Sleep and the Hypothalamic-Pituitary-Adrenocortical Activity:
Biological Processes Associated with Psychosocial Adjustment During Childhood and Adolescence

**Inauguraldissertation**
zur
Erlangung der Würde
einer Doktorin der Philosophie
vorgelegt der
Fakultät für Psychologie
der Universität Basel

von

Nadine Perkinson-Gloor

aus Birrwil, AG

Basel, 2015

UNI
BASEL

Genehmigt von der Fakultät für Psychologie

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# ACKNOWLEDGEMENTS

This dissertation would not have been possible without the help and support of the people around me.

First of all, I would like to sincerely thank my supervisor Prof. Dr. Sakari Lemola, for giving me the possibility to be a part of his ambitious and very interesting research projects, his guidance, encouragement, patience, and understanding. I would also like to thank Prof. Dr. Alexander Grob for serving as my supervisor in the first part of my doctorate.

I would like to thank Prof. Dr. Jutta Mata for acting as co-referee of my work and Prof. Dr. Rainer Greifeneder for serving in the dissertation committee.

Throughout my doctorate, a number of junior research assistants, interns, and master students put a lot of time and effort into our research projects and made them a success. I would like to thank all of them sincerely! A special thank you goes to Nathalie Schenk and Natalie Maurer, who made sure that our project ran smoothly while I was on maternity leave and who continued to do so when I came back to work, and freed my time to focus on the completion of my dissertation.

I owe my gratitude to all my co-authors and colleagues for all their support, helpful comments, and the pleasant work environment.

Last but not least, I would like to thank my family and friends. I especially thank my parents for their unconditional support and endless hours of babysitting and my brother for challenging me with his critical thinking and for looking after Evan even when he was sick. Most importantly though, I thank my husband, Shaun, for always believing in me, encouraging me to keep going and for always and again and again assuring that everything will be ok. And of course for being a wonderful dad to our amazing son Evan, who I would like to thank for making the last one and a half years so special, for bringing so much fun into our lives and for being a great sleeper from the start!

# TABLE OF CONTENTS

# ABSTRACT

Sleep and the hypothalamic-pituitary-adrenocortical (HPA) activity are two biological processes that play a vital role for physical and mental health as well as general well-being. The aim of this cumulative dissertation containing three studies is to complement and extend existing research on the role of sleep and the HPA activity for psychosocial adjustment during childhood and adolescence, as well as in very preterm children and to further extend knowledge on in-home PSG sleep. Taken together, findings showed that less restorative sleep and a shorter sleep duration were associated with poorer psychosocial adjustment during middle childhood and adolescence. A meditational model further showed that less restorative sleep partially accounted for poorer psychosocial adjustment in very preterm children. In adolescence, the association of sleep and psychosocial adjustment was mediated by daytime tiredness and behavioral persistence and furthermore, a delayed school start time was associated with longer sleep duration and less daytime tiredness. Additionally, a blunted HPA activity was related to more externalizing problems. Although very preterm children showed a faster decline in evening cortisol levels compared to full-term children, HPA activity did not mediate the association between prematurity and psychosocial adjustment. Furthermore, findings showed that sleep assessed via in-home PSG remained stable over one and a half years and thus indicated that in-home PSG constitutes a reliable measure of children's habitual sleep. The present dissertation emphasizes the importance of restorative and sufficient sleep for psychosocial adjustment during middle childhood and adolescents and even more so in very preterm children representing a population of children at risk for poor psychosocial adjustment.

## 1. Introduction

In the last few decades, research interest on the role of biological processes such as sleep and the hypothalamic-pituitary-adrenocortical (HPA) activity for physical and mental health has grown rapidly (Clements, 2013; Dinges, 2014). Sleep and the HPA activity are two biological processes that play a vital role in humans' daily life. Sleep is a state characterized by reduced behavioral control and responsiveness, that serves a number of functions essential for health, well-being, and even survival (Cappuccio, D'Elia, Strazzullo, & Miller, 2010; Rechtschaffen, Bergmann, Everson, Kushida, & Gilliland, 1989), including energy conservation, restoration and reparation of key cellular components, and facilitating learning and memory through changes in brain plasticity and synaptogenesis (Mignot, 2008). The HPA axis on the other hand, is the body's neuroendocrine response to stress and challenges, which results in the activation of a number of physiological and behavioral responses to reestablish homeostasis maintained by all living organisms (Nicolaides, Kyratzi, Lamprokostopoulou, Chrousos, & Charmandari, 2015). Inadequate responses to stress, such as a prolonged, exaggerated or blunted HPA activity may have detrimental effects on health and well-being (Nicolaides et al., 2015).

During childhood and adolescence, sleep disturbances are common (Fricke-Oerkermann et al., 2007; Gradisar, Gardner, & Dohnt, 2011) and are associated with a number of adverse physical and mental health outcomes, including obesity and behavioral problems (Astill, Van der Heijden, Van IJzendoorn, & Van Someren, 2012; Chen, Beydoun, & Wang, 2008). Similarly, alterations in the HPA activity, i.e. increased or prolonged activation as well as decreased activation of the HPA axis, for instance as a consequence of an overexposure of glucocorticoids in the perinatal period (Lemola, 2015), are related to poor psychosocial adjustment during childhood and adolescence (Hartman, Hermanns, de Jong, & Ormel, 2013).

As a population at increased risk for poor psychosocial adjustment as well as proposed poorer sleep and alterations in the HPA activity, very preterm born children constitute a population of special interest when examining sleep and HPA activity as biological predictors of psychosocial adjustment (for a review see Lemola, 2015). To date however, it remains to be explored, whether alterations in sleep and the HPA activity may be underlying mechanisms accountable for very preterm children's increased risk for poor psychosocial adjustment.

Although there is evidence that sleep and the HPA activity are two important biological processes associated with psychosocial adjustment during childhood and adolescence, there are still a number of important gaps in research. Regarding sleep, little is known about possible pathways that may explain the association between inadequate sleep and poor psychosocial adjustment. Furthermore, most studies, especially studies including childhood samples, are based on subjective measures of sleep, whereas only few studies examined sleep objectively using polysomnography (PSG) and even more rarely using unattended in-home PSG. Accordingly, there is a paucity of knowledge about sleep measured with unattended in-home PSG during childhood in general, such as its psychometric properties as well as about associations of sleep stages and other PSG parameters with psychosocial adjustment (Astill et al., 2012). Regarding HPA activity, results are still equivocal concerning its association with psychosocial adjustment during childhood (Hartman et al., 2013). Lastly, only very few studies examined objective sleep and the HPA activity in very preterm children and to date, no study examined the role of PSG-sleep and the HPA activity in association with psychosocial adjustment in very preterm children.

The present dissertation aims to fill these gaps in order to reach a better understanding of the associations of subjective and objective measures of sleep and the HPA activity as biological processes associated with psychosocial adjustment during childhood and adolescence as well as of the psychometric properties of in-home PSG during childhood.

The following chapter provides a theoretical background for the present work, with Chapter 2.1 focusing on sleep, the assessment of sleep, disturbances of sleep, and empirical evidence on the association of subjective and objective measures of sleep and psychosocial adjustment. Chapter 2.2 provides a theoretical background on the HPA activity and empirical evidence on its association with psychosocial adjustment. Chapter 2.3 focuses on very preterm birth and further provides empirical evidence for the role of sleep and the HPA activity as possible mechanisms underlying very preterm children's increased risk for poor psychosocial adjustment. Subsequently, I specify the research questions derived from the empirical background (Chapter 3). Chapter 4 includes a short description of the individual studies and the methods used, which is followed by a synopsis of the results (Chapter 5). The dissertation is concluded with a general discussion of the main findings and suggestions for future research (Chapter 6).

# 2. Theoretical Background

## 2.1 Sleep

Sleep is an active process that can be divided into rapid eye movement (REM) sleep and non-REM (NREM) sleep, which are characterized by specific brain wave patterns, eye movements, and muscle tone (Carskadon & Dement, 2011). NREM sleep can further be divided into stages 1, 2, and slow wave sleep (SWS; stages 3 and 4; American Academy of Sleep Medicine & Iber, 2007; Rechtschaffen & Kales, 1968). Throughout the night, the sleep cycle consisting of the NREM sleep stages and REM sleep are repeated and represent the sleep architecture, with sleep cycles beginning with light sleep (stage 1) and progressing through continuously deeper sleep stages 2 and SWS, followed by REM sleep (Carskadon & Dement, 2011). SWS is considered the most restorative sleep stage (Benington & Heller, 1995; Horne, 1992).

The timing of sleep and wakefulness is regulated by the interplay of two processes. The homeostatic process is dependent on the duration of prior wakefulness and responsible for the rise in sleep propensity during wakefulness and its dissipation during sleep (Borbély & Achermann, 1999). The circadian process is regulated by the body's inner clock, as well as external zeitgebers such as light and darkness, and follows a 24 hour-rhythm (Borbély & Achermann, 1999). Misalignment of the two processes or disturbances in one of the processes may lead to sleep disturbances that are characteristic of mood disorders (Wirz-Justice, 2006).

**2.1.1 Assessment of sleep.** Sleep duration and sleep problems are most commonly assessed with parent- or self-report questionnaires, which is most practical and cost-effective especially in larger samples, but also has its limitations (Sadeh, 2015). Compared to objective measures of sleep, subjectively reported sleep duration is usually overestimated, while especially parent-reported sleep disturbances, such as night wakings, are usually underestimated

(Iwasaki et al., 2010). Polysomnography (PSG) is considered the gold standard in sleep assessment and provides information on objective assessed sleep duration, sleep continuity such as sleep efficiency (the percentage of the total time spent in bed that a person is actually asleep) and night wakings, as well as the sleep architecture. However, most PSG studies are conducted in a sleep laboratory, which is very costly and may negatively influence children's sleep (Golpe, Jiménez, & Carpizo, 2002; Frölich & Lehmkuhl, 2004). PSG assessed at the children's home results in better sleep quality and may more accurately describe children's habitual sleep (Bruyneel et al., 2011). However, PSG studies usually only include one night of sleep assessment and to date it remains unknown, if one night of PSG reflects children's habitual sleep or if it is simply a snapshot of children's sleep. However, only if one night of PSG reflects children's habitual sleep, PSG constitutes a suitable method to examine associations of sleep and psychosocial adjustment. A very limited number of studies with children suggest that PSG sleep patterns remain relatively stable over time (Geiger et al., 2011; Hatzinger et al., 2013), but long-term stability of the individual PSG-derived sleep parameters has not been examined during middle childhood. Behavioral-genetic studies suggest that sleep continuity and sleep architecture are trait-like characteristics and should therefore remain highly stable over time (Linkowski, 1999; Buckelmüller, Landolt, Strassen, & Achermann, 2006). If sleep assessed via one night of in-home PSG remains stable over time, it may be concluded that one night of in-home PSG sleep assessment can be regarded as a reliable measure of children's habitual sleep. Study 3 of the present dissertation aims at filling this gap in research by examining the long-term stability of one night of in-home PSG during middle childhood.

**2.1.2 Sleep and sleep disturbances during childhood and adolescence.** During childhood, sleep disturbances including difficulties initiating and maintaining sleep, or disorders of excessive sleepiness are common and affect around 30-40% of school age children

(Fricke-Oerkermann et al., 2007; Spruyt, O'Brien, Cluydts, Verleye, & Ferri, 2005). Although less common with prevalence rates ranging between 2-5% (Rosen et al., 2003; Spruyt et al., 2005), sleep disordered breathing (SDB) is a serious sleep complaint, characterized by habitual snoring and/or partial or complete blockage of the airways (Rosen et al., 2003). If unrecognized and left untreated, SDB is associated with a number of negative consequences, including impaired cognitive function and behavioral problems (Bourke et al., 2011a; Bourke et al., 2011b).

The main concern regarding sleep during adolescence becomes apparent when considering the average sleep duration, which is around 8 h according to a recent review on sleep patterns during adolescence (Gradisar et al., 2011) and the sleep need of adolescents, which remains at around 9-9.25 h from middle childhood through to adolescence (Carskadon & Acebo, 2002). Thus, insufficient sleep and its consequences, such as excessive daytime tiredness, are a major problem concerning adolescents' sleep (Gibson et al., 2006). The discrepancy between actual sleep duration and sleep need during adolescence can be explained by later bedtimes, caused by a number of significant biological and social developmental changes. Biological developmental changes include changes in the circadian process of sleep, shown by a delayed circadian phase and accordingly an increase in evening preference in association with puberty, as well as changes in the homeostatic process of sleep, shown by a slower accumulation of sleep propensity during wakefulness (Giannotti, Cortesi, Sebastiani, & Ottaviano, 2002; Hagenauer, Perryman, Lee, & Carskadon, 2009; Jenni, Achermann, & Carskadon, 2005). Social developmental changes may include reduced parental control, increases in academic and work-related obligations, and social activities (Crowley, Acebo, & Carskadon, 2007). The interaction of later bedtimes due to the aforementioned developmental changes and early school start times results in sleep deprivation in the majority of adolescents. Large surveys on adolescents' sleep reported that 80-90% of adolescents get less than the recommended 9-9.25 h of sleep on school-nights, and around half of them regularly get an insufficient amount of sleep of less than 8 h (National Sleep Foundation, 2006; Loessl et al., 2008).

**2.1.3 Sleep and psychosocial adjustment during childhood and adolescence.** Two relatively recent meta-analyses reported that insufficient and poor sleep during childhood and adolescence is associated with poor psychosocial adjustment (Astill et al., 2012; Dewald, Meijer, Oort, Kerkhof, & Bögels, 2010). More specifically, in studies including healthy 5-12 years old children, short sleep duration but not sleep efficiency was associated with internalizing and externalizing behavioral problems (Astill et al., 2012). As only a small number of studies reported on sleep efficiency, indicating a shortage of studies applying objective measures of sleep, these results must be interpreted with caution (Astill et al., 2012). In studies including children and adolescents aged 8-18 years, both sleep duration and sleep quality were related to school performance, with sleep quality showing a stronger relation than sleep duration (Dewald et al., 2010). The majority of the studies included in the two meta-analyses were cross-sectional and do therefore not allow causal interpretation. Experimental studies with school age children, however, reported a causal impact of moderate manipulations in sleep duration on emotional and behavioral problems (Gruber, Cassoff, Frenette, Wiebe, & Carrier, 2012; Vriend et al., 2013). Additionally, a small number of longitudinal studies suggest that poor sleep precedes and predicts poor psychosocial adjustment (Fredriksen, Rhodes, Reddy, & Way, 2004; Gregory, Van der Ende, Willis, & Verhulst, 2008).

