majority at about 4 months of age (Helseth & Begnum, 2002; Weissbluth, 2005). The aetiology of colic is currently not understood, but gastrointestinal disturbance, autonomic nervous system imbalance, temperament, and serotonin/melatonin imbalances are all speculated to be causative factors (Helseth & Begnum, 2002). While infants who have colic have reduced sleep during the first 3 months when compared with other infants of the same age, it has been shown that by 6 months and older, there is no significant difference between these populations’ total sleep time (Weissbluth, 2005). Several authors have also speculated that parents can inadvertently develop parenting styles that reinforce fussy behaviours, thus encouraging poor sleep hygiene habits to persist for longer than 4 months (Helseth & Begnum, 2002; Weissbluth, 2005).

The alternative terms of FUI infant and infant fuss-cry-irritability with sleep disorder syndrome or inefficient feeding crying infant with disordered sleep (IFCIDS) are proposed to reflect the presenting symptoms. Both of FUI and IFCIDS present with excessive fussiness, feeding problems, parental attachment problems, difficulty sleeping and inconsolable crying (Miller, 2007; Viedma-Dodd, 2006). In addition, it was noted by Viedma–Dodd (2006) that the descriptions “fussy”, “unsettled” and “irritable” were used as descriptors of colic, gastro-oesophageal reflux, temperamental difficulty or sensitivity, or as a mature “non-cry” type of distress. The crying pattern of these infants is more varied rather than predominantly in the late afternoon or evening (Miller & Newell, 2012). Irritable infant syndrome of musculoskeletal origin is another descriptive variant proposed by Miller (2007) in which infants who are subject to pain, discomfort or protective postures often present with crying, restless sleep, suckling or feeding difficulty and difficulty resting supine. The course taken by IISMO is commonly reported to be between 3 weeks and 3 months of age (Miller & Newell, 2012).

Feeding disorders are common and include reflux, GORD, cow’s milk protein intolerance (CMPI) and IFCIDS. Reflux occurs when the oesophageal sphincter relaxes allowing milk to be regurgitated. It presents with frequent vomiting or regurgitation, poor weight gain, abdominal pain and the infant is often fussy or unsettled (Omari et al., 2002). Reflux often occurs because of the frequency of infant feeding and usually stops between 6 to 12 months of age. Similarly, infantile GORD has comparable symptoms to reflux, but is much more severe with persistent regurgitation, feeding refusal, difficulty breathing, and sleep disturbance (Sherman et al., 2009). Cow’s milk protein intolerance presents with the key signs of food intolerance, such as vomiting,
pruritus, erythema, bloodstained stools along with failure to thrive and crying. Miller (2007) reports that CMPI is linked to sleep difficulty and suggests food be removed or changed to reduce symptoms. A large epidemiological study conducted in the Netherlands of 1158 infants, indicates that true CMPI is rare, with an incidence rate of 2.8% in this Northern European population (Schrander et al., 1993), which may be different in other cultures with shorter agriculture history. Further studies have indicated that CMPI may be associated with GORD at a rate of 41.8% in infants who present with GORD symptoms (Icano et al., 1996). Another disorder proposed by Miller and Newell (2012) is IFCIDS which is typically seen in infants aged newborn to 6 months (although it may be up to 12 months), with frequent crying, pained faces, general irritability, difficulty falling to and maintaining sleep.

3.2.1 Infant Feeding Methods

Given the propensity for feeding problems to be associated with sleep problems, it is important to understand this aspect of infant care. Current New Zealand Ministry of Health (2013a) and World Health Organisation (2001) recommendations encourage exclusive breastfeeding until 6 months of age, with the addition of complementary foods thereafter. Within a New Zealand context, many women, regardless of ethnicity, are particularly keen to breastfeed as it is nutritionally sound, nurturing, convenient, easy and cheap (Abel, Park, Tipene-Leach, Finau, & Lennan, 2001). It has been reported in a New Zealand study by Heath, Tuttle, Cleghorn and Parnell (2002) that while 88% of mothers started exclusively breastfeeding on discharge from hospital, only 42% were exclusively breastfeeding at 3 months, and 34% were breastfeeding in conjunction with solids at 12 months. Most breastfed babies need between 8 to 12 feeds per 24 hours (Shealy, Scanlon, Labiner-Wolf, Fein, & Grummer-Strawn, 2008), while formula fed infants feed 6 to 8 feeds per 24 hours (Ministry of Health New Zealand, 2013b). Breastfed babies usually feed at least every 6 hours while most formula fed infants feed about every 7 hours with most feeding sessions lasting for less than 30 minutes regardless of feeding type (Shealy, et al., 2008). While there are several types of infant formula, the majority are derived from cow’s milk with modifications particularly to milk proteins to enable easier digestion in the infant gut, although it still takes longer to digest than breast milk (Johnston, 2010). It is a commonly held public belief that formula feeding helps infants sleep through the night, as it takes longer to digest (Abel, et al., 2001).

3.3 Subjective Sleep Definitions

Subjective sleep definitions are typically based on parental perception of what defines problematic sleep and this determination is likely to be influenced by culture and context. Mindell, et al. (2010) provide an interesting insight into the different cultural perception between predominantly Asian countries and Caucasian countries, showing that Asian parents are more likely to view their child as having a sleeping problem (52% versus 26% respectively). These
figures are based on the answer from parents to the question, “How would you describe your infant’s sleep?” with possible answers including “no problem”, “a small problem” and “a serious problem”. Further analysis shows these findings could be related to bedtime difficulties or whether the child exhibited long quiet periods and therefore appears to have slept well (Mindell, et al., 2010).

Current literature on the difference and development of problematic sleep patterns in infants is scarce. Gibson, et al. (2012) documented the difference between parentally-described problematic and non-problematic infant sleepers at 12 months of age. This study demonstrated a difference of 0.7 hours less night-time sleep for problematic infant sleepers compared with non-problematic infant sleepers in both actigraph, sleep diary and BISQ measures (Gibson, et al., 2012). This finding is in agreement with Sadeh (2004), who documented a difference of 0.76 hours less night-time sleep in clinical (problematic) compared to control (non-problematic) infants. This lower duration of night-time sleep was shown to significantly affect the total amount of sleep of the problematic sleepers (compared to non-problematic) in the Gibson, et al. (2012) study although the difference in total sleep between clinical and control groups was not significant in the Sadeh (2004) study. Nonetheless, Sadeh (2004) did report that the number of night wakes was higher in problematic compared to non-problematic sleepers (4.98 versus 1.83 times per night), and subsequent time spent awake was increased (1.05 versus 0.34 hours) (Sadeh, 2004). One difficulty with the interpretation of results from the Sadeh (2004) study is that it is unclear whether these comparisons were corrected for age, or if they were averages from the whole population. It is important that comparisons are made within age ranges, given the rapid rate of change in infant sleep patterns particularly over the first 6 months. If these infants are grouped more widely, smaller changes may not be detected between the groups, particularly as problematic sleepers are likely to be younger than non-problematic. The lack of data that clearly indicates whether there is a difference in sleep parameters between problematic and non-problematic sleepers is starting to be addressed through more recent studies utilising the BISQ (Mindell, et al., 2010; Sadeh, et al., 2009; Teng, et al., 2012).

Further studies have performed stepwise regression analysis to determine the variables associated with problematic sleep. Predictors of an infant’s sleep pattern being labelled problematic include an increased frequency of night wakings, difficulty putting the infant to sleep, decreased sleep period length, shorter daytime sleep and a younger infant (Sadeh, et al., 2009). Additionally, Gibson, Gander & Elder (2012) have found that frequent night wakings associated with breastfeeding and night wakefulness of more than 20 minutes are also predictors of problematic sleep descriptions. Putting the infant to bed asleep and co-sleeping, have been associated with more fragmented night-time sleep in a community sample of 9 month old infants (DeLeon & Karraker, 2007).
In addition, infants identified by their parent as having a difficult temperament particularly before bed, or who suffered separation distress were more inclined to have less sleep (and be labelled) problematic sleepers (DeLeon & Karraker, 2007; Gibson, et al., 2012). Irritability can be one sign of behavioural dysregulation, which has been associated with sleeping difficulties (DeLeon & Karraker, 2007). Conversely, infants that were deemed approachable or had an easy temperament, were more likely to have increased sleep duration (both night-time and 24 hour) at 3 and 6 months in a study of 20 healthy infants (Spruyt, et al., 2008). Ethnic minorities have been shown to have shorter sleep duration when compared with caucasian infants (McDonald, et al., 2014; Mindell, et al., 2010; Nevarez, Rifas-Shiman, Kleinman, Gillman, & Taveras, 2010). Both McDonald, et al. (2014) and Nevarez, et al. (2010) found that having larger households with older children or watching television for more than 1 hour per day was related to child sleep difficulties (McDonald, et al., 2014; Nevarez, et al., 2010). Similarly single parent or divorced households, lower socioeconomic strata or less maternal education were predictors of less sleep in infants (McDonald, et al., 2014).

Sleep difficulties can also be related to mental and physical health or developmental states. Children with autism are more likely to have sleep problems, particularly with insomnia and dysregulation of sleep schedules compared to controls, while their siblings are more likely to have sleep problems related to insomnia, sleep talking and nightmares (Chou et al., 2012). It is likely that the sleep of the sibling without autism is affected by the sleep of the sibling with autism and the increased anxiety around this familial situation. Moreover, other physical problems are likely to affect sleep such as asthma, rheumatological disorders or pain conditions (Owens & Witmans, 2004).