A number of hypotheses aim at explaining the role of sleep for psychosocial adjustment. One of the most prominent hypotheses is the so-called synaptic homeostasis hypothesis, which proposes that the synaptic strength of neuronal connections increases during wakefulness, while the function of sleep, and most importantly of SWS, is to downscale this synaptic strengths (Tononi & Cirelli, 2006). Thus, sleep renormalizes synaptic strength and consequently leads to energy and space savings in the brain, and further benefits learning and memory (Tononi & Cirelli, 2006). According to the sleep homeostasis theory, sleep deprivation results in a synaptic overload of neocortical or limbic circuits that may manifest in cognitive and emotional impairments (Tononi & Cirelli, 2006). Another hypothesis relevant to the role of sleep for psychosocial adjustment is the overnight therapy hypothesis (van der Helm & Walker, 2009), which proposes that during sleep, affective neural systems are modulated and recent emotional experiences are processed. These processes lead to appropriate reactivity of the limbic system and associated autonomic networks during succeeding wakefulness (van der Helm & Walker, 2009). Impaired emotional processing or inadequate emotional reactivity may play fundamental roles in poor psychosocial adjustment (Eisenberg et al., 2001). According to the overnight therapy hypothesis, REM sleep plays an important role in emotional processing as during REM sleep, affective experiences may be reactivated and integrated in pre-existing memories (van der Helm & Walker, 2009).

Both of these theories emphasize the role of specific sleep stages: SWS plays a central role in the synaptic homeostasis hypothesis (Tononi & Cirelli, 2006), whereas the role of REM sleep is emphasized in the overnight therapy hypothesis (van der Helm & Walker, 2009). The vast majority of the studies included in the two meta-analyses mentioned above were, however, based on subjectively assessed sleep, while only a small number of studies were based on PSG-sleep, mostly obtained in the laboratory. Thus, only very few studies examined associations of specific sleep stages and psychosocial adjustment in healthy children and adolescents to date. The limited number of studies that examined objectively assessed sleep via in-home PSG and its association with psychosocial adjustment in healthy children and adolescents are relative consistently reporting that decreased SWS and/or more light sleep (particularly increased stage 2 sleep) are related to increased risk of poor psychosocial adjustment in preschoolers and adolescents (Brand et al., 2010; Brand et al., 2014; Hatzinger et al., 2013). Study 2 of the present dissertation aims at replicating and extending these results by examining in-home PSG sleep and its association with psychosocial adjustment in a relatively large sample of children aged 6-10 years.

Although associations of subjectively assessed sleep and psychosocial adjustment have been examined more extensively compared to associations with objectively assessed sleep, little is known on possible pathways or mediating variables explaining the proposed associations. A common complaint related to both short sleep duration and poor psychosocial adjustment during adolescence is daytime tiredness (Anderson, Storfer-Isser, Taylor, Rosen, & Redline, 2009; Dewald et al., 2009). Excessive daytime tiredness, mostly assessed as the tendency of falling asleep in situations involving low levels of stimulation (Johns, 1993), affects around 20-40% of adolescents (Gradisar et al., 2011). Daytime tiredness is more strongly associated to school performance than sleep quality or sleep duration (Dewald et al., 2009), and is further associated with compromised well-being (Brand et al., 2010), behavioral problems (Perfect, Levine-Donnerstein, Archbold, Goodwin, & Quan, 2014), and more self-reported depression and anxiety (Moore et al., 2009). Accordingly, daytime tiredness may mediate the association between sleep duration and psychosocial adjustment.

Although only based on a limited number of studies, it is further possible that inadequate sleep and tiredness negatively influence behavioral persistence, i.e. self-discipline, motivation, and the ability to persist in achieving goals, which plays an important role in academic achievement as well as in general well-being (Andersson & Bergman, 2011; Cooper, Wood, Orcutt, & Albino, 2003; Duckworth & Seligman, 2005; Wills, Isasi, Mendoza, & Ainette, 2007). Indications for an association between inadequate sleep and tiredness with behavioral persistence mainly stem from research regarding chronotypes, reporting that students with an evening preference showed lower self-control, lower learning motivation, and greater procrastination (Digdon & Howell, 2008; Roeser, Schlarb, & Kübler, 2013). Evening preference is related to shorter sleep duration and increased daytime tiredness, especially on school days requiring early rise times (Giannotti et al., 2002). Furthermore, children who felt better rested and had a longer sleep duration reported higher achievement motivation, indicating a relationship between sleep duration, daytime tiredness, and behavioral persistence (Meijer, Habekothé, & Van Den Wittenboer, 2000). Derived from the proposed relations, Study 1 examined a meditational model, with daytime tiredness and behavioral persistence mediating the association between sleep duration and psychosocial adjustment.

As described in Chapter 2.1.2, the main concern regarding adolescents' sleep is chronic sleep deprivation as a result of a shift in bedtimes and early rise times due to early school start times. While increasing sleep duration through earlier bedtimes is often unrealistic, a number of studies have shown that a 30 to 90 minutes delay in school start times not only increases adolescents' sleep duration, but also resulted in a reduction of daytime sleepiness, fatigue, depressed mood, and improved attention and performance (Lufi, Tzischinsky, & Hadar, 2011; Owens, Belon, & Moss, 2010; Wahlstrom, 2002). However, delaying school start times is associated with logistical considerations at the community level and may lead to schedule disruptions for all parties involved (Kirby, Maggi, & D'Angiulli, 2011). Thus, it is of great importance to establish if a short delay in school start times, which may be more easily implemented, results in improved sleep and psychosocial adjustment in adolescents. Therefore, Study 1 examined the sleep duration, daytime functioning, and psychosocial adjustment of students attending an early versus late starting school, i.e. 7:40 a.m. vs. 8:00 a.m.

## 2.2 Hypothalamic-Pituitary-Adrenocortical Axis

A second biological process relevant for the present dissertation is the HPA activity. The HPA axis is activated in response to acute physical and psychological stress, leading to the secretion of a series of hormones with the end product cortisol, which in turn regulates the HPA activity through a number of feedback loops to prevent a maladaptive stress-response shown by an excessive or prolonged activation of the HPA axis (Buitelaar, 2013; Nicolaides et al., 2015). But not only a hyperactive HPA axis is dysfunctional, also a blunted stress response is associated with a number of negative mental and physical health outcomes (Tsigos & Chousos, 2002).

Additionally to the reactivity of the HPA axis in response to stress, the basal HPA activity follows a specific circadian rhythm, with the highest cortisol levels in the early morning, followed by a steady decline throughout the day, reaching its lowest levels during the first half of the night (Fries, Dettenborn, & Kirschbaum, 2009). Furthermore, cortisol levels increase rapidly after awakening, reaching peak levels within 20 to 30 minutes after awakening. This distinct increase in cortisol, the so-called cortisol awakening response (CAR), is present in the majority of children (Bäumler, Kirschbaum, Kliegel, Alexander, & Stalder, 2013) and is considered a reliable measure of the HPA reactivity (Schmidt-Reinwald et al., 1999).

The HPA axis is influenced and programmed by the fetal and neonatal environment, such that an excessive exposure to cortisol during the fetal and neonatal development may lead to permanent alterations in the basal diurnal activity and reactivity of the HPA axis (Kapoor, Dunn, Kostaki, Andrews, & Matthews, 2006). The fetal and neonatal programming of the HPA axis has been shown in animal studies, reporting that oral administration of synthetic glucocorticoids to pregnant primates lead to an hyper-reactive HPA axis in their offspring (de Vries et al., 2007) as well as in longitudinal human studies, reporting that prenatal cortisol levels were positively related to children's cortisol levels in response to a mild stressor at school age (Gutteling, Weerth, & Buitelaar, 2005). Additionally, animal and human studies reported that early maternal separation is associated with an up- or down-regulation of the basal HPA activity and the CAR in the adult offspring, depending on the developmental stage and severity of maternal separation (Kumari, Head, Bartley, Stansfeld, & Kivimaki, 2013; Nishi, Horii-Hayashi, Sasagawa & Matsunaga, 2013; Tyrka et al., 2008).

**2.2.1 HPA activity and psychosocial adjustment during childhood and adolescence.** Although the HPA activity as a biological predictor of psychosocial adjustment has been studied extensively in children and adolescents, results are still equivocal (Hartman et al., 2013). Generally, externalizing behavior problems are associated with a blunted HPA activity, while internalizing problems seem to be associated with an increased HPA activity (Alink et al., 2008; Hartman et al., 2013). But while the meta-analysis by Alink et al. (2008) only reported the inverse relation with externalizing problems to be true for basal cortisol levels but not for cortisol reactivity to a stressor, a more recent study found this association only with regard to the HPA reactivity to a stressor (Hartman et al., 2013). Concerning internalizing problems, results are less consistent, reporting both an increased and a blunted HPA activity, especially when considering the concurrent association between the HPA activity and internalizing problems (Hartman et al., 2013; Ruttle et al., 2011). Longitudinal studies, however, reported more consistently that higher basal cortisol levels precede later internalizing problems in childhood and adolescence (Halligan, Murray, Martins, & Cooper, 2007; Miller, Chen, & Zhou, 2007; Smider et al., 2002). Associations between the CAR and psychosocial adjustment are generally weak, with the most support found for the association between a higher CAR and internalizing problems (Dietrich et al., 2013). A number of hypothesized mechanisms underlying the associations between the HPA activity and psychosocial adjustment have been proposed. The fearlessness theory for instance proposes that children showing more externalizing behavior are less sensitive to stress and thus show lower arousal resulting in lower levels of anxiety and more outgoing and externalizing behavior (Raine, 1996). The same mechanisms, albeit in the opposite direction, may be working for children showing more internalizing behavior.

## 2.3 Very Preterm Birth

Very preterm birth, defined as birth before completion of the 32nd week of gestation, affects around 1% of all births in Switzerland (Rüegger, Hegglin, Adams, & Bucher, 2012) and is associated with an increased risk of poor psychosocial adjustment during childhood (Aarnoudse-Moens, Weisglas-Kuperus, van Goudoever, & Oosterlaan, 2009). According to the concept of developmental origins of health and disease (DOHaD), even small changes in the pre- and postnatal developmental environment can lead to an altered predisposition for health and disease across the life-span (Barker, 2002; Hanson & Gluckman, 2007). As very preterm born children spent what would be the last trimester of pregnancy in a non-optimal environment outside of the womb, it has been proposed that premature birth may provide a model to study the consequences of a non-optimal environment during this sensitive period of fetal development (Lemola, 2015). The developmental environment outside of the womb leads to a number of challenges for the very preterm child. Most importantly, lung development is only completed after the 32nd week of gestation, but can be accelerated by the prenatal administration of corticosteroids under the threat of premature birth (Roberts & Dalziel, 2006). The introduction of prenatal corticosteroid administration lead to a decrease in the overall mortality rate as well as an increase in survival without major complications of very preterm born children (Roberts & Dalziel, 2006). However, very preterm children are still at risk for serious complications including disorders of the respiratory system and intraventricular hemorrhage (Saigal & Doyle, 2008).

**2.3.1 Psychosocial adjustment of very preterm children.** As described in the previous section, outcomes after very preterm birth improved significantly concerning mortality and serious complications, but very preterm children still show an increased risk for subtler consequences such as poor psychosocial adjustment (Doyle & Saigal, 2009). A relatively recent meta-analysis including 9 studies on psychosocial adjustment reported that very preterm born children show more attention problems and more internalizing problems compared to full-term children (Aarnoudse-Moens et al., 2009). The strongest effect was found for attention problems, which is in line with studies reporting significantly higher prevalence rates of attention deficit/hyperactivity disorder (ADHD), specifically of the inattentive subtype, in very preterm compared to full-term children (for a review see Dempsey et al., 2015). Internalizing problems in very preterm children are mainly characterized by emotional symptoms, including anxiety, depressive symptoms, and low self-esteem (Dempsey et al., 2015). In contrast to a meta-analysis by Bhutta, Cleves, Casey, Cradock, and Anand (2002) which showed that 9 out of 13 included studies reported more externalizing problems in very preterm compared to full-term children, the meta-analysis conducted by Aarnoudse-Moens et al. (2009) found no increased risk in externalizing problems for very preterm children.

As critically raised in a recent review by Dempsey et al. (2015), little is known on causal pathways of poor psychosocial adjustment after very preterm birth. The following two paragraphs propose two possible pathways through which very preterm birth may impact on the increased risk of poor psychosocial adjustment, which have been examined in Study 2 of the present dissertation: Altered sleep patterns and alterations in the HPA activity.

**2.3.2 Sleep of very preterm children.** As summarized in Chapter 2.1.3, insufficient and poor sleep is associated with poor psychosocial adjustment in healthy school age children. Very preterm children at school age showed a 3- to 5-fold increase in the odds of SDB compared to full-term children (Rosen et al., 2003). Possible causes for the increased risk of SDB in very preterm children may be attributable to the underdeveloped respiratory system at birth and its consequences (Hibbs et al., 2008). On the other hand, parent-reported sleep during childhood and sleep assessed via actigraphy in an adult sample showed no differences in sleep duration and sleep quality of very preterm compared to full-term children and adults

(Iglowstein, Latal Hajnal, Molinari, Largo, & Jenni, 2006; Strang-Karlsson et al., 2008). However, to our knowledge, objectively assessed sleep of very preterm children at school age has not been examined to date. Therefore, it remains unknown, whether very preterm children show poorer objectively assessed PSG-sleep, including alterations of the sleep architecture at school age and whether poorer sleep may be a possible mechanism explaining the increased risk of poor psychosocial adjustment.

**2.3.3 HPA activity of very preterm children.** As summarized in Chapter 2.2, the HPA activity is highly susceptible to fetal programming. Prolonged stress during neonatal intensive care after very preterm birth, including painful treatment procedures, separation from parents as well as treatment with corticosteroids to accelerate lung development may lead to an overexposure of corticosteroids, which in turn may lead to persistent alterations of the HPA activity (Grunau et al., 2013; Karemaker et al., 2008; Mörelius, Örtenstrand, Theodorsson, & Frostell, 2015). To date, research on the HPA activity in very preterm children is scarce and results are somewhat equivocal. A number of studies report a down regulation of the HPA activity of preterm children and adults shown by a blunted cortisol response to psychosocial stress or lower diurnal cortisol levels (Buske-Kirschbaum et al., 2007; Kaseva et al., 2014; Wadsby, Nelson, Ingemansson, Samuelsson, & Leijon, 2014). However, other studies reported an increased cortisol response to psychosocial stress (Quesada, Tristão, Pratesi, & Wolf, 2014), and similar diurnal cortisol profiles of very preterm and full-term children, except that very preterm children showed slightly higher cortisol levels at bedtime (Brummelte et al., 2015). Results concerning the CAR of very preterm children are also inconclusive. Although both Buske-Kirschbaum et al. (2007) and Quesada et al. (2014) reported higher cortisol levels right at awakening, the first study found no difference in the CAR between preterm and full-term children, while the latter reported a flattened CAR in preterm children. It must be noted, that some of the previously mentioned studies included children with all degrees of prematurity (Buske-Kirschbaum et al., 2007; Quesada et al., 2014), while others included children with all degrees of prematurity but with very low birth weight (≤1500g; Kaseva et al., 2014; Wadsby et al., 2014). To the best of my knowledge, no study examined the HPA activity in very preterm children only. Furthermore, associations between the HPA activity and psychosocial adjustment in preterm children, let alone in very preterm children have not been examined to date. Thus, it remains to be explored, whether alterations in the HPA activity mediate the association between very preterm birth and psychosocial adjustment.

## 3. Research Questions

The aim of the present dissertation is to complement existing research on the role of sleep and the HPA activity as biological processes associated with psychosocial adjustment during childhood and adolescence by shedding light on possible pathways mediating the proposed associations as well as by including very preterm born children as a population at risk. Furthermore, the dissertation aims at examining the reliability of in-home PSG during childhood. In particular, the present dissertation addresses the following research questions:

1. Sleep as a biological predictor of psychosocial adjustment:
   a. Is subjective and objective sleep associated with psychosocial adjustment? (Study 1 and 2)
   b. Do daytime tiredness and behavioral persistence mediate associations of sleep and psychosocial adjustment? (Study 1)
   c. Is a modestly delayed school start time related to a longer sleep duration and better psychosocial adjustment? (Study 1)
2. HPA activity as a biological predictor of psychosocial adjustment: Is the HPA activity associated with psychosocial adjustment? (Study 2)
3. Sleep and the HPA activity as biological predictors of psychosocial adjustment in very preterm children:
   a. Do alterations in objective measures of sleep mediate the effect of very preterm birth on psychosocial adjustment? (Study 2)
   b. Do alterations in the HPA activity mediate the effect of very preterm birth on psychosocial adjustment? (Study 2)
4. Intra-individual stability of in-home PSG: Does one night of in-home PSG show long-term intra-individual stability during middle childhood? (Study 3)

# 4. Methods

## 4.1 Studies and Samples

**Study 1 (Perkinson-Gloor, Lemola, & Grob, 2013).** The aims of Study 1 were to examine the association of sleep duration and psychosocial adjustment indicated by school grades and positive attitude towards life as well as the potentially mediating role of daytime tiredness and behavioral persistence in the proposed association. Additionally, we examined whether a modestly delayed school start time was associated with sleep duration, daytime tiredness, behavioral persistence, and psychosocial adjustment. The sample for Study 1 was recruited from 8th and 9th grade classes of all six lower track secondary schools of Basel, Switzerland during spring of 2010 and 2011. The final sample consisted of 2716 students with a mean age of 15;5 years old (*SD* = 0;10 years).

**Study 2 (Perkinson-Gloor, Hagmann-von Arx, Brand, Holsboer-Trachsler, Grob, Weber, & Lemola, 2015) and Study 3 (Perkinson-Gloor, Hagmann-von Arx, Brand, Holsboer-Trachsler, Grob, Weber, & Lemola, *submitted*).** The aim of Study 2 was to examine the associations between PSG-sleep and the HPA activity with psychosocial adjustment and further examine whether alterations in sleep and the HPA activity in very preterm children account for differences in psychosocial adjustment between very preterm and full-term children. The sample of Study 2 consisted of 113 children, including 58 healthy very preterm children (<32nd gestational week; age: *M* = 8.2 years, *SD* = 1.3) and 55 full-term children (age: *M* = 8.3 years, *SD* = 1.3).

The aim of Study 3 was to examine the reliability of one night of in-home PSG by examining its long-term intra-individual stability in order to strengthen the findings from Study 2. Therefore, on average 18.5 months after completion of Study 2, 69 (T1: age: *M* = 8.2 years, *SD* = 1.3; T2: age: *M* = 9.8 years, *SD* = 1.3) of the 113 children completed a follow-up assessment.

The very preterm children were recruited from an initial cohort of 217 very preterm children born between June 2001 and December 2005 and treated at the University Children's Hospital Basel, Switzerland. Of the initial sample, 84 (39%) children met the exclusion criteria (no information on neurobehavioral development until age 2 years, severe developmental delay, insufficient German language skills of parents to give informed consent) and 28 (13%) were excluded because they lived outside of Switzerland or more than 100km away from the study center. Of the remaining 105 (48%) eligible children, 90 (86% of eligible children) were contacted by phone and 58 (55% of eligible children and 27% of initial sample) agreed to participate in Study 2. Of the 52 very preterm children with successful PSG, 34 (65%) agreed to participate in the follow-up for Study 3.

The full-term children (>37 weeks of gestation) were recruited from official birth notifications. Study 2 consisted of 55 and Study 3 of 35 full-term children.

### 4.2 Measures

**Sleep.** Study 1 included a subjective measure of sleep duration, asking students to indicate their usual bedtime and rise time on school days and weekends on preselected time categories. Sleep duration was estimated by calculating the difference between bedtime and rise time using the mean point of the given answering category. The average total sleep duration was calculated as the weighted average school night and weekend sleep duration.

Study 2 and Study 3 both included objective measures of sleep obtained by unattended in-home PSG using the Compumedics Somté PSG (Melbourne, Australia). The following sleep parameters were derived: Sleep duration (total sleep time = time in bed minus time spent awake in hours), sleep continuity (sleep efficiency = total sleep time/time in bed × 100;

nocturnal awakenings = number of arousals from sleep), and sleep architecture (stage 1 sleep, stage 2 sleep, SWS (stages 3 and 4), REM sleep, and REM latency). Study 2 additionally included a subjective measure to assess SDB with the SDB subscale of the Children's Sleep Habits Questionnaire (CSHQ; Owens, Spirito, & McGuinn, 2000).

**HPA activity.** The HPA activity was assessed with saliva samples to measure free salivary cortisol concentrations. The morning cortisol secretion was assessed with four samples at 0, 10, 20, and 30 min after the child's awakening and the evening cortisol secretion was assessed with four saliva samples at 0, 30, 60, and 90 min after the beginning of the home-visits, which started between 1:00 p.m. and 6:45 p.m. (*M* = 5:01 p.m., *SD* =44 min).

**Psychosocial adjustment.** In Study 1, psychosocial adjustment was measured by assessing adolescents' positive attitude towards life with two items from the Berne Questionnaire on Adolescent Subjective Well-being (Grob, Little, Wanner, Wearing, & EURONET, 1996). Additionally, academic achievement, represented by school grades in mathematics and German language from the school database, was included as an objective measure of psychosocial adjustment, which is closely linked to externalizing and internalizing problems (Masten et al., 2005).

In Study 2, psychosocial adjustment was assessed with the Strengths and Difficulties Questionnaire (SDQ; Goodman, 1997). Parents rated their child's psychosocial adjustment on two domains of behavioral problems (conduct problems, hyperactivity-inattention) and two domains of emotional problems (emotional symptoms, peer problems). Additionally, the four domains build a composite score of total behavioral/emotional difficulties.

**Daytime tiredness and behavioral persistence.** Study 1 additionally included a measure for daytime tiredness (two items) and a measure for behavioral persistence (four items; Fend & Prester, 1986).

# 5. Synopsis of Results

The following section summarizes the results of the studies included in the present dissertation according to the aforementioned research questions.

## 5.1 Sleep as a Biological Predictor of Psychosocial Adjustment

Results confirmed that both inadequate subjective sleep and less restorative objective sleep was related to poorer psychosocial adjustment. Adolescents with an insufficient sleep duration of less than 8 h showed a less positive attitude towards life and lower academic achievement compared to their counterparts sleeping more than 8 hours (Study 1). Regarding objective measures of sleep, more stage 2 sleep and less SWS were related to more total behavioral/emotional difficulties. Furthermore, more stage 2 sleep was associated with more hyperactivity-inattention, while less SWS was associated with more peer problems. More parent-reported SDB was related to more conduct problems (Study 2).

Turning the focus on the proposed mediating variables daytime tiredness and behavioral persistence, structural equation models revealed that daytime tiredness and behavioral persistence partially mediated the association of sleep duration and positive attitude towards life, and fully mediated the association of sleep duration and academic achievement (Study 1).

Regarding school start times, results showed that a modestly delayed school start time by 20 min (starting at 8:00 a.m. instead of 7:40 a.m.) is related to a longer sleep duration on school-nights and less daytime tiredness. However, the modestly delayed school start time was not related to psychosocial adjustment, such that there were no differences in positive attitude towards life between students from early or late starting schools (Study 1).

## 5.2 HPA Activity as a Biological Predictor of Psychosocial Adjustment

The results of Study 2 revealed that the increase in morning cortisol secretions (AUCi) and the evening cortisol secretion (AUCg) were associated with psychosocial adjustment, shown by negative associations with conduct problems. Cortisol secretion was not associated with any other dimension of psychosocial adjustment.

### 5.3 Sleep and the HPA Activity as Biological Predictors of Psychosocial Adjustment in Very Preterm Children

Study 2 showed that prematurity status was associated with poorer psychosocial adjustment, shown by increased total behavioral/emotional difficulties and increased emotional symptoms. To examine whether differences in sleep and/or the HPA activity accounted for the differences in psychosocial adjustment between very preterm and full-term children, mediation analysis was conducted, if the preconditions were fulfilled, i.e. (1) a significant association between the independent variable (prematurity status) and the mediator (sleep and/or HPA activity indices), and (2) a significant association between the mediator (sleep and/or HPA activity indices) and the dependent variable (psychosocial adjustment; Baron & Kenny, 1986). Regarding the first precondition, prematurity status was negatively associated with SWS and positively with stage 2 sleep and nocturnal awakenings. However, prematurity status was not related to other objective measures of sleep or SDB. Regarding the HPA activity as a potential mediator, prematurity status was associated with a faster decline in evening cortisol secretion and a lower overall evening cortisol secretion, but not with morning cortisol secretion. Regarding the second precondition, only stage 2 sleep and SWS were associated to the dimensions of poor psychosocial adjustment that differed between very preterm and full-term children, shown by a positive association of stage 2 sleep and a negative association of SWS with total behavioral/emotional difficulties. Therefore, stage 2 sleep and SWS fulfilled the preconditions of mediation. As SWS and stage 2 sleep were negatively related and as they were differentially related to total behavioral/emotional difficulties, mediation analysis was conducted with the ratio of SWS and light sleep (stages 1 and 2 together), representing an index of a favorable sleep pattern. Mediation analysis showed that the association between prematurity status and total behavioral/emotional difficulties was partially mediated by sleep, such that prematurity status was negatively associated with the deep sleep to light sleep ratio, representing a favorable sleep pattern, which in turn was negatively associated with total behavioral/emotional difficulties.

There was no indication that alterations in the HPA activity mediate the effect of very preterm birth on psychosocial adjustment, as the preconditions for mediation were not fulfilled.

### 5.4 Intra-Individual Stability of In-Home PSG

Study 3 showed that one night of in-home PSG shows substantial stability over 18.5 months with regard to sleep duration, moderate stability with regard to stage 2 sleep (min) and SWS (min, %), and fair stability with regard to sleep efficiency, nocturnal awakenings, stage 2 sleep (%), and REM sleep (min, %). However, no significant stability was found for stage 1 sleep (min, %) and REM latency.

# 6. General Discussion

The aim of the present dissertation was to expand the current knowledge of sleep and the HPA activity as biological processes associated with psychosocial adjustment by including subjective and objective measures of sleep and two measures of the HPA activity as well as by examining mediating factors and by including very preterm born children as a population at risk. Furthermore, building on criticism raised regarding the reliability of one night of in-home PSG, the present dissertation additionally examined the stability of this measure.

## 6.1 Sleep as a Biological Predictor of Psychosocial Adjustment

Both subjective and objective sleep was related to psychosocial adjustment, which is in line with previous research (Astill et al., 2012; Dewald et al., 2009). In adolescence, an insufficient subjective sleep duration of less than 8 h was associated with poorer psychosocial adjustment compared to a sleep duration of more than 8 h. However, there were no indications that a sleep duration of more than 9 h, corresponding to adolescents' estimated sleep need of 9-9:15 h (Carskadon & Acebo, 2002), is beneficial with regard to psychosocial adjustment when compared to a borderline sufficient sleep duration of 8-8:59 h. Our results highlight the importance for adolescents to strive for at least 8 h of sleep every night, which may be more realistic than striving to meet the estimated sleep need of 9 h, especially on school days with early school start times, given that social influences and circadian changes often hinder adolescents from falling asleep as early as required (Crowley et al., 2007).

With regard to objective measures of sleep, our results are in line with previous research conducted with preschoolers and adolescents (Hatzinger et al., 2013; Brand et al., 2010, Brand et al., 2014), showing that more stage 2 sleep and less SWS is associated with poorer psychosocial adjustment. Thus, our results are in accordance with the synaptic homeostasis hypothesis, which emphasizes the role of SWS in downscaling synaptic strength

(Tononi & Cirelli, 2006). On the other hand, we found no association between REM sleep and psychosocial adjustment. Therefore, the results of the present dissertation do not support the overnight therapy hypothesis, which emphasizes the role of REM sleep in emotional processing (van der Helm & Walker, 2009). However, the overnight therapy theory is manly based on findings regarding sleep abnormalities in association with mood disturbances such as major depression or post-traumatic stress disorder in adults and may not apply to a non-clinical sample of children (van der Helm & Walker, 2009).

We were further able to show that the association between sleep duration and psychosocial adjustment is partially mediated by daytime tiredness and behavioral persistence with regard to positive attitude towards life and fully mediated with regard to academic achievement in adolescents. It may be argued that intervention approaches to improve adolescents' psychosocial adjustment could aim at improving daytime tiredness, for instance by incorporating naps in the school routine or at improving behavioral persistence, for instance through interventions aiming at enhancing self-discipline. However, it is questionable whether such intervention approaches are desirable and as successful as addressing the underlying problem, i.e. a chronic sleep deprivation, directly. The present work indicated that one of the most promising approaches to increase adolescents sleep duration may be a delay in school start times, by showing that even a modestly delayed school start time by 20 min enabled adolescents to obtain a longer sleep duration. However, although the later school start time was associated with less daytime tiredness, it was not associated with adolescents' psychosocial adjustment, which may indicate that a school start time at 8:00 a.m. is still too early for adolescents. Previous studies reporting positive effects of delayed school start times on psychosocial adjustment were based on schools starting at 8:30 a.m. or later (Lufi et al., 2011; Owens et al., 2010; Wahlstrom, 2002). In fact, only recently the American Academy of Pediatrics (2014) issued a policy statement regarding school start times for adolescents, urging high schools and middle schools to aim for school start times no earlier than 8:30 a.m., to allow students to attain sufficient sleep on school nights. The findings of the present dissertation significantly influenced the decision to change school start times of all primary and secondary schools in Basel to 8 a.m. effective with the start of the school year 2015/2016 (Regierungsratsbeschluss, 2013). This delay in school start times offers the opportunity to examine the impact of later school start times on students across childhood and adolescence longitudinally, allowing to examine how later school start times affect sleep and psychosocial adjustment across different age groups and whether the effects persist over the long term.