Even with the difficulty surrounding a generally accepted definition of problematic sleep, infant sleep problems are widely reported to affect approximately 30% of infants up to 2 years of age (France, et al., 2003; Gibson, et al., 2012; Teng, et al., 2012). The range of factors that can interplay to impact parental perception of infant sleep as problematic is vast and encompassing. Consequently, it makes determining the difference in objective sleep measures difficult and unclear.

### 3.4 Effects of Problematic Sleep on Infants

Because of the vast and inter-related range of factors linked to sleep disturbance in infants, it is difficult to determine specific causes or effects. Immediate symptoms of sleep deficit that are noticeable to caregivers include irritability, negative mood, daytime sleepiness, short attention span, and decreased threshold for frustration (Davis, Parker, & Montgomery, 2004; Owens & Witmans, 2004). With increased nocturnal and 24-hour sleep, an increase in approachability, rhythmicity and adaptability has been noted (Spruyt, et al., 2008). There is also increasing evidence that insufficient sleep has negative effects on cognitive, emotional and behavioural...
development. The full nature of these effects are not completely understood, but problematic sleeping during childhood has been associated with attention deficit hyperactivity disorder in children and adolescents (Hemmi, et al., 2011), higher rates of obesity in children (Sekine, et al., 2002), an increased number of injuries in children (Valent, Brusaferro, & Barbone, 2001) and decreased immune function (Giglio, et al., 2007). Infants do not live in isolation but with their family and often disturbed sleep seems more problematic to parents as it causes disruption to their own sleep routine. Inadequate sleep in parents can result in fatigue, poor mental health (Bayer, et al., 2007; Meltzer & Montgomery-Downs, 2011), increased levels of stress, anxiety and depression leading to impaired cognitive ability (Meltzer & Mindell, 2007; Plessow, Kiesel, Petzold, & Kirschbaum, 2011) and poor physical health (Bayer, et al., 2007).

The importance of parental perception regarding infant sleep problems is a crucial indicator of infant development and regulation as well as familial dynamics. As Owens (2005) suggests, it may serve to better consider sleep problems along a continuum of those that range from transient and self-limiting syndromes to disorders that meet clinical criteria. Regardless, treatment is often sought because infants’ sleep patterns not only disturb themselves but the sleep of the other family members as well (Owens, 2005).
4 Improving Sleep

At present, there are no best practice recommendations for infants who suffer from problematic sleep. The currently endorsed measures include short-term pharmacotherapy and long-term behavioural interventions. Additionally, physical therapies (chiropractic, osteopathy and massage therapy) are also claiming that treatment is helpful in alleviating sleep problems, with a growing body of literature exploring the feasibility of these claims. Most interventions are focused on infants 4 months or older as sleep patterns should have started to consolidate (France, et al., 2003; Meltzer & Montgomery-Downs, 2011).

4.1 Behavioural Treatments

Many behavioural interventions are suggested by health professionals and subsequently tried by parents. The first avenue advised upon is sleep hygiene, encompassing the sleeping environment and child’s routine. The sleeping environment should be dark, quiet, comfortable bedroom with minimal background noise to ensure an optimum chance for the infant to be able to sleep (Sheldon, 2005a). Routines should be structured, reinforced and constant, with appropriate behaviour modifications to achieve these outcomes; excess fluid, caffeinated food/drink or vigorous activity before bedtime should be avoided and nap times should be spaced to not accumulate sleep during the day period (Sheldon, 2005a).

Another technique that can be used is “crying it out” in which the parents put the child to bed, then proceed to let them exhaust themselves into sleep through crying. This method can be very stressful to infants and disruptive to families. It can also lead to separation anxiety or learned helplessness linking into other sleep related difficulties and depression (Sheldon, 2005a; Terman & McMahan, 2012). A modification of the “crying it out” strategy is controlled crying which the parents wait a set amount of time before comforting the child. This time gradually increases until the infant falls asleep themselves without parental intervention. The retraining of sleep onset is helpful to allow the infant to resettle themselves without parental intervention (Sheldon, 2005a). Often behavioural interventions can cause a temporary worsening in the sleep problem until the new routine is learnt, and because parents are not always made aware of this, many may abandon treatment (Sheldon, 2005a).

4.2 Pharmaceutical Treatments

Pharmaceutical agents are generally only used in paediatric or child populations when behavioural interventions are ineffective. Common pharmaceutical agents prescribed by
physicians for paediatric sleep problems include melatonin, antihistamines, benzodiazepines and chloral hydrate (Heussler et al., 2013; Pelayo & Dubik, 2008).

Antihistamines have a sedating effect due to their availability within the central nervous system; the antagonistic action to several types of receptors within the brain, particularly H1 receptors causes sedation (Schweitzer, 2007). Benzodiazepines are commonly prescribed for anxiety, insomnia and drug withdrawal in adults but on occasion, they are prescribed to children. They bind to gamma-aminobutyric acid receptors causing sedation (Schweitzer, 2007). Choral hydrate is a hypnotic drug that acts similarly to benzodiazepine. It is frequently used for children when undertaking medical or dental procedures and is occasionally used for sleep problems. Synthetic melatonin appears to both affect sleep-wake cycles and provide a sedating effect for patients (Kuhn & Weidinger, 2000). A recent survey of Australian paediatricians shows that melatonin was the preferred drug choice for infants, due to its endogenous nature (Heussler, et al., 2013).

The effectiveness and safety of drugs to combat sleep problems are often not tested on paediatric populations but theorised from adult studies (Pelayo & Dubik, 2008). Sleep phases show a preferential rebound effect for whichever sleep phase is altered by medication. For example, in adults, benzodiazepines suppress slow wave sleep (passive sleep) whilst tricyclic antidepressants, serotonin reuptake inhibitors and monoamine oxidase inhibitors suppress REM sleep (active sleep). Withdrawal from these drugs produces a rebound effect of that sleep stage (Carskadon & Dement, 2011). It is theorised that the effects from these medications are similar between adults and children, but there is no research to confirm this theory.

4.3 Chiropractic, Osteopathy and Massage Therapy

Chiropractic, osteopathy and massage therapy all aim to improve an individual’s health and wellbeing through physical therapy. These modalities have been suggested by some to be effective for treating infant sleep problems. Anecdotal evidence is found in texts (such as Parsons & Marcer, (2006)) and on many clinic websites advertising the benefits of these treatments for infants, but little research has been published to help build evidence to verify this. All of these modalities assess patients holistically, encompassing multiple factors in diagnosis and utilise individual treatment approaches for each patient. This makes it particularly difficult to conduct effective and accurate research with blinded controlled trials, so many utilise the individual as their own control within single systems designs (Domholdt, 2000). Within in an adult population this approach can be particularly effective, but within an infant population becomes difficult due to the quick rate of maturation. In adult studies, sham treatments have been applied but it becomes ethically challenging when dealing with an infant population. Due
to the emerging nature of this aspect of physical therapy, many studies have low sample numbers making it difficult to draw clear conclusions.

The chiropractic profession has more published literature than osteopathy or massage therapy. Although many positive results are suggested by the chiropractic literature, the rigour of some of the interventional studies is lacking in structure, controls and publication of figures. Many studies focus primarily on colic but often encompass sleep disturbance as a measured variable. For example, Browning & Miller (2008) compared spinal manipulation and occipital-sacral decompression in the treatment of 48 colicky infants over a 2 week period. Parental diaries reported a decrease of approximately 3 hours and sleep increased by approximately 1 hour after the treatment period. There was no control in this sample, so it is unclear how infants would have progressed without treatment.

Long-term follow-up on infants who received chiropractic treatment has been conducted by Miller & Phillips (2009). These authors report that children who received treatment performed less tantrums, fell asleep faster and slept through the night significantly more than their counterparts who received no treatment. Unfortunately, the authors do not present figures for comparison, define how they measured tantrums and make vague statements about the improvements of the treatment group. Additionally, the sample was of convenience (clinic parents compared to local preschool parents), had limited baseline measures, and did not identify other variables including other treatments sought by parents. Thus, it is difficult to determine how effective the treatment was, given that clear initial measures were not taken, other influential factors were not examined and the sample does not accurately represent the wider population. Another retrospective analysis has revealed that it is unclear if chiropractic treatment is successful in treating colicky infants (Wiberg & Wiberg, 2010). Data in this study was collected retrospectively via interpretation of clinical records where the practicing chiropractor subjectively interpreted infant changes as reported by the parents, based on the assumption that the same assessment questions were asked of all parents (Wiberg & Wiberg, 2010). This study had no control group, instead comparing their results to median crying times from another study; it is unclear if these median crying times were from a healthy infant population or from infants suffering from colic but were not undergoing treatment.

One study focussed particularly on sleep behaviours in infants, following a massage therapy intervention. Kelmanson & Adulas (2006) monitored 50 infants who received massage therapy interventional treatments between 2 and 8 months of age. Infants were of low birth weight and matched with controls that were similar in geographical distribution, age, weight and gestational variables. It is not clear whether the infants were randomised to treatment and non-treatment groups, possibly causing expectation bias from the parents. Measurement was by weight increase and parental questionnaire, with results indicating that the interventional infants gained
more weight than controls (8345g versus 7986g at 8 months) and showed improve sleep through decreased snoring episodes (4% usually/sometimes snore versus 20% ) when compared to controls (Kelmanson & Adulas, 2006). Although the population of these studies is preterm infants, the positive result of improved sleep quality with massage therapy suggests the benefit of manual therapy in the management of infants with sleep problems. Other literature has shown that massage therapy decreases blood pressure, heart rate, cortisol levels and increase in oxytocin and immune function, although there are no indications of how long these affects last for (Field, 2010).