### 6.2 HPA Activity as a Biological Predictor of Psychosocial Adjustment

Regarding the HPA activity as a biological process associated with psychosocial adjustment, our results showed an inverse relation between evening cortisol secretion and conduct problems, which is in line with a meta-analysis reporting a hypoactive HPA in association with externalizing problems in school age children (Alink et al., 2007). Thus, our findings are in line with the fearlessness theory proposing a lower sensitivity to stress, resulting in lower arousal in children showing more externalizing behavior, which leads to lower levels of anxiety and consequently more outgoing behavior (Raine, 1996). Furthermore, we found an inverse relation between the CAR and conduct problems, which is in line with previous research reporting a reduced CAR in children with early-onset conduct disorder (von Polier et al., 2013). However, the inverse association between the CAR and externalizing problems was not found in a study conducted with a healthy non-clinical sample (Dietrich et al., 2013). Methodological differences, such as differences in the timing of saliva sampling, may explain the inconsistent results (Michels et al., 2012).

In contrast to our hypothesis, we found no association between the HPA activity and internalizing problems. Previous research found both an increased and a blunted HPA activity when examining associations between the HPA activity and internalizing problems concurrently, most likely dependent on the time elapsed since the onset of internalizing problems (Ruttle et al., 2011). Therefore, it is conceivable that opposing associations between the HPA activity and internalizing problems within our sample lead to the insignificant result, as we were not able to control for the duration since the onset of internalizing problems.

### 6.3 Sleep and the HPA Activity as Biological Predictors of Psychosocial Adjustment in Very Preterm Children

Confirming our hypothesis and in line with previous research, results of the present dissertation indicated that compared to full-term children, very preterm children showed more behavioral problems, i.e. more total behavioral/emotional difficulties and more emotional symptoms (Aarnoudse-Moens et al., 2009; Bhutta et al., 2002), poorer sleep, i.e. more nocturnal awakenings, more stage 2 sleep, and less SWS, indicating a less restorative sleep pattern, and alterations in the HPA activity, i.e. a faster declining as well as a lower overall evening cortisol secretion (Kaseva et al., 2014; Wadsby et al., 2014), indicating a down-regulation of the HPA activity, which may be the result of an overexposure to corticosteroids in the perinatal phase (Grunau et al., 2013; Karemaker et al., 2008).

In contrast to previous findings, we found no differences in hyperactivity-inattention (Aarnoudse-Moens et al., 2009; Bhutta et al., 2002), SDB (Rosen et al., 2003), and morning cortisol secretion (Buske-Kirschbaum et al., 2007; Quesada et al., 2014) between very preterm and full-term children. Methodological issues may explain these contrasting findings. With regard to hyperactivity-inattention, limited statistical power to detect modest effects may explain our non-significant result, as the effect size for the difference in hyperactivity-inattention between very preterm and full-term children was $d = .28$. With regard to SDB, our findings were based on parent-reported SDB, whereas Rosen et al. (2003) used objective measures of respiratory events. However, the less restorative sleep pattern of very preterm children reported in this work may be an indication of breathing problems undetected by the parents. Regarding the morning cortisol secretion, previous studies used a different assessment method of the CAR and included older children of all degrees of prematurity (Buske-Kirschbaum et al., 2007; Quesada et al., 2014).

To my knowledge, we were the first to show that less restorative sleep partially accounted for poorer psychosocial adjustment in very preterm children. Therefore, we were able to show that one pathway through which very preterm birth impacts on psychosocial adjustment during childhood includes alterations in sleep, emphasizing the role of restorative sleep in a population of very preterm children at risk for poor psychosocial adjustment. In contrast to our hypothesis we did not find that alterations in the HPA activity accounted for differences in psychosocial adjustment in very preterm and full-term children. However, our results showed alterations in the HPA activity in very preterm compared to full-term children. It is conceivable, that the HPA reactivity in response to stress would shed more light on associations of the HPA activity and psychosocial adjustment in very preterm children.

## 6.4 Intra-Individual Stability of In-Home PSG

To the best of my knowledge, our study was the first to report that sleep assessed via in-home PSG showed fair to substantial stability over a time period of one and a half years regarding sleep duration, sleep efficiency, nocturnal awakenings as well as the amount and percentage of time spent in stage 2 sleep, SWS, and REM sleep. Thus, our results are in line with behavioral-genetic studies indicating strong trait-like characteristics of sleep architecture in adults (Linkowski, 1999) and further indicated that one night of unattended in-home PSG can be regarded as a reliable method to assess children’s habitual sleep. The strongest stability was found for sleep duration, stage 2 sleep, and SWS, suggesting that these parameters may represent the most reliable sleep indices when assessing sleep with unattended in-home PSG, which is in line with studies conducted with adult samples (Quan et al., 2002). The finding that one night of unattended in-home PSG constitutes a reliable measure of children's habitual sleep, that shows moderate to substantial long-term stability with regard to stage 2 sleep and SWS, further strengthens our findings from Study 2 regarding the association of stage 2 sleep and SWS with psychosocial adjustment, as well as regarding the partial mediation effect of the deep sleep to light sleep ratio on the association between prematurity status and psychosocial adjustment. Furthermore, our findings indicate that unfavorable sleep patterns have the potential to stabilize at an early age and therefore require careful attention in order to counteract the detrimental effects of poor sleep on psychosocial adjustment.

### 6.5 Strengths and Limitations

The strengths of the present dissertation include the multiple methods used to assess biological processes, i.e. subjective (self- and parent-reported sleep parameters) and objective measures (unattended in-home PSG and cortisol levels) of sleep and the HPA activity. Especially the assessment of PSG sleep at the children's home is a major strength of the present dissertation, as it improves the ecological validity of the sleep assessment (Frölich & Lehmkuhl, 2004). Furthermore, the long-term stability of unattended in-home PSG during childhood has not been examined to date, thus the present dissertation contributed greatly to the knowledge on this method of sleep assessment, which has several advantages compared to PSG assessment in the laboratory, including lower subject burden, which is of great importance especially when conducting studies with children (Jacob et al., 1995).

A further strength of the present dissertation is the inclusion of different age groups, i.e. school age children and adolescents, as well as very preterm children as a population at increased risk for poor psychosocial adjustment, allowing a differentiated picture of the role of sleep and the HPA activity as biological associates of psychosocial adjustment dependent on specific child characteristics. For instance, the present work confirmed that insufficient sleep and its association with psychosocial adjustment is a major concern during adolescence, but not during middle childhood, which most likely indicates that preadolescents are still able to fulfill their sleep need, while adolescents are not. However, during middle childhood, less obvious indicators of sleep quality, which can only be assessed using PSG, such as more restorative sleep as indicated by less stage 2 sleep and more SWS were associated with psychosocial adjustment. Therefore, the present dissertation points to the advantage of assessing sleep using PSG, especially in preadolescent children, in order to obtain a more detailed picture of the role of sleep with regard to specific sleep stages for psychosocial adjustment.

Furthermore, by including a sample of very preterm children the present dissertation shed light on the role of sleep and the HPA activity for psychosocial adjustment in a group of generally healthy children at risk for poor psychosocial adjustment, which has not been examined to date. With the rising incidence of very preterm birth and the improved outcomes, the number of very preterm born children who are visiting public school is increasing (Saigal & Doyle, 2008). Accordingly, studying outcomes after very preterm birth and especially mechanisms impacting on these outcomes, such as sleep and the HPA activity is of growing interest and provides important information on possible intervention approaches.

Although the present dissertation has a number of strengths and is able to extent the knowledge in a number of important research areas, it also has its limitations. Most important, the results concerning associations of sleep and the HPA activity as biological associates of psychosocial adjustment are based on cross-sectional designs, and consequently do not allow conclusions on causal relations among the studied variables.

Regarding the assessment of sleep, both our subjective and objective assessment methods have their limitations. In Study 1, sleep duration was estimated from usual bed- and rise times, thus our measure does not account for sleep onset latency and does not include any information on sleep quality. Although objective measures of sleep such as actigraphy or PSG would have been desirable, the implementation in a large sample as the one included in Study 1 would have been very costly and for organizational reasons very difficult to accomplish. Study 2 did include objectively assessed sleep using PSG, but only on a single night, which may reduce reliability of sleep parameters. However, we assessed sleep at the children's home, improving the ecological validity of the sleep assessment and further showed in Study 3, that one night of in-home PSG can be regarded as a reliable method to assess children's habitual sleep patterns. One shortcoming regarding the assessment of sleep in Study 2 is that we did not include objective measures of SDB, which would have been valuable, especially with regard to the very preterm sample, but also entails an increased burden on subjects and may negatively affect children's sleep.

Limitations regarding the assessment of the HPA activity include the assessment on one day only and that no assessment of the HPA activity in response to a standardized psychosocial stressor was included. It is conceivable that the HPA reactivity to psychosocial stress would have resulted in more distinct differences between very preterm and full-term children, which may have accounted for very preterm children's increased risk for poor psychosocial adjustment (cf. Kaseva et al., 2013).

Similarly, assessment of psychosocial adjustment would have benefitted from including multiple informants, including for instance teacher reports or diagnostic interviews to assess clinical symptoms of psychosocial adjustment.

With regard to the intra-individual stability of PSG sleep, our methods do not allow to distinguish between the reliability of the measure and the actual long-term stability of sleep parameters. We hypothesized that sleep architecture would remain stable over time based on behavioral-genetic studies reporting trait-like characteristics of sleep stages (Linkowski, 1999), and therefore concluded that one night of in-home PSG was reliable as sleep architecture did remain relatively stable over time. However, only consecutive nights of unattended in-home PSG repeated after a longer time period would allow examining the test-retest reliability as well as the long-term stability of sleep parameters during childhood.

### 6.6 Conclusions and Outlook

Taken together, the results of the present dissertation point to the importance of sleep and to some extent of the HPA activity as biological processes associated with psychosocial adjustment during childhood and adolescence. Specifically, with regard to middle childhood, restorative sleep patterns are critical for psychosocial adjustment and even more so in a sample of very preterm children at increased risk for poor psychosocial adjustment, while an adequate sleep duration is of great importance for adolescents daytime functioning and psychosocial adjustment. Furthermore, by showing that sleep remains relatively stable over time, the present dissertation shows that it is imperative to put great focus on good sleep quality and adequate sleep duration from an early age.

However, findings of the present dissertation with regard to associations of sleep and the HPA activity with psychosocial adjustment await replication from longitudinal studies, in order to examine whether less restorative sleep, a shorter sleep duration, and alterations in the HPA activity predict and precede poor psychosocial adjustment during middle childhood and adolescence as well as in very preterm children. Similarly, results regarding the stability of in-home PSG-sleep need replication applying a more elaborate study design, including consecutive nights of in-home PSG repeated after a longer interval, which would greatly enhance knowledge regarding in-home PSG and PSG sleep during childhood in general.

Although only of cross-sectional nature, the results of the present dissertation regarding sleep and psychosocial adjustment raise the interest of identifying determinants of adequate and restorative sleep. By adapting the ecological system theory by Bronfenbrenner (1979) to sleep, El-Sheikh and Sadeh (2015) proposed that sleep is influenced by child characteristics (e.g. genetics), the immediate context (e.g. parenting behavior), the social context (e.g. school start times), and the cultural context (e.g. beliefs about sleep), as well as the interaction of these systems. The present dissertation covered few aspects of child characteristics by including different age groups and very preterm born children as well as an important social context by including school start times. Future research should aim at including a wider range of child characteristics and contextual factors influencing sleep and its association with psychosocial adjustment to offer an integrated view on sleep as well as indications for interventional approaches to improve sleep and consequently psychosocial adjustment. With regard to the immediate context for instance, future research should aim at examining the role of the family context, family structure, and parental behavior in association with sleep, including parenting and sleeping arrangements, which may provide important information on interventional approaches. Parenting behavior may for instance influence children's and adolescents' sleep hygiene practices, e.g. by implementing a consistent bedtime routine, setting adequate bedtimes, and limiting electronic devices in the bedroom, which has been associated with more adequate sleep (Mindell, Meltzer, Carskadon, & Chervin, 2009; Calamaro, Mason, & Ratcliffe, 2009). Therefore, future research should examine the role of sleep related parenting behavior as well as the efficacy of interventions aiming at improving sleep hygiene and whether these interventions result in longer sleep duration and more restorative sleep patterns, as well as improved psychosocial adjustment. Behavioral sleep interventions including information on good sleep hygiene showed promising results with regard to parent-reported sleep and psychosocial adjustment (Quach, Hiscock, Ukoumunne, & Wake, 2011).

Concerning the social context, the present dissertation showed that one promising way to increase adolescents' sleep duration is a delay in school start time. Future research may shed more light on other aspects of the social context with regard to sleep, including the role of peers, electronic media use, and social activities, which may become more important during adolescence and are closely related to sleep hygiene practices (El-Sheikh & Sadeh, 2015). One social activity that may positively influence sleep includes physical activity, which has been related to more restorative sleep including less light sleep and more SWS in adolescents (Brand et al., 2010). Accordingly, future research should examine the role of physical activity for restorative sleep and psychosocial adjustment in childhood and whether an experimental increase in physical exercise may improve sleep and psychosocial adjustment in children and adolescents, even in the absence of obvious sleep disturbances. In very preterm children, who engage in less physical activity especially during adolescence and adulthood, promoting physical activity at an early age may be particularly beneficial for sleep and psychosocial adjustment (Dahan-Oliel, Mazer, & Majnemer, 2012).

With regard to child characteristics, future research would benefit greatly from longitudinal studies from childhood through to adolescence to examine maturational changes with regard to sleep and its associations with psychosocial adjustment. For instance, previous research reported a decrease of SWS during adolescence, which may reflect aspects of brain organization and brain development (Jenni & Carskadon, 2004). It would be of great interest to examine how these maturational changes in sleep relate to psychosocial adjustment.

With regard to the HPA activity as a biological process associated with poor psychosocial adjustment, many questions remain unanswered. As stated by Clements (2013), the HPA activity and its associated systems are very complex and associations are seldom as simple as hoped. Future research should aim at shedding more light in this complex research field, for instance by using a longitudinal approach and by including different assessment methods of the HPA activity, such as the CAR, diurnal cortisol levels, the cortisol reactivity in response the stress, as well as hair cortisol, which provides information on the average long-term activity of the HPA axis over time periods of weeks or months independent of situational characteristics (Meyer & Novak, 2012). A longitudinal approach would allow examining developmental trajectories of the associations of the HPA activity and psychosocial adjustment, which would be of special interest with regard to very preterm children.

In sum, findings of the present dissertation point to the importance of a good nights' sleep for psychosocial adjustment during childhood and adolescence. Our findings speak for the necessity to carefully observe sleep and aim at treating possible underlying sleep disturbances, when concerned with children's or adolescents' poor psychosocial adjustment.

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# APPENDIX A

Study 1

Perkinson-Gloor, N., Lemola, S., & Grob, A. (2013). Sleep duration, positive attitude towards life, and academic achievement: The role of daytime tiredness, behavioral persistence, and school start times. *Journal of Adolescence, 36,* 311–318. doi:10.1016/j.adolescence.2012.11.008

Journal of Adolescence 36 (2013) 311–318

Contents lists available at SciVerse ScienceDirect

Journal of Adolescence

journal homepage: www.elsevier.com/locate/jado

# Sleep duration, positive attitude toward life, and academic achievement: The role of daytime tiredness, behavioral persistence, and school start times

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*Keywords:*
Sleep duration
Daytime tiredness
Behavioral persistence
Positive attitude toward life
Academic achievement
School start times

ABSTRACT

Sleep timing undergoes profound changes during adolescence, often resulting in inadequate sleep duration. The present study examines the relationship of sleep duration with positive attitude toward life and academic achievement in a sample of 2716 adolescents in Switzerland (mean age: 15.4 years, SD = 0.8), and whether this relationship is mediated by increased daytime tiredness and lower self-discipline/behavioral persistence. Further, we address the question whether adolescents who start school modestly later (20 min; $n = 343$) receive more sleep and report better functioning.

Sleeping less than an average of 8 h per night was related to more tiredness, inferior behavioral persistence, less positive attitude toward life, and lower school grades, as compared to longer sleep duration. Daytime tiredness and behavioral persistence mediated the relationship between short sleep duration and positive attitude toward life and school grades. Students who started school 20 min later received reliably more sleep and reported less tiredness.



During adolescence, bedtime shifts to later in the evening, due to both biological maturation and environmental factors such as decreased parental influence on children's bedtimes, an increase in academic obligations and workload, and social activities (Carskadon, Acebo, & Jenni, 2004; Crowley, Acebo, & Carskadon, 2007). Despite going to bed later, adolescents are usually required to wake up just as early or even earlier than they did during mid- and late childhood, due to early school start times, resulting in sleep deprivation in most adolescents (National Sleep Foundation, 2006).

Insufficient sleep during adolescence is associated with a host of negative outcomes, including emotional, cognitive, and behavioral problems (Fallone, Owens, & Deane, 2002; Fredriksen, Rhodes, Reddy, & Way, 2004; O'Brien & Mindell, 2005). In a recent study on more than 15,000 adolescents, later bedtimes were related to a higher risk of depression and suicidal ideation (Gangwisch et al., 2010). Further, sufficient sleep is important for learning and cognitive performance, which is particularly relevant for adolescents striving to meet academic demands at school. Experimentally induced sleep restriction/deprivation impairs verbal processing and abstract reasoning of children and adolescents (Randazzo, Muehlbach, Schweitzer, & Walsh, 1998) and school-based surveys indicate that adolescents who sleep less than others achieve lower school grades (Chung & Cheung, 2008; Dewald, Meijer, Oort, Kerkhof, & Bogels, 2010; Wolfson & Carskadon, 2003).

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0140-1971/$ – see front matter © 2012 The Foundation for Professionals in Services for Adolescents. Published by Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.adolescence.2012.11.008

One possible mediator of the effect of short sleep is excessive daytime tiredness, which is a frequent condition in adolescence (Fallone et al., 2002). Higher levels of daytime tiredness are associated with short sleep duration (O'Brien & Mindell, 2005), compromised well-being (Brand, Gerber, Beck, et al., 2010), and lower academic achievement (Chung & Cheung, 2008; Dewald et al., 2010). A further possible pathway through which short sleep and daytime tiredness affect well-being and academic performance is via students' diminished ability to persist in achieving goals and to engage efficiently on school work. Behavioral persistence and self-discipline have been shown to play an important role in academic performance (Andersson & Bergman, 2011; Duckworth & Seligman, 2005; Fortier, Vallerand, & Guay, 1995; Tangney, Baumeister, & Boone, 2004). Dweck (1986) differentiated between individuals with mastery goals and individuals with performance goals. Individuals with mastery goals believe that their abilities are malleable and therefore seek challenges and show high persistence to improve their skills. By contrast, individuals with performance goals believe that their abilities are fixed traits. Thus, their motivation is not oriented toward improving skills but directly toward gaining positive and avoiding negative judgments. They therefore avoid challenges and show low persistence when facing obstacles. Independent of intellectual ability, individuals with mastery goals learn new tasks easier and display higher achievement in the end, when compared to individuals with performance goals (Dupeyrat & Mariné, 2005). Beyond the impact on academic achievement, behavioral persistence can be important for general well-being, as it aids adolescents in exercising regularly, eating a healthy diet (Gillison, Standage, & Skevington, 2011; Wills, Isasi, Mendoza, & Ainette, 2007), and refraining from risky or problematic behaviors such as substance use, early sexual behavior, and delinquency (Cooper, Wood, Orcutt, & Albino, 2003).

While both sleep duration and behavioral persistence are important for well-being and achievement, few studies examine the relationship of short sleep and tiredness with behavioral persistence. One study found that a delayed sleep schedule was correlated with low self-control, a tendency to postpone tasks, and poor time management (Digdon & Howell, 2008), which can be considered indicators of behavioral persistence. Additionally, better-rested children tend to report higher achievement motivation, indicating a relationship between daytime tiredness and motivation (Meijer, Habekothé, & Van den Wittenboer, 2000).

The first aim of the present study was to examine the association of sleep duration with well-being and academic achievement. Based on recommendations for adolescent sleep made by the National Sleep Foundation, a sleep duration of less than 8 h is considered as insufficient. In comparison, borderline sufficient sleep duration is 8–8:59 h for this age, and an optimal sleep duration is considered to be 9 h or more (National Sleep Foundation, 2006).

The second aim of the study was to examine the potentially mediating roles of daytime tiredness and behavioral persistence in the relationship of sleep duration with well-being and academic achievement. We expected shorter sleep duration to be associated with more daytime tiredness, which in turn was expected to be associated with lower levels of behavioral persistence. Finally, we expected more daytime tiredness and lower behavioral persistence to be associated with compromised well-being and impaired academic achievement.

The third aim of the study was to examine the role of school start times taking advantage of the variation in school start times between the schools that participated on the study. Specifically, we compared sleep duration, daytime tiredness, behavioral persistence, and well-being of students at a school with modestly delayed start time (i.e., 8:00 am) with students at the five other schools that started 20 min earlier (i.e., at 7:40 am). There is evidence that later school start times are associated with longer sleep duration as well as improved health and well-being of adolescents (Owens, Belon, & Moss, 2010; Wahlstrom, 2002; Wolfson, Spaulding, Dandrow, & Baroni, 2007). Delay of school start times by 1 h or more has been shown to result in an extension of sleep time on school nights, less daytime sleepiness, depressive symptoms, and tardiness due to oversleeping (Wahlstrom, 2002; Wolfson et al., 2007). Despite these favorable findings, delaying school start times by 1 h or more can also raise opposition from local communities due to effects on family life and has thus not been widely introduced (Eliasson, Eliasson, King, Gould, & Eliasson, 2002; Wahlstrom, 2010). On the other hand, knowledge on effects of more modest delays of school start times is limited. An exception is a recent intervention study that found that a modest delay of school start time by 30 min resulted in increased sleep duration, less daytime sleepiness and improved alertness, mood and health (Owens et al., 2010). We compare sleep duration, daytime tiredness, behavioral persistence, and well-being of students at the school that starts modestly delayed (i.e., 20 min later) with students at the early starting schools.

In general, it is well-known that children and adolescents from families of lower socio-economic status (SES) and/or immigration status are at increased risk for mental health problems, poor school achievement, as well as poor sleep (Buckhalt, 2011; Vazsonyi, Trejos-Castillo, & Huang, 2006). Moreover, it has been argued that the role of insufficient sleep for adolescent's health, well-being, and school achievement is amplified by low SES of their families (Buckhalt, 2011). For the present work we studied lower track secondary school students in northwestern Switzerland with a large proportion of students of immigration status who are generally of lower socio-economic status (Swiss Federal Office of Statistics, 2011) than adolescents of higher track secondary schools or adolescents from the host country.

## Method

### *Procedure*

Participants were recruited from 8th and 9th grade classes of all six lower track secondary schools of a mid-size city in northwestern Switzerland, which were located in close proximity (i.e., the maximum distance between the most distant schools was 2 miles). Lower track secondary school qualifies for vocational training. The students were informed of the purpose of the study and provided consent to participation. The study was carried out in the spring of 2010 and 2011 in accordance to the ethical standards required by the University of Basel and by the Ethics Committee of both Cantons of Basel, which are laid down in the Declaration of Helsinki (World Medical Association, 2011).

Participants completed an online questionnaire during regular school classes while being supervised by an informatics teacher. The questionnaire assessed sleep habits, daytime tiredness, behavioral persistence, and attitude toward life along with school climate and satisfaction with various aspects of the school. Additionally, school grades in mathematics and German language were obtained from the school database and were linked with the questionnaire data.

*Participants*

Of 3323 students attending six lower track secondary schools (i.e., $n = 1686$ students during year 2010 and $n = 1637$ during year 2011), 2716 (81.7%) agreed to participate and were included in the present study. Six hundred and seven students were not included because they did not complete the questionnaire or because school grades could not be linked to the questionnaire data. Among the included students, 1397 (51.4%) were male and they were between 13; 5 and 18; 7 years old, with a mean age of 15; 5 years (SD = 0; 10 years). 1431 students (52.7%) were in the 8th grade and 1285 students (47.3%) were in 9th grade. Approximately two thirds of the sample (65.4%) indicated a different language than German or Swiss German as their native language. There was a high number of students ($n = 1140$, 42.0%) with a native language from the immigration regions of Turkey (Turkish or Kurdish: $n = 473$), former Yugoslavia (Serbian, Croatian, Bosnian, or Albanian: $n = 552$), and Portugal (Portuguese: $n = 115$), who are on average from families of lower socio-economic status than the average Swiss family, or immigrant families from Germany or France (Swiss Federal Office of Statistics, 2011). It is noteworthy that a large number of adolescents with immigration status is common in lower track secondary schools in Swiss cities. Most of the participants ($n = 2650$; 97.6%) were attending general public school where a high level of German language skills is required. They were therefore expected to possess sufficient German language skills to understand the questions presented in the questionnaire. A small minority of 66 students (2.4%) were allocated in a special foreign language class for students with insufficient German skills where learning German is one of the main goals. We assume that teachers supported these students when they needed help in completing the questionnaire.

**Measures**

*Sleep habits*

To assess sleep habits, students were asked to indicate their usual bedtime and rise time on school days and weekends. The six answer categories for school night bedtime were 'before 9:30 pm', '9:30–9:59 pm', '10–10:29 pm', '10:30–10:59 pm', '11–11:29 pm' and 'after 11:30 pm'. The answer categories for rise time on school days were 'before 6 am', '6–6:29 am', '6:30–6:59 am' and '7 am or later'. Usual weekend bedtime and rise time were assessed with six answer categories, which were 'before 10 pm', '10–10:59 pm', '11–11:59 pm', '0–0:59 am', '1–2 am' and 'after 2 am' for bedtime and 'before 8 am', '8–8:59 am', '9–9:59 am', '10–10:59 am', '11–12 am' and 'after 12 pm' for rise time. To estimate sleep duration the mean point of each answer category was used and the difference between bedtime and rise time was taken (e.g., bedtime '10–10:29 pm' and rise time '6–6:29 am' resulted in the difference between 10:15 pm and 6:15 am, which is an estimated sleep duration of 8 h). The average total sleep duration was calculated as the weighted average of school night and weekend sleep duration, using the formula: [(5 × school night sleep duration) + (2 × weekend sleep duration)]/7.

*Daytime tiredness*

Daytime tiredness was measured with two items (e.g., "At school I am often so tired that I almost fall asleep") using a 6-point scale ranging from 1 (don't agree at all) to 6 (completely agree; Cronbach's alpha = 0.80). Higher mean scores reflect higher levels of daytime tiredness.

*Behavioral persistence*

Behavioral persistence was measured with four items (e.g., "I often quit when I am facing the first difficulty") from a questionnaire designed to measure volitional control of students (Fend & Prester, 1986), using a 6-point scale ranging from 1 (don't agree at all) to 6 (completely agree; Cronbach's alpha = 0.72). The scale was coded such that higher mean scores reflect higher behavioral persistence.

*Positive attitude toward life*

Positive attitude toward life was measured with two items (e.g., "I am satisfied with how my life plans are getting fulfilled") from the Berne Questionnaire on Adolescent Subjective Well-being (Grob, Little, Wanner, Wearing, & EURONET, 1996), using a 6-point scale ranging from 1 (don't agree at all) to 6 (completely agree; Cronbach's alpha = 0.78).

*School grades*

After completion of the term, schools provided final school grades for mathematics and German language from the school database, which were then matched with the questionnaire data. Swiss school grades range from 1 (lowest) to 6 (highest). Grades <4 are considered failing grades, while grades of 4–6 are considered satisfactory to excellent.