Cranial osteopathy has been shown to improve sleep and decrease crying bouts in a population of infants suffering from colic. A sole practitioner treated 28 infants for 4 weeks and parental measures of time sleeping and crying were recorded. The control group received the same amount of time with the osteopath but minimal touch. The authors state that the intervention group reported a mean increase of approximately 1.4 hours in restful sleeping during the 4 week treatment period versus 0.2 hours in the control group (Hayden & Mullinger, 2006). Qualitative studies conducted by Gibson (2008) and Viedma-Dodd (2006) have assessed maternal and osteopathic perspectives in association with fussy unsettled infants, and report that parents find osteopathic treatment helpful for their infants.
5 Conclusion

Infant sleep patterns undergo considerable change over the first year of life, particularly in the first 6 months. Within this initial period, sleep moves from frequent fragmented bouts to a prolonged sleep period at approximately 4 to 6 months. When this change does not occur, sleep problems are indicated, which is reported in approximately 30% of infants. The full extent of problematic sleep is not completely understood but negative associations with an individual’s cognitive, emotional and behavioural development have been reported. While this is understandably concerning, the effects of problematic sleep are not confined to the infants themselves, but often expand to the wider family unit becoming associated with parental health problems. Currently, data on problematic sleep is scarce, limited to a few cross sectional studies with inadequate information on the developmental trends of healthy problematic sleepers. This research project endeavours to contribute to the literature by comparing the longitudinal sleep patterns of problematic and non-problematic infants between 3 and 13 months.
6 References


Section 2: Manuscript
Original Research Article:

Sleep patterns of problematic and non-problematic infant sleepers aged between 3-13 months: a longitudinal study

Running Title: Longitudinal study of infant sleep patterns

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Abstract

Sleep patterns of problematic and non-problematic infant sleepers aged between 3-13 months: a longitudinal study

This study describes and compares the sleep patterns of parentally-perceived problematic and non-problematic infant sleepers aged 3 to 13 months. Parents of 63 infants completed brief infant sleep questionnaires (BISQ) and 7-day sleep diaries each month for up to 3 months. Problematic sleepers showed poorer sleep quality and quantity than their non-problematic counterparts over the 3-month period. For problematic sleepers, diaries indicated $1.3 \pm 0.4$ (mean $\pm$ SE) more night wakes per night ($p=0.002$), $0.92 \pm 0.3$ hours less total sleep over 24 hours ($p=0.008$), shorter sleep periods by $2.0 \pm 0.7$ hours ($p=0.009$), $0.54 \pm 0.3$ hours less night-time sleep ($p=0.046$) and more time awake between 2200 – 0600 by $0.27 \pm 0.09$ hours ($p=0.05$) and by $0.41 \pm 0.1$ hours ($p=0.009$) from BISQ. Expected developmental changes were observed in both groups, with day naps decreasing from $3.0 \pm 0.1$ to $2.5 \pm 0.1$ ($p<0.001$), night wakes decreasing from $2.1 \pm 0.2$ to $1.6 \pm 0.2$ per night ($p=0.008$), and sleep periods lengthening on average from $8.8 \pm 0.4$ to $9.8 \pm 0.4$ hours per night ($p=0.007$) over 3 months. Problematic sleepers were more likely to have experienced a birth with intervention (forceps, ventouse or caesarean) than non-problematic sleepers (75% versus 58%; $p=0.03$). This study indicates that problematic sleepers have increased sleep fragmentation and sleep deficit when compared to non-problematic sleepers, leading to poorer sleep quality and quantity. Perinatal factors may also contribute to problematic sleep patterns in infants.

Keywords
infant, sleep, problematic, birth experience, sleep diaries, longitudinal
Introduction

The effects of sleep deficit in infants can be recognised with short-term behavioural signs such as irritability, short attention span, and decreased threshold for frustration (1, 2). Infants exhibiting sleep problems are more likely to have experienced either pre-natal, perinatal or feeding difficulties (3) and are more likely to display adverse behavioural (4) and temperamental effects later in childhood (5). The full nature of these effects is not completely understood but problematic sleep during childhood has been associated with attention deficit hyperactivity disorder in children and adolescents (4), higher rates of obesity in children (6), an increased number of injuries in children (7), and decreased immune function (8). The effects of disturbed infant sleep are not isolated to infants themselves but may also affect other family members and disturbed infant sleep may seem more problematic to parents as it causes disruption to their own sleep routine. Inadequate sleep in parents can result in fatigue, poor mental health (9, 10), increased levels of stress, anxiety and depression leading to impaired cognitive ability (11, 12), and poor physical health (9).

Problematic sleep may be defined according to age-specific reference ranges or by subjective perceptions of caregivers. Objective definitions for infants aged between 6 and 12 months are based on the amount of sleep, frequency of night wakes, prolonged night wakefulness and difficulty with sleep onset have been used in previous studies (13-15). Reference values for infant sleep often have wide intervals as they encompass babies with problematic and non-problematic sleep patterns (16). Other authors have used parental perception to determine whether infants have a sleeping problem (15, 17-19). However, different cultures have been shown to have differing interpretations of what constitutes problematic sleep so the reported rate of problematic sleepers varies between Asian and Caucasian countries (52% vs 26% respectively) (20).

Despite the high variability of reported sleep patterns according to age, clear developmental trajectories for sleep are evident (16). Sleep consolidation between 4 and 6 months is a key aspect of sleep development, as infant sleep patterns move from short frequent bursts of sleep to longer sleep periods (13, 21) although this has been suggested to occur as young as 2 months old (22). It is often when sleep patterns do not consolidate, that problematic sleep patterns emerge (14, 15, 17).

While the incidence of problematic sleeping has been estimated, further information about the subject is scarce. Two studies have demonstrated that problematic infant sleepers have decreased night time sleep and increased sleep fragmentation at night when compared with
their non-problematic counterparts \cite{15,19}. However, there is limited information on the developmental trends of problematic infant sleepers, despite the documented consequences of sleep problems past infancy. Therefore, the primary aim of this study was to compare the longitudinal sleep patterns of problematic and non-problematic infant sleepers aged between 3 and 13 months through subjective measures. An additional aim was to establish whether differences exist in pregnancy, birth, and feeding characteristics between infants described as problematic sleepers and those who are not.
Methods

Participants
Data reported here are part of a broader study investigating sleep-patterns of first-born infants and their parents using a non-experimental developmental research design.

Inclusion Criteria
The target population for this study was families living in New Zealand, consisting of two parents with a single first born infant aged between 4 and 9 months. Parents were defined as adults of either sex who lived with and cared for their infant.

Exclusion Criteria
Families were excluded from the study if infants were born prematurely (<37 weeks gestation), or had a serious medical condition (i.e. asthma, recurrent otitis media, obstructive sleep apnoea). Additionally, families with either caregiver working shifts or with additional live-in caregivers were also excluded.

Families were recruited through website advertising (http://www.OHbaby.co.nz, http://www.kiwifamilies.co.nz, www.bellybeyond.co.nz), research recruitment websites (www.getparticipants.com, www.researchstudy.co.nz), Facebook advertising, community newspapers, flyers at Plunket centres in Auckland, and Clinic 41 osteopathy clinic. Initial recruitment resulted in a smaller proportion of problematic infants, so subsequent recruitment targeted this population through snowball sampling via Facebook and other internet forums.

Approval for this study was obtained from the Unitec Research and Ethics Committee (2012/1074) and Royal New Zealand Plunket Society Ethics Committee (2012) [see Appendix A].

Measures and Procedures
Families were contacted by email to obtain postal information for sending a package containing study information, consent forms and all study materials [see Appendix B]. They were then phoned 3 to 5 days after the parcel was sent, to answer any questions or concerns regarding the study and provide a start date for data collection. The initial Brief Infant Sleep Questionnaire (BISQ), [see Appendix C] as well as additional demographic and socioeconomic information was completed and returned with consent forms. The BISQ is used to gather data relating to sleep times and habits after reflection on the infants sleep for the past week \(^{15}\). A second BISQ was also completed in Week 9.

Parental perception of infant sleep was identified through the response to the question “Do you consider your child’s sleep a problem?” When either parent indicated that they considered their
infant had either a very serious or small sleeping problem, as opposed to indicating that sleep was not a problem, the infant was identified as a problematic sleeper.

Following the completion of the questionnaire, parents were asked to fill in a sleep diary for their infant for 7 days in Weeks 1, 5, and 9 (for month 1, 2 and 3). Parental sleep diaries are considered to be a reference standard for recording infant sleep-wake patterns in descriptive studies (23-25). The sleep diary used in this study is a modified version of the sleep diary used by Quillin & Glenn (26) [see Appendix D]. Parents recorded infant behaviour (sleep, crying and feeding) with predetermined symbols on the sleep diaries. Sleep diaries for Weeks 5 and 9 were sent the week prior with final questionnaires included in the Week 9 pack. Families were contacted the day before commencement of Weeks 5 and 9 as a reminder to start data collection and answer any further questions that might have arisen. Completed sleep diaries and questionnaires were returned to the researchers after each data collection period.

**Data Analysis**

The variables derived from the sleep diary included onset and duration of sleep; time and duration of wakes; time and method of feeding; and any illness or disruption to normal routine (e.g. social events). Sleep diary variables were classified as total daytime sleep duration between 0700-1900 (TST daytime), total night-time sleep duration between 1900-0700 (TST night-time) and total sleep time over 24 hours between 0700-0700 (TST 24) as per Gibson, Gander and Elder (19). Other variables examined include the longest self-regulated sleep period (LSRSP), night wakefulness between 2200 - 0600, number of night wakings and number of daytime naps. Weekly diaries that had more than 24 hours of missing data were excluded from analysis (n=5). When a single night of data was missing from a week’s data collection (n=5), night sleep for the 7th night was extrapolated from an average of the other 6 nights. Sleep-related variables calculated from the BISQ included daytime sleep, night-time sleep, number of night wakings, and night wakefulness between 2200 – 0600.

Statistical analysis was completed using IBM SPSS™ (version 22). Key variables were assessed for normality taking account of skewness and kurtosis parameters, Kolmogorov-Smirnov test and visual inspection of frequency distribution (27). Differences between problematic and non-problematic sleepers were assessed using Chi-square analysis for categorical data, and analysis of variance (ANOVA) models that included age for sleep parameters. Violations of assumptions of equal variance and sphericity were determined using Levene’s and Mauchly’s tests. When repeated measures ANOVA models violated the assumption of sphericity, adjustment was applied using Hyndt-Feldt corrections where epsilon values were greater than 0.75, or Greenhouse-Geisser corrections otherwise (27). Reliability was evaluated by considering statistics of measurement error, systematic change in the mean and test-retest correlation (28). Intraclass correlation coefficient (ICC) values were calculated
assuming random selection of sample periods and averages of daily measures over each week (Model, Form: 2,7) for both sleep diary and BISQ measures. Standard errors of measurement (SEMs) were derived using the formula SEM =σ*(√ (1-ICC)) \(^{(29)}\), where σ was estimated as the pooled standard deviation of the repeated measurements. The level of statistical significance was set at α=0.05.
Results

Participants

Of the 133 families who expressed interest in participating in the study, 84 were eligible and 21 declined to participate leaving 63 families randomised into the study. Of these, nine failed to provide either their infant’s age or to indicate whether they perceived their infant’s sleep to be problematic, and were thus excluded from analyses.

Of the remaining 54 families, 38 completed diaries for all three data collection weeks, 11 families completed two weeks, and five families completed one week, producing a total of 141 weeks of sleep data for analysis (Figure 1).

Infant age was rounded to the nearest month with those 6 months and under (n=27) compared to those 7 months and older (n=27). Although the criteria for participation in the study specified that infants were between 4 and 9 months of age at commencement, upon analysis it was found that one infant was 3 months old and another three were 10, 11, and 13 months old respectively. These infants were included in analyses reported here. Thus, infants ranged in
age from 3 to 13 months at initiation of the study and those whose parents completed the third sleep diary were 5 to 15 months at completion.

The majority of parents were NZ European (87%; n=104), with other European (7%; n=8), Maori (4%; n=5) and Pacific Island (1%; n=1) and Indian (1%; n=1) ethnicities represented. Average age of parents was 33 ± 5 years (mean ± SD). Sixty percent of parents had a university education, 49% were waged employees and 33% homemakers. Over half of the parents earned >NZ$45,000 annually, compared with the median waged income for the June 2013 quarter of NZ$44,000 (30). Most couples were married (71%) or living in a defacto relationship (29%). One same-sex couple participated in the study.

Cross-Sectional Analyses
Cross-sectional analyses using the initial BISQ and Week 1 sleep diary for each infant were undertaken to establish differences at study outset between infants perceived as problematic sleepers and those who were not. Data followed an approximately normal distribution so parametric tests were applied. Infants who were aged ≤6 months at the initiation of study were classified as younger infants, whilst infants aged ≥7 months were classified were older infants.

Sleep Diary Measures
Younger problematic sleepers had an average of 1.2 hours less TST daytime compared with non-problematic sleepers; older problematic sleepers showed a smaller deficit of 0.3 hours when compared with non-problematic sleepers (mean ± SE; ≤6 months 3.0 ± 0.26 versus 4.2 ± 0.23 hours; ≥7 months 2.8 ± 0.22 versus 3.1 ± 0.29 hours; p=0.003) [see Appendix E]. An increased frequency and variability of night wakes were recorded for problematic infants when compared with non-problematic infants regardless of age group (≤6 months 2.4 ± 0.37 versus 1.4 ± 0.33 wakes; ≥7 months 2.7 ± 0.31 versus 1.2 ± 0.41 wakes; p=0.001). Problematic infants spent more time awake during the 2200-0600 period than non-problematic infants by approximately 0.3 hours regardless of age group (≤6 months 2.1 ± 0.14 versus 1.8 ± 0.13 hours; ≥7 months 2.0 ± 0.12 versus 1.7 ± 0.16 hours; p=0.038). Total sleep over 24 hours showed an interaction between both problematic effect and age effect (p=0.046 for interaction). This interaction was clearly illustrated in younger problematic sleepers who had an average of 1.7 hours less sleep per 24 hours than their non-problematic counterparts, compared to older problematic infants who averaged only 0.4 hours less sleep over TST24 than non-problematic infants (≤6 months 12.5 ± 0.35 versus 14.2 ± 0.31 hours; ≥7 months 12.9 ± 0.29 versus 13.3 ± .38 hours; p=0.004).

Age group differences were observed for TST daytime, where younger infants had more sleep than older infants in line with sleep development trends (problematic 3.0 ± 0.26 versus 2.8 ± 0.22; non-problematic 4.2 ± 0.23 versus 3.1 ± 0.29 hours; p=0.02). There was a significant difference between the amount of daytime sleep problematic and non-problematic sleepers
experience \((p=0.003)\). The number of daytime naps also displayed age group differences, with an average decrease of 0.7 naps between younger and older infants (problematic 3.4 ± 0.22 versus 2.6 ± 0.18; non-problematic 3.4 ± 0.19 versus 2.8 ± 0.24; \(p=0.002\)) [see Appendix E].

**Brief Infant Sleep Questionnaire (BISQ) Measures**

Problematic sleepers had 1.1 hours less daytime sleep at ≤6 months and 0.8 hours less for infants ≥7 months (mean ± SD; ≤6 months 3.0 ± 1.18 versus 4.1 ± 1.24 hours; ≥7 months 2.7 ± 0.66 versus 3.5 ± 1.16 hours; \(p=0.003\)). An interaction between age group and problematic sleep was noted \((p=0.05)\) for TST night-time. Younger problematic infants had significantly less TST night-time compared to non-problematic infants, but differences between older infants were minimal (≤6 months 9.2 ± 1.63 versus 10.6 ± 1.08 hours; ≥7 months 10.4 ± 1.03 versus 10.5 ± 0.97 hours; \(p=0.03\)). Problematic infant sleepers had an increased frequency and variability of night wakets when compared with non-problematic infants (≤6 months 1.5 ± 1.19 versus 1.0 ± 0.61 wakets; ≥7 months 2.4 ± 1.47 versus 1.0 ± 0.69 wakets; \(p=0.002\)), which seemed to increase when the infants are older. Night wakefulness was higher for problematic infants than for non-problematic infants, regardless of age group (≤6 months 1.2 ± 0.76 versus 0.5 ± 0.58 hours; ≥7 months 0.9 ± 0.58 versus 0.3 ± 0.21 hours; \(p<0.001\)).

**Pregnancy complications**

Pregnancy complications included gestational diabetes (n=1), anaemia (n=5), hyperemesis gravidarum (n=3), elevated blood pressure (n=2), group B strep infection (n=3), preeclampsia (n=3), cholestasis (n=2), depression (n=2) and an unidentified condition (n=2). A total of n= 46 responded to that question from a sample population of n=57, with n=13 reporting at least one complication. There was no link between participant reported pregnancy complications and problematic sleepers \((p=0.2)\).

**Labour Complications**

Labour complications were described as infants becoming stuck in the birth canal, labour failing to progress or meconium expulsion present, all of which required labour interventions. A total of n = 21 reported labour complications were reported from a total response pool of n = 46. A borderline trend between sleep problems and labour complications was noted: 66% of infants described as problematic sleepers experienced labour complications compared with 40% of non-problematic infant sleepers \((p=0.07)\).

**Birth Experience**

Birth experiences were categorised as unassisted vaginal birth (n=32), assisted vaginal birth, including forceps and ventouse (n=8) and caesarean section (n=13). To determine if there was an association between labour experience and subsequent reporting of infant sleeping, caesarean section and assisted vaginal birth categories were combined (n=21). Analysis showed a relationship between birth experience and problematic sleeping: 75% infants
described as problematic sleepers experienced a birth with intervention compared with 58% of non-problematic sleepers who experienced an unassisted delivery (p=0.03).

**Feeding Method**

Three feeding response categories were provided: breast, bottle and solids. Due to the age range studied, most infants were consuming some solid food in combination with milk feeding. We elected to not use this as a separate variable, instead all infants were divided into milk feeding categories: breast, bottle or mixed (breast and bottle). A total of 48 of 57 participants responded, of whom 28 indicated breast-feeding as the most common form of milk feeding compared with 10 for bottle feeding and 10 for mixed feeding methods. There was no link between feeding type and problematic sleeping (p=0.5).