*Statistical analysis*

We performed analysis of covariance (ANCOVA) and planned contrasts to compare the variables of interest between students sleeping less than 8 h, 8–8:59 h and 9 h or more, as well as between students from early starting schools and from late starting schools. Analyses were conducted separately for males and females controlling for age and native language. Effect sizes were calculated following Cohen (1988), with $d = 0.20$ indicating small, $d = 0.50$ indicating medium, and $d = 0.80$ indicating large effect sizes. The role of daytime tiredness and behavioral persistence in mediating the association of sleep duration with well-being and academic achievement was tested using structural equation modeling (SEM) in AMOS 20 (Arbuckle & Wothke, 1999). Total sleep duration was entered as an observed variable, while daytime tiredness, behavioral persistence positive attitude toward life, and academic achievement were entered as latent variables with two indicators each. The indicators of behavioral persistence were formed by parceling two items together per indicator; the indicators of the latent construct of academic achievement were the Mathematics and Language (German) school grades; the indicators for daytime tiredness and positive attitude toward life were the items of these scales. Structural equation modeling was conducted applying the multi-group approach specifying separate models for males and females, which constrained factor loadings of latent constructs equal across gender. A model with path coefficients constrained to be invariant was compared to a model with the path coefficients allowed to be unequal across groups by using $\chi 2$-difference test. Further, to ascertain robustness of the findings across grade levels and assessment waves, models for 8th ($n = 1431$) and 9th grade students ($n = 1285$), were compared as well as models for students assessed in spring 2010 ($n = 1308$) and 2011 ($n = 1408$). To evaluate the goodness of fit, the comparative fit index (CFI; >0.95 indicates a good fit (McDonald & Ho, 2002)) and the root-mean square error of approximation (RMSEA; <0.05 indicates an excellent fit (Browne & Cudeck, 1989)) were considered.

**Results**

*Descriptive statistics*

On average, participants' sleep duration was 8:36 h (SD = 0:48 h), the average estimated bedtime on school nights was 10:29 pm, and the average estimated rise time on school days was 6:29 am. On weekends, average estimated bedtime and rise time were considerably later (00:48 am and 10:46 am, respectively). In Table 1, means and standard deviations of the study variables are shown separately for male and female students. Compared to males, female students reported earlier bed- and rise times on school days and earlier bedtimes on weekends. They were higher in daytime tiredness, lower in behavioral persistence, and had better grades in German language, but they achieved worse grades in math. No gender difference was found regarding positive attitude toward life.

Table 2 shows the results of the analysis of covariance and planned contrasts, comparing daytime tiredness, behavioral persistence, positive attitude toward life, and academic achievement of students sleeping less than 8 h, between 8 and 8:59 h, as well as 9 h or more. Male and female students sleeping less than 8 h were more tired than their counterparts sleeping 8–8:59 h, who in turn were more tired than those sleeping 9 h or more. Behavioral persistence and positive attitude toward life were higher in male and female students who sleep 8 h or more than among those who sleep less than 8 h. However, there was no difference in behavioral persistence and positive attitude toward life between those sleeping 8–8:59 h and the ones sleeping more than 9 h. Finally, male and female students sleeping less than 8 h had lower Mathematics and German grades than their counterparts sleeping more. No significant advantage in school grades could be found in students sleeping more than 9 h compared to those in the intermediate category sleeping 8–8:59 h. Effect sizes (Cohen's d) of the comparisons of longer sleep duration with the group with a sleep duration below 8 h were small to medium with regard to daytime tiredness ($d = 0.33$–0.50), small with regard to behavioral persistence ($d = 0.17$–0.28) and positive attitude toward life ($d = 0.20$–0.36), and very small for school grades ($d = 0.07$–0.22).

Table 3 presents means and standard deviations for sleep variables, daytime tiredness, and behavioral persistence, and positive attitude toward life comparing students from early and late starting schools separately for males and females. Students attending the school with a later school start time reported a school night sleep duration that was on average 16 min longer than that of students attending the earlier starting schools. The increase in sleep duration on school nights was entirely due to differences in rise times on school days: students at the later starting school got up 27 min later than students at the earlier starting schools; while bedtime on school nights were only 11 min later. The effects of school start time on weekday sleep duration were remarkably similar across males and females. Weekend sleep duration, bedtimes, and rise times were not different between early and late starting students. Further, students from early starting schools reported significantly more daytime tiredness than students from late starting schools. No differences were found for behavioral persistence and positive attitude toward life.

Fig. 1 presents structural equation models that were used to test whether the relation of sleep duration with positive attitude toward life and academic achievement was mediated by daytime tiredness and behavioral persistence. The fit for

**Table 1**
Descriptive statistics.

| | Male ($N$ = 1397) | | Female ($N$ = 1319) | | $p$ |
|---|---|---|---|---|---|
| | *Mean N* | *SD %* | *Mean N* | *SD %* | |
| Age (years) | 15.49 | 0.83 | 15.39 | 0.78 | 0.002 |
| Native language (% German) | 471 | 33.7 | 470 | 35.6 | 0.29 |
| Academic achievement | | | | | |
| Mathematics grade | 4.27 | 0.87 | 4.08 | 0.86 | <0.001 |
| German grade | 4.29 | 0.68 | 4.48 | 0.62 | <0.001 |
| Total sleep duration (h) | 8.56 | 0.77 | 8.56 | 0.80 | 0.87 |
| Sleep duration school nights (h) | 8.08 | 0.81 | 7.93 | 0.85 | <0.001 |
| Bedtime school nights | 10:35 pm | 45 min | 10:23 pm | 44 min | <0.001 |
| Before 9.30 pm | 55 | 3.9 | 97 | 7.4 | <0.001 |
| 9.30–9.59 pm | 225 | 16.1 | 287 | 21.8 | |
| 10.00–10.29 pm | 446 | 31.9 | 428 | 32.4 | |
| 10.30–10.59 pm | 295 | 21.1 | 259 | 19.6 | |
| 11.00–11.29 pm | 199 | 14.2 | 158 | 12.0 | |
| After 11.30 pm | 177 | 12.7 | 90 | 6.8 | |
| Rise time school days | 6:40 am | 30 min | 6:19 am | 31 min | <0.001 |
| Before 6.00 am | 78 | 5.6 | 264 | 20.0 | <0.001 |
| 6.00–6.29 am | 398 | 28.5 | 606 | 45.9 | |
| 6.30–6.59 am | 681 | 48.7 | 375 | 28.4 | |
| 7.00 am or later | 240 | 17.2 | 74 | 5.6 | |
| Sleep duration weekends (h) | 9.79 | 1.33 | 10.15 | 1.29 | <0.001 |
| Bedtime weekends | 1:00 am | 1 h 19 min | 0:36 am | 1 h 20 min | <0.001 |
| Before 10.00 pm | 17 | 1.2 | 29 | 2.2 | <0.001 |
| 10.00–10.59 pm | 90 | 6.4 | 136 | 10.3 | |
| 11.00–11.59 pm | 256 | 18.3 | 293 | 22.2 | |
| 0.00–0.59 am | 258 | 18.5 | 301 | 22.8 | |
| 1.00–2.00 am | 368 | 26.3 | 337 | 25.5 | |
| After 2.00 am | 408 | 29.2 | 223 | 16.9 | |
| Rise time weekends | 10:47 am | 1 h 19 min | 10:45 am | 1 h 12 min | 0.42 |
| Before 8.00 am | 40 | 2.9 | 25 | 1.9 | 0.002 |
| 8.00–8.59 am | 103 | 7.4 | 87 | 6.6 | |
| 9.00–9.59 am | 224 | 16.0 | 225 | 17.1 | |
| 10.00–10.59 am | 369 | 26.4 | 384 | 29.1 | |
| 11.00–12.00 am | 375 | 26.8 | 399 | 30.3 | |
| After 12.00 am | 286 | 20.5 | 199 | 15.1 | |
| Daytime tiredness | 3.27 | 1.49 | 3.56 | 1.39 | <0.001 |
| Behavioral persistence | 3.73 | 1.00 | 3.59 | 1.03 | <0.001 |
| Positive attitude toward life | 4.72 | 1.05 | 4.76 | 0.98 | 0.23 |

models with factor loadings constrained to be invariant across gender was good ($\chi^2(60) = 145.2$, $p < .001$, CFI = 0.986, RMSEA = 0.023). The models revealed that short sleep was related to more daytime tiredness, which in turn was related to lower behavioral persistence. More daytime tiredness and lower behavioral persistence were predictive of less positive attitude toward life. Moreover, behavioral persistence was a moderately strong predictor of academic achievement. To a modest degree, short sleep duration also directly predicted less positive attitude toward life. A $\chi^2$-difference test revealed that the relation between daytime tiredness and behavioral persistence was stronger for female students than for males, as

**Table 2**
Association between sleep duration and academic achievement, daytime tiredness, behavioral persistence, and attitude toward life.

| | Total sleep duration | | | | | | Contrasts | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | <8 h | | 8–8:59 h | | ≥9 h | | <8 h *vs.* 8–8:59 h | | <8 h *vs.* ≥9 h | | 8–8:59 h *vs.* ≥9 h | |
| | *Mean* | *SE* | *Mean* | *SE* | *Mean* | *SE* | *d* | *p* | *d* | *p* | *d* | *p* |
| Math | 4.16 | 0.05 | 4.32 | 0.03 | 4.27 | 0.04 | 0.19 | 0.007 | 0.15 | 0.009 | −0.05 | 0.40 |
| | 3.99 | 0.05 | 4.08 | 0.03 | 4.16 | 0.05 | 0.12 | 0.15 | 0.22 | 0.01 | 0.11 | 0.15 |
| German | 4.24 | 0.04 | 4.33 | 0.03 | 4.27 | 0.03 | 0.15 | 0.04 | 0.07 | 0.52 | −0.08 | 0.15 |
| | 4.44 | 0.04 | 4.52 | 0.02 | 4.46 | 0.03 | 0.16 | 0.04 | 0.08 | 0.64 | −0.08 | 0.11 |
| Daytime tiredness | 3.69 | 0.08 | 3.20 | 0.06 | 3.04 | 0.07 | −0.33 | <0.001 | −0.44 | <0.001 | −0.12 | 0.07 |
| | 3.98 | 0.08 | 3.51 | 0.05 | 3.30 | 0.07 | −0.35 | <0.001 | −0.50 | <0.001 | −0.15 | 0.02 |
| Behavioral persistence | 3.58 | 0.06 | 3.80 | 0.04 | 3.74 | 0.05 | 0.23 | 0.001 | 0.17 | 0.04 | −0.05 | 0.36 |
| | 3.39 | 0.06 | 3.63 | 0.04 | 3.70 | 0.05 | 0.23 | 0.001 | 0.28 | <0.001 | 0.07 | 0.28 |
| Positive attitude toward life | 4.53 | 0.06 | 4.75 | 0.04 | 4.80 | 0.05 | 0.20 | 0.002 | 0.26 | 0.001 | 0.06 | 0.43 |
| | 4.53 | 0.06 | 4.81 | 0.04 | 4.88 | 0.05 | 0.27 | <0.001 | 0.36 | <0.001 | 0.09 | 0.23 |

*Note.* Upper values are for males (<8 h: $n$ = 316; 8–8:59 h: $n$ = 684; ≥9 h: $n$ = 397), lower values for females (<8 h: $n$ = 313; 8–8:59 h: $n$ = 631; ≥9 h: $n$ = 375). Math = Mathematics grade; German = German grade (higher values indicate better grades). All values are adjusted for age and native language.

**Table 3**
Sleep duration, bed and rise times, daytime tiredness, behavioral persistence, and attitude toward life in early and late starting schools.

| | Early school start time $n = 2373$ | | Late school start time $n = 343$ | | *d* | *P* |
|---|---|---|---|---|---|---|
| | *Mean* | *SD* | *Mean* | *SD* | | |
| Total sleep duration (h) | 8.54 | 0.77 | 8.76 | 0.75 | 0.29 | <0.001 |
| | 8.55 | 0.80 | 8.66 | 0.78 | 0.15 | 0.09 |
| Sleep duration school nights (h) | 8.04 | 0.80 | 8.32 | 0.86 | 0.34 | <0.001 |
| | 7.90 | 0.85 | 8.14 | 0.89 | 0.27 | 0.001 |
| Bedtime school nights | 10:34 pm | 45 min | 10:41 pm | 46 min | 0.16 | 0.04 |
| | 10:22 pm | 43 min | 10:37 pm | 46 min | 0.35 | <0.001 |
| Rise time school days | 6:37 am | 28 min | 7:01 am | 32 min | 0.80 | <0.001 |
| | 6:15 am | 27 min | 6:45 am | 35 min | 0.93 | <0.001 |
| Sleep duration weekends | 9.77 | 1.36 | 9.86 | 1.14 | 0.06 | 0.44 |
| | 10.17 | 1.30 | 9.98 | 1.21 | −0.15 | 0.08 |
| Bedtime weekends | 0:59 am | 1 h 19 min | 1:08 am | 1 h 16 min | 0.13 | 0.11 |
| | 0:34 am | 1 h 20 min | 0:50 am | 1 h 14 min | 0.21 | 0.02 |
| Rise time weekends | 10:45 am | 1 h 19 min | 10:59 am | 1 h 14 min | 0.19 | 0.02 |
| | 10:44 am | 1 h 12 min | 10:49 am | 1 h 13 min | 0.07 | 0.43 |
| Daytime tiredness | 3.32 | 1.49 | 2.92 | 1.40 | −0.28 | <0.001 |
| | 3.59 | 1.40 | 3.33 | 1.34 | −0.19 | 0.03 |
| Behavioral persistence | 3.73 | 1.01 | 3.71 | 0.91 | −0.03 | 0.74 |
| | 3.60 | 1.04 | 3.54 | 0.95 | −0.07 | 0.46 |
| Positive attitude toward life | 4.71 | 1.07 | 4.73 | 0.97 | 0.02 | 0.80 |
| | 4.77 | 0.98 | 4.69 | 0.97 | −0.09 | 0.30 |

*Note.* Upper values are for males (early school start time: $n = 1208$; late school start time: $n = 189$), lower values for females (early school start time: $n = 1165$; late school start time: $n = 154$). *P*-values adjusted for age and native language.

was the relation between behavioral persistence and positive attitude toward life (both $p < .05$). Apart from these differences, the models were remarkably similar across gender. Further multi-group comparisons showed that the models were robust across students of the 8th and the 9th grade ($\chi^2(7) = 2.8$, $p = .91$) as well as across assessment waves in spring 2010 and spring 2011 ($\chi^2(7) = 4.7$, $p = .69$) implying similarity of findings across grade levels and year of assessment. In sum, the models revealed an effect of short sleep on positive attitude toward life that was partly mediated by daytime tiredness and behavioral persistence and an effect of sleep duration on academic achievement that was fully mediated.