**Longitudinal Analyses**

**Sleep Diary Measures (Figure 2)**

Longitudinal analysis compared change between problematic and non-problematic sleepers by age group over time. Significant changes were observed across the three data collection points in day naps (p<0.001; Figure 2B), night wakes (p=0.008; Figure 2D), and LSRSP (p=0.007; Figure 2G) when measured by sleep diary, with changes over time in TST daytime attaining borderline statistical significance (p=0.058; Figure 2A). Problematic sleepers reported less TST night-time (p=0.046; Figure 2C), more night wakes (p = 0.002; Figure 2D), shorter LSRSP (p=0.009; Figure 2G) and less TST 24 (p=0.008; Figure 2F) than non-problematic infants. The frequency of daytime naps decreased for both younger and older infants (p = 0.01; Figure 2B).

**Brief Infant Sleep Questionnaire (BISQ) Measures (Figure 3)**

The BISQ showed reductions over time for night wakefulness (p=0.03; Figure 3D), and reductions in TST daytime were of borderline significance (p=0.054; Figure 3A). Problematic sleepers were reported to spend more time in night wakefulness compared to non-problematic sleepers (p=0.009; Figure 3D). Increases in TST night-time were displayed from the younger to older group of infants (p=0.048; Figure 3B). For this measure an interaction between age, time and problematic sleeping effects was also shown (p=0.03), whereby younger problematic sleepers and older non-problematic sleepers displayed clear increases in night-time sleep over the course of the study, while younger non-problematic sleepers and older problematic sleepers changed minimally (Figure 3B).
Figure 2: Longitudinal changes in sleep diary variables for problematic (P) and non-problematic (NP) sleepers. Graph A. TST daytime; B. number of day naps; C. TST night-time; D. number of night wakes; E. night wakefulness between 2200 and 0600; F. TST 24 hours; G. LSRSP. For infants who began the study aged ≤6 months, data has been plotted at 4, 5 and 6 months representing the three time points, and at 7, 8, 9 months for those over starting the study ≥7 months. Error bars are standard error of the mean (SEM) calculations. Statistical significance of time, sleep, age and interaction effects using mixed model linear regression modeling are shown below.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Effects</th>
<th>Interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Time (T)</td>
<td>Age (A)</td>
</tr>
<tr>
<td>TST Daytime</td>
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<td>Day Naps</td>
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<td>0.01*</td>
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<td>TST Night-time</td>
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<tr>
<td>Night wakes</td>
<td>0.008**</td>
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</tr>
<tr>
<td>Night wakefulness</td>
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<td>0.98</td>
</tr>
<tr>
<td>TST 24</td>
<td>0.17§</td>
<td>0.65</td>
</tr>
<tr>
<td>LSRSP</td>
<td>0.007**</td>
<td>0.35</td>
</tr>
</tbody>
</table>

*p<0.05, **p<0.01, ***p<0.001. Note: § - Huynh-Feldt correction applied.
Figure 3: Longitudinal BISQ results for problematic (P) and non-problematic (NP) sleepers. Graph A – total sleep time (TST) daytime; B – TST night-time; C – number of night wakes; D – night wakefulness between 2200-0600 hours. Data has been plotted at 4 and 6 months for younger infants and 7 and 9 months for older infants. Error bars are standard error of the mean (SE) calculations. A summary of the effects and interactions between sleep variables, time, age, and problematic sleeping for BISQ sleep variables are shown below.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Effects</th>
<th>Interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td>Age (A)</td>
</tr>
<tr>
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<tr>
<td>TST night time</td>
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<td>Night wakes</td>
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</tr>
<tr>
<td>Night wakefulness</td>
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<td>0.90</td>
</tr>
</tbody>
</table>

*p<0.05, **p<0.01, ***p<0.001. Note: § - Huynh-Feldt correction applied.
Reliability

Reliability of measures was derived from the two BISQs and weekly averages from Weeks 1 and 5 sleep diaries. Data from Week 9 were not used due to the greater likelihood of meaningful change over the 3 month study duration, as well as the reduced sample size as a consequence of poorer compliance and withdrawal from the study. The reliability of weekly-averaged diary data overall was strong, with ICC values between 0.73 – 0.90 for all sleep diary variables over the whole population (Table 2). Younger infants (0.69 – 0.87) and problematic infants (0.66 – 0.87) had slightly less reliable data when compared to older infants (0.75 – 0.91) or non-problematic infants (0.72 – 0.93) respectively [see Appendix F]. Brief infant sleep questionnaire variables were less reliable, displaying a moderate correlation range of (0.48 – 0.68) over the whole population. Younger infants had a higher rate of reliability (0.67 – 0.76) than older infants, with the exception of night wakes (-0.16). Reliability of the sleep diary was very good, particularly when compared to the BISQ.

Standard errors of measurement (SEM) represent the within-subject variability of repeated measures (29) and ranged between 3 – 31% of the mean for sleep diary variables. Night wakes when measured by sleep diary had a higher rate of error than the other sleep diary variables (Table 1). The BISQ shows a higher level of measurement error, between 8 – 65% of the mean. Particularly high errors were noted for both night wakes and night wakefulness likely indicating the difficulty in subjectively estimating these variables accurately, either when half awake at night or remembering what to record the next morning.

Systematic change is indicated by the mean difference between Week 1 and Week 5 time points (Table 1). Most variables displayed a decrease between Week 1 and Week 5 except for LSRSP and night wakefulness (sleep diary) and TST night-time (BISQ) which showed no change or slight increase. The largest changes were seen in TST 24, TST daytime, day naps in sleep diary measures, and TST daytime, night wakes and night wakefulness BISQ measures. Problem-sleeping infants showed a greater amplitude of change over sleep diary measured day naps (-0.33), night wakes (-0.39) and LSRSP (0.36) whereas non-problematic sleepers showed greater changes in TST 24 (-0.55) and TST daytime (-0.37).
Table 1: Within infant reliability and systematic changes over time for whole study population.

<table>
<thead>
<tr>
<th>Diary Variables</th>
<th>Within Infant Reliability</th>
<th>Systematic Change</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ICC (2,7)</td>
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<tr>
<td>TST daytime</td>
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<td>0.33</td>
</tr>
<tr>
<td>TST night-time</td>
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</tr>
<tr>
<td>LSRSP</td>
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<td>Day Naps</td>
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</tr>
<tr>
<td>Night Wakes</td>
<td>0.79</td>
<td>0.59</td>
</tr>
<tr>
<td>Night Wakefulness</td>
<td>0.73</td>
<td>0.23</td>
</tr>
<tr>
<td>BISQ Variables</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TST daytime</td>
<td>0.68</td>
<td>0.64</td>
</tr>
<tr>
<td>TST night-time</td>
<td>0.50</td>
<td>0.78</td>
</tr>
<tr>
<td>Night Wakes</td>
<td>0.48</td>
<td>0.83</td>
</tr>
<tr>
<td>Night Wakefulness</td>
<td>0.61</td>
<td>0.36</td>
</tr>
</tbody>
</table>

*p<0.05, **p<0.01, ***p<0.0001. Note: ICC - Intraclass Correlation Coefficient; SEM - Standard Error of Measurement; MDC - Minimally Detectable Change; SED - Standard Error of Difference; TST - Total Sleep Time; LSRSP - Longest Self Regulated Sleep Period; BISQ – Brief Infant Sleep Questionnaire.
Discussion

The primary objective of this study was to assess the difference between parentally described problematic and non-problematic sleep patterns in infants aged between 3 and 12 months. The results show that problematic infant sleepers had lesser quality and quantity of sleep compared with non-problematic infant sleepers as measured in both the sleep diary and BISQ results.

Problematic sleepers reported less sleep time than infants with no perceived sleep problems. Initially, cross-sectional differences were noted in daytime sleep, but as the infants progressed through the study, differences became apparent in night-time sleep and total sleep over 24 hours as well. Younger infants with sleep problems averaged 1.7 hours less sleep over 24 hours than their non-problematic counterparts. To put this in perspective, infant sleep cycles are approximately 50 – 60 minutes duration \(^{(31)}\), so effectively these infants had their sleep reduced by 2 sleep cycles. Similar trends of problematic sleepers having decreased night-time sleep and decreased total sleep over 24 hours when compared to non-problematic infants have been reported by other studies \(^{(15, 19)}\).

Problematic sleepers also demonstrated poorer sleep quality through increased sleep fragmentation when compared to non-problematic sleepers. A higher frequency of night wakes, greater amounts of time awake at night, and shorter sleep periods were noted in sleep diary measures for the problematic sleeper group. It has been proposed that frequent night waking in infants with problematic sleep is due to their inability to self-soothe and thus get back to sleep \(^{(32, 33)}\). It is possible that this increased fragmentation makes it difficult for infants to resume sleep, and this is also translated into sleep deficits at night. The finding from serial measures of the BISQ indicating more night wakefulness in problematic sleepers compared to non-problematic sleepers is not unexpected, as increased night wakefulness would likely disrupt the parents’ own sleep leading to greater likelihood that parents would class their infants sleeping as problematic.

Normal developmental trends are noted within the longitudinal data regardless of parental perception of infant sleep. Day naps showed consistent decreases over the 3 months, while night wakes tended to decrease over time although this trend was weaker. The longest sleep period continued to increase over the study, although problematic sleepers continued to have less sleep than infants without sleep problems. As sleep cycles for both problematic and non-problematic groups follow similar developmental trends, it would seem more likely that problematic sleepers represent the tail end of the normal population. It is currently unclear where the arbitrary point at which non-problematic sleepers transition to problematic sleepers. Regardless, the variance between sleep measures for problematic and non-problematic
sleepers is concerning, particularly given the long term associations with other health problems (4, 5).

Previous research into infant sleep patterns does not differentiate between problematic and non-problematic sleepers. Therefore the averages represented in these studies incorporate a broad spectrum of results. Non-problematic sleepers from this study appeared to have greater sleep quantity for total sleep and the longest sleep period when compared to previous studies (16-18, 21). Night-time sleep shows considerable variability in age-based comparisons with non-problematic data (17, 18). Daytime sleep, in contrast, has been reported to be relatively consistent amongst infants regardless of culture or environment indicating that there may be a stronger regulatory role than initially anticipated (20). The frequency of night waking was similar across all previous studies for non-problematic sleepers in both sleep diary and BISQ reports (16-18).

Currently, there is limited understanding of differences in sleep quality or quantity between infants with problematic versus non-problematic sleeping patterns or of how sleep develops in infants experiencing sleep problems. Symptoms of problematic sleep in infants have been identified and show problematic sleep to be increasingly fragmented and sleep consolidation delayed compared to non-problematic infant sleepers (18). Clinical guidelines have been suggested by Sadeh (15), and France (14) for infants 6 months or older, but it would seem these are not completely accepted and thus a clear objective definition of problematic sleep in infants is lacking. Cultural differences in sleep perception have been observed between Asian and Caucasian countries, emphasizing the role social expectation has in parental identification of infant sleep problems (20). Nevertheless, understanding around parental expectations of sleep is limited. The clear difference in objective sleep measures between problematic and non-problematic sleepers reported here would give credibility to the notion that infants experiencing problematic sleep are successfully identified by their parents.

Variability within the infants themselves was low, with minimal variability between duplicate measurements of weekly-averaged sleep variables measured by sleep diaries. Younger infants and problematic infants had slightly lower reliability ranges, but still moderate to strong agreements within the data sets. However, lower reliability and higher measurement error was reported for BISQ measures, in particular for night wakes and night wakefulness, which should thus be interpreted with caution. Systematic change was shown to be greater in younger infants than older infants, in agreement with the premise that infant sleep cycles change most significantly in the first 6 months (21). Surprisingly, infants with sleep problems displayed a larger range of systemic improvement for day naps, night wakes and sleep periods whereas non-problematic sleepers showed larger improvements in daytime and total sleep over 24 hours. Differing serial changes between problematic and non-problematic sleepers for indices of sleep
fragmentation could be attributed to delayed regulatory system development or involve other factors not ascertained within our study.

**Pregnancy, Birth and Feeding Characteristics**

Another aim of this study was to compare pregnancy, birth and feeding characteristics with the prevalence of problematic infant sleeping. Currently, few, if any, studies document the association between perinatal factors and problematic sleep in healthy infants. Here, problematic sleepers were more likely to have had a birth requiring intervention, such as forceps, ventouse or caesarian section. Sadeh (34) reported that newborn infants who were delivered via caesarean spent more time in active sleep compared to vaginally delivered infants. Furthermore, a small number of studies demonstrated associations between perinatal factors and reported sleep problems in autistic populations in China and Australia (3, 35). The findings from this study strengthen suggestions that perinatal factors may contribute to infant sleep problems.

Additionally, there was a slight tendency for the mothers of problematic sleepers to have experienced labour complications, although given the small sample size this would be worth investigating on a larger scale particularly given the likely confounding with birth interventions. No associations between pregnancy complications and sleep problems were demonstrated.

In contrast to other studies, our results showed that feeding methods displayed no association with problematic sleeping. This result was surprising as breastfeeding has been reported as a predictor of problematic sleep (19) and increased night waking (18) in previous studies. Breastfeeding rates decrease over time, particularly with the introduction of solid food groups usually between 4 to 6 months (36). It is possible that some mothers found that night waking for feeding were a normal part of breastfeeding and felt that this was not a problem, or that weaning practices were the same regardless of feeding type. The continuity of feeding methods was not inquired about over the course of this study.

**Limitations and Future Research**

There are several limitations to this study. The first is the difficulty with generalising results to a culturally and socio-economically diverse population. Participants here were predominantly middle class New Zealand Europeans who were part of traditional nuclear families with first born infants.

Secondly, the sample size is relatively small particularly for subgroup comparisons and for longitudinal analyses to the final week of data collection, due to drop-off in participation and diary completion compliance. Due to the smaller numbers, it is possible that some of the smaller changes in variables and differences according to sleeping status existed but were unable to be detected.
Thirdly, we did not provide a structured definition of problematic sleep. As such, parents were at liberty to decide if their infant was problematic or not, potentially increasing the variability within both problematic and non-problematic groups. The lack of an objective definition may also present difficulties with comparisons with future studies.

In addition, some aspects of development that may be important influences on infant sleep development, such as teething, childcare arrangements and parental (maternal) return to work, were deemed outside of the scope of this study and not addressed here.

Further investigation of the longitudinal sleep patterns of infants with problematic sleeping patterns is necessary to validate these results and provide an understanding of larger cultural and socioeconomic factors that may play a part. Birth experience and labour complications warrant further investigation to determine if there is a connection with problematic infant sleep.

In conclusion, this study shows that infants classed by parents as problematic sleepers show developmental trends similar to non-problematic sleepers, although slower rates of sleep consolidation leading to poorer quality and quantity of sleep when compared to non-problematic sleepers are noted. Problematic sleep patterns are clearly seen through increased night wakings, more time spent awake at night and sleep deficit consistent with other studies. Births with intervention are also associated with problematic sleep, indicating that perinatal factors may play a role in sleep regulation. This research has practical implications for all health professionals interacting with children and their families. Recognising deviations in key sleep measures that identify problematic infant sleep enables early recognition, and early intervention strategies. Greater understanding of how problematic sleep is manifested and changes with infant development may further enable its successful management to potentially minimize the long term effects that may result. Additionally, if parents understand that there may be an association between birth interventions and sleep problems, this may help mothers to prepare for and deal with sleep problems earlier.

Acknowledgements
Thank you to our sponsors for their generous contribution of gratitude gifts for our participants in this study: Belly Beyond, Plunket, Icebreaker, Kiwi Families, New World (Remuera and Mount Wellington), OhBaby!, Sutton McCarthy Limited, The Sleep Store and Pumpkin Patch.
References

Section 3: Appendices
Appendix A: Unitec and Plunket Ethics Committee Approval Letters
LeeAnn Jefferies and Gracela Gregorio

c/o: LeeAnn Jefferies
60 Asquith Ave
Mt Albert
Auckland

23.8.12

Dear LeeAnn,

Your file number for this application: 2012-1074
Title: Sleep in the Family: Sleep patterns of parents and first-born infants from 4 – 12 months of age.

Your application for ethics approval has been reviewed by the Unitec Research Ethics Committee (UREC) and has been approved for the following period:

Start date: 22.8.12
Finish date: 22.8.13

Please note that:

1. The above dates must be referred to on the information AND consent forms given to all participants.

2. You must inform UREC, in advance, of any ethically-relevant deviation in the project. This may require additional approval.

You may now commence your research according to the protocols approved by UREC. We wish you every success with your project.

Yours sincerely,

Gillian Whalley
Deputy Chair, UREC

Cc: Cynthia Almeida
Catherine Bacon
30th August 2012

LeeAnn Jefferies
60 Asquith Ave
Mt Albert
Auckland 1025

Dear Ms Jefferies

Sleep in the family: sleep patterns of parents and first-born infants from 4-12 months of age

Thank you for sending me your letter and revised forms. I have been through these carefully and, subject to one point, I am pleased to give final approval to your application.

The one matter relates to the involvement of Plunket: point 7 of your letter. You will doubtless talk further with the relevant Plunket leaders about how best to involve Plunket. If you decide on a poster, the Ethics Committee usually likes to check this and so I would be grateful if you could send me a copy, if one is prepared. I do not envisage this as causing any difficulties from our point of view.

On behalf of the Committee I wish you all the best with the project.

Yours sincerely,

Bill Atkin
Professor of Law
Acting Chair
Plunket Ethics Committee
Appendix B: Subject Information Sheet and Consent Form
Thank you for your interest in this research project. You, your partner and your infant are invited to participate in a study, which aims to measure sleep patterns of infants and their parents by collecting data through actigraph monitoring and completion of sleep diaries over 7 days per month for 3 months.

**Purpose of Study**

Sleep is an important part of growth and development. Approximately 30% of infants suffer from problematic sleep, which can have long-term effects on the infant’s health and can negatively affect family relationships. There is limited knowledge about the sleep patterns of infants and their parents over the 4 to 12 month age group. This study aims to measure the sleep patterns of problematic and non-problematic infant sleepers and their parents.

**Sleep Diary**

Participants will be asked to complete daily sleep diaries that will help us observe the sleep patterns of you, your partner and your infant over a 7-day data collection time. At the end of each week, you will be asked to return the completed diaries to the researchers for analysis and new diaries will be mailed to you before the beginning of each month.

**Actigraph**

Some families in this study will be asked whether they would be willing to wear an actigraph depending on the availability of devices and proximity of your home. The actigraph is an accelerometer that measures movement and can be used to determine sleep and wake times. It is approximately 2cm square in size (similar to a watch face) and is worn by adults on their wrist, and on the infant attached using a soft tubular band around the ankle. Both parents and infant will be asked to wear the actigraphs continuously for 24 hours over the 7-day data collection time. The actigraph is not water-proof so must be removed for bathing, but is water resistant so if soiled can be wiped clean and continue to be used.