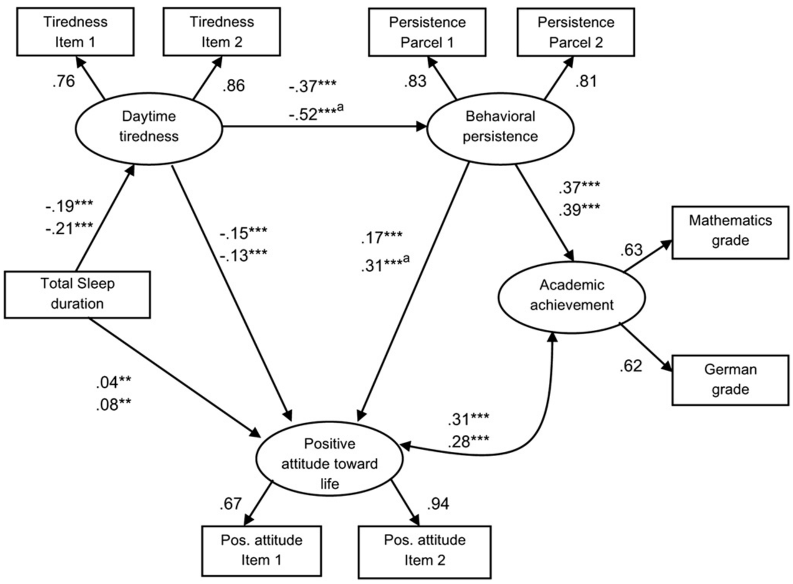


**Fig. 1.** Prediction of positive attitude toward life and academic achievement by sleep duration, daytime tiredness, and behavioral persistence: Structural equation model ($\chi^2(60) = 145.2$, $p < .001$, CFI = 0.986, RMSEA = 0.023). Upper path coefficients are for males ($n = 1397$), lower path coefficients are for females ($n = 1319$). Factor loadings were set equal across males and females. The models adjust for participants' age and native language (coefficients not presented). Non-significant path coefficients were omitted. ***$p < .001$. **$p < .01$. *$p < .05$. [a] coefficients are different between males and females.

## Discussion

We found that students with an insufficient sleep duration of less than 8 h showed more daytime tiredness, less behavioral persistence, less positive attitude toward life, and had lower school grades in mathematics and German language, in comparison to their counterparts who sleep longer. Thus, our findings are consistent with existing evidence that insufficient sleep during adolescence is associated with behavioral and emotional difficulties (Fallone et al., 2002; Fredriksen et al., 2004; O'Brien & Mindell, 2005) and poor performance at school (Chung & Cheung, 2008; Dewald et al., 2010; Wolfson & Carskadon, 2003). Further, our findings extend previous knowledge by showing that the relationship of sleep duration with positive attitude toward life and school grades was partly mediated by daytime tiredness and behavioral persistence. Finally, the results indicated that students in a school that started 20 min later than the other schools, reported getting 16 min more sleep on school nights, which was also associated with less tiredness during the day. This finding is in line with a recent study showing that a delay in school start time by half an hour resulted in longer sleep on school nights among adolescents due to later rise up times in the morning (Owens et al., 2010). However, behavioral persistence and positive attitude toward life were not affected by later school start times in the present study.

Our findings point to the importance of sufficient night time sleep for feeling well-rested, possessing high levels of behavioral persistence, experiencing positive well-being, and achieving good school grades. Effect sizes were in the small to moderate range, and match effect sizes of sleep duration reported in the literature (Dewald et al., 2010). While there was on average a reliable disadvantage for students sleeping less than 8 h, we, however, did not find strong support for differences between students who sleep in the borderline sufficient range (8–8:59 h) and students sleeping 9 h or more, regarding behavioral persistence, positive attitude toward life, and school grades.

Based on these findings, we suggest recommending that families strive to attain a sleep duration of at least 8 h for adolescents. Furthermore, a short delay of school start times by 20 min may already have ascertainable and relevant effects on adolescents' sleep duration and daytime tiredness, although 20 min appears too short to produce noticeable effects on behavioral persistence, positive attitude toward life, and school grades. While changing school start times by 1 h might probably have stronger positive effects, it may also imply substantial logistic considerations at the community level and an impact on family life. By contrast, a 20-min delay in school start time might keep these difficulties at a minimum while still resulting in positive effects for adolescent students.

The present study had several limitations that could be addressed in future work. First, the cross-sectional design did not allow for conclusions to be drawn regarding the development of, and causal relations among, the studied variables. While it was possible to compare schools with different start times in the present study, an experimental design studying the effect of a delay in school start times in pre-to-post comparison and in comparison with a control group would have allowed for a causal interpretation of the findings, and should be an area for future research. Further, although all six schools were located in close proximity to one another, and our analyses controlled for age, gender, and native language, it is still possible that the students from the schools with different start times differed on other variables that we did not assess. Second, we estimated sleep duration from reported usual bed- and rise times on school days and weekends. Thus, sleep onset latency (i.e., the time it takes to fall asleep after bedtime) was not taken into consideration in estimation of sleep duration. On the other hand, calculated sleep duration from usual bedtime and rise time is considered to be more accurate than self-reported sleep duration in hours and minutes, which tends to be underestimated by adolescents (Loessl et al., 2008). Although there is evidence that sleep data from sleep logs and questionnaires do fit well with objective data (cf. Brand, Gerber, Hatzinger, et al., 2010; Werner, Molinari, Guyer, & Jenni, 2008) assessment of sleep via actigraphy or sleep-EEG probably would have revealed results of higher validity. Third, we did not assess sleep difficulties. From other studies, it is known that sleep difficulties may have an impact on adolescents' well-being and functioning at school (Dewald et al., 2010; Meijer et al., 2000). Moreover, we did not assess use of substances, such as smoking, drinking alcohol, and caffeine consumption, which can also interfere with the ability to fall asleep and sleep quality. As a strength of the study, a majority of all lower track secondary school students of the region with a large proportion of students of immigration status and low SES (Swiss Federal Office of Statistics, 2011), considered at increased risk for mental health and school problems (Vazsonyi et al., 2006), participated in the study, thus adding to knowledge about sleep in less advantaged groups.

## Acknowledgments

The study was supported by the Department of Education of the Canton Basel-Stadt. We thank the students of the participating schools for taking part on the study. We further thank Dr. K. Lavallee (University of Basel, Department of Psychology) for proofreading the manuscript.

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# APPENDIX B

Study 2

Perkinson-Gloor, N., Hagmann-von Arx, P., Brand, S., Holsboer-Trachsler, E., Grob, A., Weber, P., & Lemola, S. (2015). The role of sleep and the hypothalamic-pituitary-adrenal axis for behavioral and emotional problems in very preterm children during middle childhood. *Journal of Psychiatric Research, 60,* 141-147. doi:10.1016/j.jpsychires.2014.10.005

Journal of Psychiatric Research 60 (2015) 141–147

Contents lists available at ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/psychires

# The role of sleep and the hypothalamic-pituitary-adrenal axis for behavioral and emotional problems in very preterm children during middle childhood

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ARTICLE INFO

*Article history:*
Received 3 July 2014
Received in revised form
17 September 2014
Accepted 7 October 2014

*Keywords:*
Preterm birth
Sleep
Polysomnography
Hypothalamic-pituitary-adrenocortical activity
Behavioral problems
Emotional problems

ABSTRACT

Very preterm children are at higher risk to develop behavioral and emotional problems, poor sleep, and altered hypothalamic-pituitary-adrenocortical activity (HPAA). However, knowledge on objective sleep and HPAA as well as their role for the development of behavioral and emotional problems in very preterm children is limited. Fifty-eight very preterm children (<32nd gestational week) and 55 full-term children aged 6–10 years underwent one night of in-home polysomnographic sleep assessment. HPAA was assessed with four saliva samples in the morning (morning cortisol secretion) and four saliva samples in the evening (evening cortisol secretion). Parents completed the Strengths and Difficulties Questionnaire (SDQ) to assess children's behavioral and emotional problems and a subscale of the Children's Sleep Habits Questionnaire to assess sleep disordered breathing. Very preterm children showed more behavioral and emotional problems (SDQ total behavioral/emotional difficulties, emotional symptoms), poorer sleep (more nocturnal awakenings, more stage 2 sleep, less slow wave sleep), and faster decreasing evening cortisol secretion compared to full-term children. Across the whole sample, more stage 2 sleep and/or less slow wave sleep were associated with more SDQ total behavioral/emotional difficulties, hyperactivity-inattention, and peer problems. Lower morning cortisol secretion and lower evening cortisol secretion were associated with more conduct problems. In very preterm children, increased SDQ total behavioral/emotional difficulties was partially explained by less restorative sleep including more stage 2 sleep and less slow wave sleep. This result points to the importance of restorative sleep for the behavioral and emotional development of very preterm children during middle childhood.



## 1. Introduction

Pre- and perinatal adversities shape the development of health problems throughout the life-span, including mental health disturbance (Barker et al., 2002). The present study aims at shedding light on possible pathways through which very preterm birth (<32nd gestational week) – a major perinatal adversity involving medical complications and invasive and often painful treatment procedures, which occurs in around 1% of all births in the western world (Beck et al., 2010) – may impact on mental health during childhood, namely by altering (a) sleep patterns and (b) hypothalamic–pituitary–adrenocortical activity (HPAA).

Generally healthy very preterm born children are at higher risk for lower mental health including psychosocial impairments such as more behavioral problems (e.g. attention problems) and emotional problems (e.g. emotional symptoms such as anxiety and depression) (Aarnoudse-Moens et al., 2009; Bhutta et al., 2002) with an up to three times increased prevalence of mood disorders during childhood and adolescence (Burnett et al., 2011). One reason for decreased psychosocial adjustment of formerly preterm

*Abbreviations:* AUC, area-under-the-concentration-time-curve; EEG, electroencephalography; HPAA, Hypothalamic–pituitary–adrenocortical activity; PSG, Polysomnography; REM sleep, rapid eye movement sleep; SDB, sleep-disordered breathing; SDQ, Strengths and Difficulties Questionnaire; SWS, slow wave sleep.

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http://dx.doi.org/10.1016/j.jpsychires.2014.10.005
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children includes persistent alterations in sleep regulation (Rosen et al., 2003; Lemola, in press). Particularly, sleep disordered breathing (SDB) is more prevalent in formerly very preterm children (Rosen et al., 2003).

Generally, adequate sleep is an important determinant of psychosocial adjustment in childhood. School-age children (i.e., between 6 and 11 years) have a high sleep need of around 9–11 h per night (Iglowstein et al., 2003), while sleep disturbances are common with a prevalence of around 30% (Fricke-Oerkermann et al., 2007). Importantly, a large body of evidence shows that children with disturbed sleep are at higher risk for behavioral and emotional problems (for a meta-analysis see Astill et al., 2012). Experimental studies further indicate that already modest changes in sleep duration have a causal impact on children's behavioral problems (Gruber et al., 2012). However, studies measuring sleep objectively in non-clinical samples are scarce. Particularly, research conducted in an ecological setting, i.e., at the children's home, measuring sleep objectively applying sleep-electroencephalography (EEG) to examine the relationship between sleep architecture and children's behavior problems are rare. One study applying in-home sleep-EEG in 58 healthy preschoolers showed that increased stage 2 sleep and decreased slow wave sleep (SWS, or deep sleep) were associated with more behavioral and emotional problems (Hatzinger et al., 2013). Similarly, in-home polysomnography (PSG) studies in adolescents reported that more light sleep (sleep stages 1 and 2) and less SWS was associated with subclinical depressive symptoms (Brand et al., 2010), and lower scores on personality traits associated with resilience such as mental toughness (Brand et al., 2014). Taken together, these studies applying in-home PSG in healthy children and adolescents indicate that less restorative sleep (i.e., more light sleep, less SWS) is related to poor psychosocial adjustment. In particular decreased SWS, which is considered to be the most restorative sleep stage (Borbély and Achermann, 1999), has been suggested to involve decreased energy levels for the next day and therefore increased vulnerability for psychological difficulties.

A second possible reason for decreased psychosocial adjustment of preterm children include persistent alterations of the HPAA, which may be caused by painful treatment procedures, separation from parents, and treatment with artificial glucocorticoids during the perinatal phase (Karemaker et al., 2008; Kaseva et al., 2014; Lemola, in press). A large body of evidence shows that alterations in the HPAA in childhood and adolescence are related to psychosocial impairments. Generally, a hypoactive HPAA is associated with more behavioral problems, while a hyperactive HPAA is associated with more emotional problems (Hartman et al., 2013). Research on the HPAA in preterm children is scarce, but two studies lend support to the notion that preterm children show an altered HPAA. One study with 18 preterm children aged 8-14 found a trend towards a decreased cortisol response to psychosocial stress, but an increase of morning cortisol secretion (Buske-Kirschbaum et al., 2007). Similarly, Kaseva et al. (2014) found a blunted cortisol response to psychosocial stress in young adults born preterm with very low birth weight.

Taken together, there is evidence that very preterm children are at higher risk for psychosocial impairments, poor sleep and an altered HPAA. However, there are important gaps in research. First, studies examining objectively assessed sleep using PSG in very preterm children are missing. Second, studies on the relationship between sleep architecture as assessed with in-home sleep-EEG and psychosocial adjustment are rare. Third, studies on HPAA in very preterm children during middle childhood are rare, too, and missing altogether for associations between HPAA and psychosocial adjustment. Finally and most importantly, to date no study has tested whether alterations in sleep and/or HPAA are possible mediators of the effect of preterm birth on psychosocial adjustment. The main goal of the present study was therefore to shed light on possible underlying mechanism in the association between very preterm birth and psychosocial adjustment by examining the role of sleep and HPAA. The following hypotheses were proposed. First, we hypothesized to find more behavioral and emotional problems, poorer sleep (i.e., shorter sleep duration, lower sleep efficiency, more nocturnal awakenings, more light sleep (stage 1 and/or stage 2 sleep), less SWS, more SDB) and an altered HPAA in very preterm compared to full-term children. Second, we hypothesized that poorer sleep is associated with more behavioral and emotional problems and that HPAA is negatively associated with behavioral problems and positively associated with emotional problems. Third, we hypothesized that less favorable sleep-EEG and/or altered HPAA characteristics in very preterm children account for differences in behavioral and emotional problems between very preterm and full-term children.

## 2. Methods

### 2.1. Study population

Fifty-eight healthy very preterm children (<32nd gestational week; age: $M = 8.2$ years, $SD = 1.3$; range: 6.0–10.9) and 55 full-term children (age: $M = 8.3$, $SD = 1.3$; range: 6.3–10.6) were recruited for the present study.