**Procedures**

If you consent to your family being involved in the study, we'll ask the following of you:

- Complete a questionnaire that provides demographic information for both you and your partner.
- Complete three different questionnaires regarding your infant’s sleep, and both you and your partners sleep and frame of mind.
- You and your partner will be asked to fill out a sleep diary for the infant as well as for themselves for the 7-day (one week) period the actigraph is worn per month, for up to 3 months.
- Your infant may be asked to wear an actigraph monitor on their ankle for 7 days (one week) per month, for up to 3 months.
- You and you partner may be asked to wear an actigraph on their wrist for 7 days (one week) per month, for up to 3 months.

**Risks, Discomforts and Benefits**

This method of sleep monitoring is commonly used internationally. There have been no negative effects from actigraph usage reported to date. The tubular bandage that holds the actigraph is specially designed for use with infants, to minimise any discomfort from wearing the device. There is a small possibility that skin irritation or a red rash may happen with the use of the bandage. If that does occur, please remove the band with actigraph and contact the principal researchers. If the rash persists for more than 12 hours, we recommend visiting your pharmacist or doctor. If you or your infant feel distressed or are uncomfortable from wearing the device, then the ability to withdraw from the study is available at any time during the data collection period.

If your family does take part in this study, we will be able to accurately monitor your family’s sleep patterns. This information will contribute to understanding the relationships, of sleep amongst mothers, fathers and their first-born infants. The results from this study will be very helpful in determining the variation of sleep patterns in problematic sleepers and the effectiveness of any future intervention.

**Incentives**

All participating families will go into a draw to win gifts generously donated by Pumpkin Patch, Icebreaker, Goughs and New World Remuera upon completion of total data collection.

**Confidentiality**

The information provided in this study will be kept strictly confidential. Your family will be allocated identification codes at the commencement of the study that will remain confidential to the researchers, LeeAnn Jefferies and Gracela Gregorio, and study supervisors Catherine Bacon, Clive Standen and Jamie Mannion. All data will be kept securely as per Unitec’s stringent privacy policy.

The results of this study will be reported but it will not be possible to identify any individual participants.

**Request for more information**

You are encouraged to discuss any concerns regarding this study with the Principal Researchers or Supervisors at any time and ask any questions that you may have. If you would like a summary of the study’s conclusions, please ask and this can be provided upon completion as well as a link to the final e-version of the theses.

**Refusal or withdrawal**

*You do not have to agree to participate in this study.* If you do consent to participate, you may withdraw at any time during data collection without fear of prejudice. It is preferable that
participant families are involved for 3 months, however if you do decide to withdraw, please contact the Principal Researchers at the earliest opportunity.

**Contact Information**

If you have any questions or queries now or later, please direct them in the first instance to:

**Principal Researchers**

LeeAnn Jefferies (Principal Researcher)  
Email: leeann@infantsleepstudy.co.nz  
Phone: 0274606877

Gracela Gregorio (Principal Researcher)  
Email: gracela@infantsleepstudy.co.nz  
Phone: 021875809

**Alternatively, to Research Supervisors**

Dr Catherine Bacon, Ph.D, Department of Osteopathy, Unitec, Auckland  
Email: cbacon@unitec.ac.nz  
Phone: 09-815 4321 ext 5229

Associate Professor Clive Standen, Department of Osteopathy, Unitec, Auckland  
Email: cstanden@unitec.ac.nz  
Phone: 09-815 4321 ext 8475

Jamie Mannion, MSc, Department of Osteopathy, Unitec, Auckland  
Email: Jamie.mannion@getparticipants.com  
Phone: 09-815 4321 ext 5229

This study has been reviewed and approved by the Unitec Research Ethics Committee and Plunket Ethics Committee, to ensure that all participants are protected from harm. The study is authorised to run from 22.08.2012 to 22.08.2013. If you have any further queries please contact ethics@unitec.ac.nz, reference number 2012-1074.
Infant Consent Form (P1)

Sleep in the family: sleep patterns of parents and first-born infants from 4–12 months of age

Name of Infant: ____________________________________________________________

Name of Parent: __________________________________________________________________

I have seen and read the information sheet for subjects taking part in the project titled “Sleep in the family: sleep patterns of parents and first-born infants from 4-12 months of age” and have had the opportunity to discuss the project with LeeAnn Jefferies or Gracela Gregorio.

I understand that I am making a decision on behalf of my infant to take part in this study.

I understand that my infant’s participation in this project is confidential and that no material that could personally identify my infant or me will be used in any reports on this project.

I understand that I may withdraw my infant’s participation from the study at any time during data collection with no prejudice. If so, I undertake to contact the principal researcher/s at the earliest opportunity.

I understand I can review the finished research document.

I have had enough time to consider whether I want my infant to take part and acknowledge that any raw data collected during the study will be stored securely so that only the researchers and supervisors may access them.

The principal researchers for this project are LeeAnn Jefferies and Gracela Gregorio, and their supervisors are Catherine Bacon, Clive Standen and Jamie Mannion.

Contact details:

LeeAnn Jefferies email: leeann.jefferies@gmail.com Mobile: 027 460 6877

Gracela Gregorio email: gracela_graeme@hotmail.com Mobile: 021 875 809

Parent’s Signature: ________________________________ Date: __________________

This study has been reviewed and approved by the Unitec Research Ethics Committee and Plunket Ethics Committee, to ensure that all participants are protected from harm. The study is authorised to run from 22.08.2012 to 22.08.2013. If you have any further queries please contact ethics@unitec.ac.nz, reference number 2012-1074.
Appendix C: Brief Infant Sleep Questionnaire
The Brief Infant Screening Questionnaire (BISQ)

Participant Code:

Please mark only one (most appropriate) choice, when you respond to items with a few options.

Name of Responder: ____________________ Date: ____________

Role of Responder:  □ Father □ Mother □ Grandparent □ Other, Specify:

Name of the child: ______________ Date of Birth: Month ______ Day: ______ Year: ______

Sex: □ Male □ Female

Birth order of the child: □ Oldest □ Middle □ Youngest

Sleeping arrangement:
□ Infant crib in a separate room □ Infant crib in parents’ room □ In parents’ bed
□ Infant crib in room with sibling □ Other, Specify: ______________

In what position does your child sleep most of the time?
□ On his/her belly □ On his/her side □ On his/her back

How much time does your child spend in sleep during the NIGHT (between 7 in the evening and 7 in the morning)?
Hours: _____ Minutes: ______

How much time does your child spend in sleep during the DAY (between 7 in the morning and 7 in the evening)?
Hours: _____ Minutes: ______

Average number of night wakings per night: ______________

How much time during the night does your child spend in wakefulness (from 10 in the evening to 6 in the morning)?
Hours: _____ Minutes: ______

How long does it take to put your baby to sleep in the evening?
Hours: _____ Minutes: ______

How does your baby fall asleep?
□ While feeding □ Being rocked □ Being held □ In bed alone
□ In bed near parent

When does your baby usually fall asleep for the night:
Hours: _____ Minutes: ______

Do you consider your child’s sleep as a problem?
□ A very serious problem □ A small problem □ Not a problem at all
Appendix D: Infant Sleep Diary
# Night time Sheet

**Infant Name:**

**Parent Name:**

**Week:**

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<th>Day/Date</th>
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<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>12 midnight</th>
<th>1 am</th>
<th>2</th>
<th>3</th>
<th>4</th>
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Appendix E: Cross Sectional Data Table
Comparing sleep measures in problematic and non-problematic infants between 3 – 6 months and 7 - 12 months. Reported measures are in hours, except for daytime naps and night wakes which are reported as number of occurrences during the time period specified.

<table>
<thead>
<tr>
<th></th>
<th>Infants 3 - 6 months</th>
<th>Infants 7 - 12 months</th>
<th>Effects</th>
<th>A</th>
<th>P</th>
<th>A &amp; P</th>
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<td>Non-Problematic</td>
<td>Problematic</td>
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<td>P</td>
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<td>TST Daytime</td>
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<td>4.2 1.01</td>
<td>2.8 0.61</td>
<td>3.1 1.24</td>
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<td>No. Daytime Naps</td>
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<td>3.4 0.92</td>
<td>2.6 0.61</td>
<td>2.8 0.52</td>
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<tr>
<td>TST Night-time No. Night wakes</td>
<td>9.5 0.73</td>
<td>10.0 1.19</td>
<td>10.1 0.99</td>
<td>10.1 0.99</td>
<td>0.3</td>
<td>0.4</td>
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<td>1.4 1.03</td>
<td>2.7 1.54</td>
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<td>LSRSP</td>
<td>7.4 1.92</td>
<td>9.4 2.03</td>
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<td>n=11</td>
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<td>TST Night-time No. Night wakes</td>
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<td>10.6 1.08</td>
<td>10.4 1.03</td>
<td>10.5 0.97</td>
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<td>2.4 1.47</td>
<td>1.0 0.69</td>
<td>0.1</td>
<td>0.002</td>
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| Note: TST - Total Sleep Time; LSRSP - Longest Self Regulated Sleep Period; A - age; P - problematic; A & P - age and problematic
Appendix F: Reliability Table
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<th>Within Infant Variability</th>
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*Problematic*
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Note: ICC - Intraclass Correlation Coefficient; SEM - Standard Error of Measurement; MDC - Minimally Detectable Change; SED - Standard Error of Difference; TST - Total Sleep Time; LSRSP - Longest Self Regulated Sleep Period; BISQ - Brief Infant Sleep Questionnaire
Appendix G: Requirements for submission of manuscripts to Sleep and Biological Rhythms
AUTHOR GUIDE

Thank you for your interest in Sleep and Biological Rhythms. Please take a moment to consult the following instructions to help you prepare your manuscript, and feel free to contact us with any questions. To ensure fast peer review and publication, manuscripts that do not follow the instructions are returned to the corresponding author for technical revision before undergoing peer review.

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1. ABOUT THE JOURNAL

Scope: Sleep and Biological Rhythms is the official English language journal of the Japanese Society of Sleep Research (JSSR), and publishes original research articles on basic clinical and sociological issues, dealing with sleep and biological rhythms. Both members and non-members of the JSSR are welcome to submit papers to the journal.

Editor in Chief: Kazuichi Homma, MD, PhD, Department of Chronomedicine, Hokkaido University Graduate School of Medicine. Frequency: 4 issues per year. ISSN: 0446-9225 (print), 1779-8429 (online). Journal abbreviation: Sleep Biol Rhythms. Publisher: Wiley-Blackwell, an imprint of John Wiley & Sons, Inc.

Indexed/abstracted in: EMBASE, EMBASE, PubMed, Abstract Journal Database, PsyINFO, Science Citation Index Expanded, SCOPUS.

2. EDITORIAL REVIEW AND ACCEPTANCE

Acceptance: The acceptance criteria for all papers are the quality and originality of the research and its significance to our readership. All manuscripts are peer reviewed. The Editor reserves the right to refuse any material for publication. Final acceptance or rejection rests with the Editorial Board.

Review process: A submitted paper is assigned to one of the associate editors according to the topic of paper. The responsible associate editor appoints more than two reviewers for evaluating the paper and decides whether the paper should be accepted for publication, revised or rejected, according to the reviewers' comments.

Before publication: All manuscripts should be written in a clear, concise, direct style so that they are intelligible to the professional reader who is not a specialist in the particular field. Where contributions are judged as acceptable for publication on the basis of content, the Editor reserves the right to modify manuscripts to eliminate ambiguity and repetition and improve communication between author and reader. If extensive alterations are required, the manuscript will be returned to the author for revision.

3. MANUSCRIPT CATEGORIES

(1) ORIGINAL ARTICLE
Full-length reports of current research in either basic or clinical research.

Word limit: 6000 words excluding abstract but including references, tables and figures.

Abstract: 120 words maximum, unstructured (no use of subheadings).

Description: For arranging the text, please refer to 5. STRUCTURE OF MANUSCRIPT.

(2) SHORT PAPER
Short papers cover new findings that substantially and immediately affect research or clinical practice. Short papers do not include case reports.

Word limit: 1800 words excluding abstract but including references, tables and figures.

Abstract: 100 words, unstructured (no use of subheadings).

References: Maximum 10.

Figures/Tables: Maximum 2.

Description: For arranging the text, please refer to 5. STRUCTURE OF MANUSCRIPT.

(3) CASE REPORT
Clinical cases of exceptional interest and novelty are considered for publication. If appropriate, the Editor may ask authors to rewrite case reports as letters to the Editor.

Word limit: 1200 words excluding abstract but including references, tables and figures.

Abstract: 100 words, unstructured (no use of subheadings).

References: Maximum 10.

Figures/Tables: Maximum 2.

Description: For arranging the text, please refer to 5. STRUCTURE OF MANUSCRIPT.

(4) LETTERS TO THE EDITOR
Letters may be submitted to the Editor on any topic of discussion: clinical observations, as well as comments on papers published in recent issues. Letters to the Editor are subject to peer review. Letters can use an arbitrary title.

The responses to the letter from authors must cite the title of the letter. E.g. Response to [Title of Letter]. This ensures that readers can track the line of discussion.

Word limit: 500 words.

Abstract: No abstract.

References: Maximum 3.

Figures/Tables: Maximum 2.

(5) REVIEW ARTICLE
Survey, evaluation, and critical interpretation of recent research, data and concepts in the fields covered by the journal review articles will undergo peer review prior to acceptance.
Word limit: 8000 words excluding abstract but including references, tables, figures.
Abstract: 250 words maximum, unstructured (no use of subheadings).
Figures/tables: Minimum 1. If figures or tables have been reproduced from another source, a letter from the copyright holder (usually the Publisher) stating authorization to reproduce the material must be attached to the covering letter.
Discussion: Reviews are comprehensive analyses of specific topics.

4. Submission of Manuscript
Manuscripts must be submitted online at: http://mc.manuscriptcentral.com/str
If there are any problems using the site or managing a manuscript, please contact Manuscript Central/ScholarOne for technical support: Support@ScholarOne.com
Authors must supply an email address at all correspondence will be by email.

1. General
All articles submitted to the Journal should comply with these instructions. Otherwise, the manuscript will be returned to the author and publication may be delayed.

- Do not use ‘Enter’ at the end of lines within a paragraph.
- Turn the hyphenation option off, include only those hyphens that are essential to the meaning.
- Specify any special characters used to represent non-English characters.
- Do not use i (i.e.) for (one), O (capital o) for 0 (zero) or ß (German esszett) for β (Greek beta).
- Use a tab, not spaces, to separate data points in tables. If you use a table editor function, ensure that each data point is contained within a unique cell (i.e. do not use carriage returns within cells).

2. Covering Letter
Authors must provide the covering letter separately from the title page, and must declare in it that the content has not been published or submitted for publication elsewhere except as a brief abstract in the proceedings of a scientific meeting or symposium.

The covering letter must also contain an acknowledgment that all authors are in agreement with the content of the manuscript. It is required that all authors be registered at Manuscript Central by submission.

Authors must also state that the protocol for the research project has been approved by an Ethics Committee (ref. 8). In the case of human experiments, the authors must conform to the provisions of the declaration of Helsinki in 1995 (as revised in Edinburgh 2000), and provide a statement that the subject of the study gave informed consent. Patient anonymity should be preserved.

In a case of clinical trial, authors should include the name of the trial register and the registration number (ref. 9) in the cover letter if you wish the editor(s) to consider an unregistered trial, please explain briefly why the trial has not been registered.

5. Structure of Manuscript
The length of manuscripts must adhere to the specifications under the section Manuscript Categories. Manuscripts that do not adhere to the following instructions will be returned to the corresponding author for technical revision before undergoing peer review (unsubmitted).

Manuscripts should be presented in the following order: (1) title page; (2) abstract and key words; (3) text; (4) acknowledgments including disclosure; (5) references; (6) figure legends; (7) tables and (8) figures. Note that the text is not allowed and any such material should be incorporated into the text as parenthetical matter.

1. Title Page
The title page should contain: (i) manuscript category; (ii) the title of the paper; (iii) the running title of the paper; (iv) the full names of the authors and their institutions; (v) the addresses of the institutions at which the work was carried out together; (vi) the full postal and email address, plus facsimile and telephone numbers, of the corresponding author; and (vii) a word count.

The title should be less than 120 characters. Do not use abbreviations in the title, other than common abbreviations such as RCT, DNA and so on. A short running title (less than 40 characters including spaces) should also be provided.

2. Abstract and Keywords
The abstract must adhere to the specifications in Manuscript Categories. The abstract should not contain abbreviations other than common abbreviations or references. 3 to 7 key words should be supplied below the abstract in the main text.

3. Text
Authors should set out the sections of the manuscript as follows: Introduction, Materials and Methods, Results, Discussion, in this order. Please note that the requirements differ according to manuscript types. Please refer to Manuscript Categories.

4. Acknowledgments/Disclosure
Authors should declare any financial support or relationships that may pose a conflict of interest. The source of financial grants and other funding must be disclosed.

Authors may consider, as a guide for financial disclosure, reporting interests as described in the following list: (i) employment/leadership position/consultancy/advocacy role; (ii) stock ownership; (iii) patent royalties/licensing fees; (iv) honoraria (e.g., lecture fees); (v) fees for promotional materials (e.g., manuscript fees); (vi) research funding; or (vii) other (e.g., travel, gifts which are not related to research).

5. References
The Vancouver System of referencing should be used http://www.universityofcanada.ca/ohm/vancouver-system-for-ehr-refrences/
In the text, references should be cited using superscript Arabic numerals in the order in which they appear. If cited only in tables or figure legends, number them according to the first identification of the table or figure in the text. In the reference list, the references should be numbered and listed in order of appearance in the text. List all authors in the reference list. References to unpublished data and personal communications should not appear in the list but cited in the text only (e.g. Smith A, 2000, unpublished data).


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83
US$53.00/£40.00 for the first three color figures and
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13. TRACKING MANUSCRIPT

1) BEFORE ACCEPTANCE

Authors can track a manuscript's progress through the review process at:
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2) AFTER ACCEPTANCE

Authors can get information about the production process of their paper by registering at
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accepted, through the production process to publication online and in print. Authors can
receive automated emails at key stages of production or they do not need to contact the
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cation in a printed issue. The article is therefore available as soon as it is ready. The
EarlyView article is given a Digital Object Identifier (DOI), which allows the article to be
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valid and can continue to be used to cite and access the article. More information about
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