Fig. 1 describes the inclusion procedure of very preterm children, who were recruited from an initial cohort of 217 prematurely born children treated at the University Children's Hospital Basel (Switzerland). Participating preterm children did not differ from non-participants with regard to birth weight (1302 g vs. 1284 g, $F(1,216) = .09$; $P = .76$), gestational age (29.7 weeks vs. 29.7 weeks,

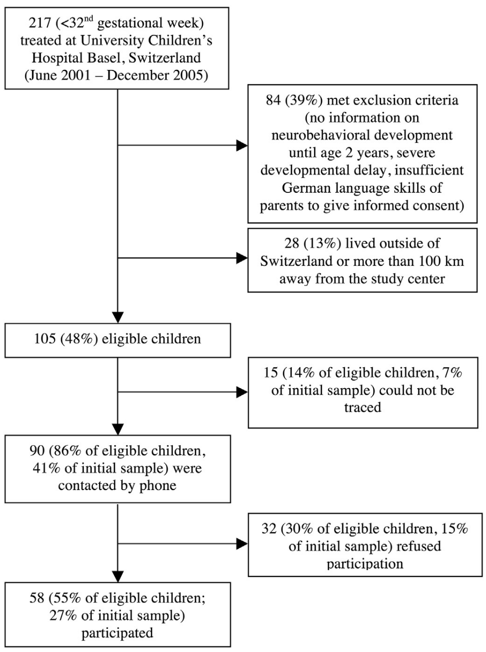


**Fig. 1.** Scope diagram describing the inclusion procedure of very preterm children.

$F(1,216) = .003$; $P = .96$) or length of hospital stay (53.9 days vs. 53.1 days, $F(1,180) = .05$; $P = .83$). The sample characteristics are presented in Table 1.

The full-term children (>37 weeks of gestation) were recruited from official birth notifications. The two samples were comparable regarding age and gender. All children attended primary school in Switzerland. Among the preterm children eight received additional support at school (e.g. by a remedial teacher) or visited small group classes, while none of the full-term children received any additional support.

To estimate the statistical power given the sample size of the study, post-hoc power analysis was performed with G*Power (Faul et al., 2007). Regarding mean differences between preterm and full-term children, the power analysis indicated an 84% chance of detecting effects of medium size ($d = .50$) at a .05 alpha level (one-sided). Regarding correlations between two variables the chance of detecting effects of medium size ($r = .30$) was 95% at a .05 alpha level (one-sided; based on the total sample size). The study was thus sufficiently powered to detect medium size effects (Cohen, 1988).

Parents gave written informed consent for the children to participate and assent was obtained from the child. The study was approved by the Ethics Committee of Basel and performed in accordance with the ethical standards laid down in the Declaration of Helsinki.

### 2.2. Procedure

Trained study personnel visited the children at home on a regular school day to complete cognitive assessments (which are not reported here), collect saliva samples, and administer in-home PSG. Parents completed questionnaires to assess demographic data, children's psychosocial impairments, and SDB. Children received gift vouchers of CHF 40 for participating (1 CHF = 1.12 USD; September 2014). Mothers and fathers received CHF 30 each for completing questionnaires, removing the PSG device, and collecting morning cortisol saliva samples. Information on neonatal health of the very preterm sample was obtained from the medical files of the University Children's Hospital Basel.

### 2.3. Assessment of children's behavioral and emotional problems

Psychosocial impairments were assessed with the German version of the Strengths and Difficulties Questionnaire (SDQ; Goodman, 1997) measuring two domains of behavioral problems (conduct problems, hyperactivity-inattention) and two domains of emotional problems (emotional symptoms, peer problems) with five items each, as well as a composite score of total behavioral/emotional difficulties. The fifth domain of the SDQ assessing prosocial behavior was not included in the present study, as the study focus is on behavioral and emotional difficulties. Items were rated on a 3-point Likert scale ranging from 0 (*not true*) to 2 (*certainly true*). Higher subscale scores reflect more difficulties. Cronbach's alpha for total behavioral/emotional difficulties was $\alpha = .64$ for mothers and $\alpha = .74$ for fathers. As an index of interrater agreement intra-class correlations (ICC) were calculated for mother- and father-reports. The agreement for total behavioral/emotional difficulties was high ($ICC = .67$, $P < .001$). Cronbach's alpha for emotional symptoms was $\alpha = .66$ (mothers), $\alpha = .77$ (fathers; $ICC = .52$, $P < .001$), for conduct problems $\alpha = .47$ (mothers), $\alpha = .48$ (fathers; $ICC = .58$, $P < .001$), for hyperactivity-inattention $\alpha = .81$ (mothers), $\alpha = .80$ (fathers; $ICC = .72$, $P < .001$), and for peer problems $\alpha = .53$ (mothers), $\alpha = .46$ (fathers; $ICC = .62$, $P < .001$). As intra-class correlations for mother and father reports were high (ranging between .52 and .72) and to increase reliability, mother and father ratings were combined. Mother questionnaires were available for 109 children, father questionnaires were available for 92 children, and for 4 children, no parent questionnaires were available. For 17 children no father ratings were available while they had mother ratings, so only the mother ratings were used.

**Table 1**
Sample characteristics of very preterm and full-term children.

| | Very preterm ($n = 58$) | | Full-term ($n = 55$) | | P |
|---|---|---|---|---|---|
| | M/N | (SD/%) | M/N | (SD/%) | |
| Age, years | 8.2 | (1.3) | 8.3 | (1.3) | .53 |
| Sex, male | 40 | (69.0) | 35 | (63.6) | .55 |
| Gestational age, weeks | 29.7 | (1.9) | 39.7 | (1.6) | <.001 |
| Birth weight, grams | 1302.1 | (408.3) | 3338.4 | (441.3) | <.001 |
| Prenatal treatment with glucocorticoids | 40 | (69.0) | 0 | (0) | <.001 |
| Postnatal treatment with glucocorticoids | 4 | (6.9) | 0 | (0) | .12 |
| Infant respiratory distress syndrome | 45 | (77.6) | 0 | (0) | <.001 |
| Apnea of Prematurity | 46 | (79.3) | 0 | (0) | <.001 |
| Bronchopulmonary Dysplasia | 3 | (5.2) | 0 | (0) | .24 |
| First language (German) | 38 | (65.5) | 46 | (83.6) | .03 |
| Maternal education | | | | | <.001 |
| No vocational training | 9 | (15.5) | 3 | (5.5) | |
| Vocational education | 41 | (70.7) | 25 | (45.5) | |
| University | 8 | (13.8) | 27 | (49.1) | |

*Note. P*-values of the $\chi^2$ test, Fisher's exact test, or analyses of variance.

### 2.4. Sleep assessment

Sleep was assessed using in-home PSG during the night following the home-visit. Polysomnogram signals C3/A2 and C4/A1 EEG, right and left electrooculogram and bipolar submental electromyogram were obtained using the Compumedics Somté PSG. Sleep polygraphs were visually analyzed by two experienced raters according to the standard procedures (Rechtschaffen and Kales, 1968). Parents completed a short sleep log for the night of assessment and reported on children's exact awakening time to determine the end of sleep scoring. The following sleep parameters were derived: Sleep continuity: Total sleep time (time in bed minus time spent awake in hours), sleep efficiency (total sleep time/time in bed × 100), and nocturnal awakenings (number of arousals from sleep). Sleep architecture (min): Stages 1, 2, SWS (slow wave sleep: stages 3 and 4), REM sleep, and REM latency. Polysomnographic sleep data was available for 52 (89.7%) very preterm and 50 (90.9%) full-term children.

To assess SDB, parents completed the SDB subscale of the Children's Sleep Habits Questionnaire (CSHQ; Owens et al., 2000) including three items on snoring and breathing problems in children rated on a 3-point Likert scale ranging from 0 (*rarely*) to 2 (*usually*). Mother and father ratings were combined to increase reliability. Cronbach's alpha was $\alpha = .84$ for mothers and $\alpha = .85$ for fathers. Agreement between mothers and fathers was very high ($ICC = .88$, $P < 0.001$).

### 2.5. HPAA assessment

#### 2.5.1. HPA activity

HPAA was assessed by saliva cortisol samples collected during the home-visit in the evening before and in the morning after PSG assessment. Morning cortisol secretion: In the morning after PSG assessment, parents collected four saliva samples at 0, 10, 20, and 30 min after the child's awakening. Parents were instructed that the children were not allowed to eat or drink before collecting saliva samples. The children were asked to brush their teeth after saliva sampling was completed. Awakening times ranged from 5:20 a.m.

to 8:33 a.m. ($M = 06{:}45$ a.m., $SD = 28$ min) and did not differ between very preterm ($M = 06{:}42$ a.m.) and full-term children ($M = 06{:}48$ a.m.; $F(1, 101) = 1.3$, $P = 0.26$). Evening cortisol secretion: Trained study personnel collected four saliva samples at 0, 30, 60, and 90 min after the beginning of the home-visit. Children were asked not to eat or drink before collecting saliva samples. Home-visits started between 1:00 p.m. and 6:45 p.m. ($M = 05{:}01$ p.m., $SD = 44$ min). Average starting times did not differ between very preterm (04:58 p.m.) and full-term children (05:05 p.m.; $F(1, 108) = 0.75$, $P = 0.39$). Morning cortisol secretion is available for 54 (93.1%) very preterm and 48 (87.3%) full-term children and evening cortisol secretion is available for 55 (94.8%) very preterm and 52 (94.5%) full-term children.

*2.5.2. Saliva cortisol sampling technique and cortisol analysis*

Saliva samples were collected using the "Salivette" device (Sarstedt, Nümbrecht/Germany). Children were instructed to gently chew on a cotton swab for approximately 1 min and then transfer it into the small plastic tube. Free salivary cortisol concentrations were analyzed using a time-resolved immunoassay with fluorometric detection "Coat-A-Count" Cortisol RIA from DPC (Diagnostics Products Corporation; obtained through H. Biermann GmbH, Bad Nauheim, Germany).

### 2.6. Statistical analysis

All analyses were controlled for first language, maternal education, children's age, and gender, if not stated otherwise. We performed analysis of covariance (ANCOVA) to compare behavioral and emotional problems and sleep variables of very preterm and full-term children. Effect sizes were calculated following Cohen (1988) with $d = 0.20$ indicating small, $d = 0.50$ indicating medium, and $d = 0.80$ indicating large effect sizes. Slopes of morning and evening cortisol secretion of very preterm and full-term children were compared using repeated-measures ANCOVA to assess between-subjects effects (very preterm vs. full-term) and group × time interaction effects. Analyses involving evening cortisol were additionally controlled for the clock time of saliva sampling.

To test the association of sleep and HPAA with behavioral and emotional problems hierarchical regression analyses were performed, additionally controlling for prematurity status and for evening cortisol analyses for the clock time of saliva sampling. For these hierarchical regression analyses the area-under-the-concentration-time-curve (AUC) of cortisol secretion was calculated with the AUCg referring to the area under the curve with respect to the ground and the AUCi referring to the area under the curve with respect to the increase (Pruessner et al., 2003). Cortisol values were log-transformed before building these features as distributions of cortisol concentrations were skewed.

Finally, it was assessed whether differences in sleep and/or HPAA characteristics accounted for significant differences in behavioral and emotional problems between very preterm and full-term children applying mediation analysis according to Baron and Kenny (1986). The mediation analysis was conducted by taking only sleep and/or HPAA characteristics into account that fulfilled the preconditions for mediation based on the preceding analyses (Baron and Kenny, 1986): (1) The sleep and/or HPAA indices (the mediator) had to be significantly related to prematurity status (the independent variable) and (2) the sleep and/or HPAA indices (the mediator) had to be significantly related to behavioral and emotional problems (the dependent variable). For hypotheses involving directional predictions the reported $p$-values are one-tailed. All statistical computations were performed with IBM® SPSS® Statistics 20 (IBM Corporation, Armonk NY, USA) for Apple Mac®.

## 3. Results

### 3.1. Differences in behavioral and emotional problems, sleep, and HPAA between very preterm and full-term children

Table 2 shows the results of the ANCOVAs comparing behavioral and emotional problems and sleep of very preterm and full-term children. Very preterm children showed more SDQ total behavioral/emotional difficulties ($F(1,102) = 3.99$, $P = .02$) and emotional symptoms ($F(1,102) = 4.89$, $P = .01$), as well as more nocturnal awakenings ($F(1,95) = 3.65$, $P = .03$), stage 2 sleep ($F(1,95) = 3.94$, $P = .03$), and less SWS ($F(1,95) = 4.01$, $P = .02$) than full-term children. There were no mean differences in conduct problems, hyperactivity-inattention, and peer problems nor in total sleep time, sleep efficiency, stage 1 sleep, REM sleep, REM latency, and SDB between very preterm and full-term children.

Cortisol secretion in the morning increased in 82 (80.4%) children across the first 30 min after awakening indicating a cortisol awakening response in the majority of the children with no differences between very preterm and full-term children (very preterm: $n = 43$; full-term: $n = 39$; $\chi^2(1) = .4$, $P = 0.83$). A repeated-measures ANCOVA showed no main effect of preterm status on morning cortisol secretion ($F(1,95) = 0.39$; $P = .54$) and no group × time interaction effect in the morning cortisol secretion ($F(1,95) = 0.65$; $P = .42$) as well as no mean differences at any time point. In the evening, cortisol secretion declined in both groups. A repeated-measures ANCOVA showed that this decline was faster among very preterm compared to full-term children with a significant group × time interaction effect ($F(1,99) = 4.99$; $P = .03$). The repeated-measures ANCOVA further indicated lower overall evening cortisol secretion of very preterm compared to full-term children ($F(1,99) = 4.05$; $P = .047$). Means of evening cortisol secretion differed at 60 min ($F(1,101) = 4.05$; $P = .047$) and at 90 min ($F(1,99) = 7.97$; $P = .006$) after the beginning of the home-visit.

### 3.2. Association of sleep and HPAA with behavioral and emotional problems

Table 3 shows hierarchical regression analyses for the association of sleep and HPAA with behavioral and emotional problems.

**Table 2**
Behavioral and emotional problems and sleep in very preterm and full-term children.

| | Very preterm | | Full-term | | $d$[a] | $P$[a] |
|---|---|---|---|---|---|---|
| | $M$ | (SD) | $M$ | (SD) | | |
| Behavioral and emotional problems (SDQ) | | | | | | |
| Total behavioral/emotional difficulties | 8.7 | (4.4) | 6.3 | (4.6) | 0.40 | .02 |
| Emotional symptoms | 1.9 | (1.7) | 1.1 | (1.3) | 0.44 | .01 |
| Conduct problems | 2.0 | (1.3) | 1.5 | (1.3) | 0.30 | .07 |
| Hyperactivity-inattention | 3.4 | (1.8) | 2.6 | (2.3) | 0.28 | .08 |
| Peer problems | 1.4 | (1.3) | 1.1 | (1.2) | 0.12 | .28 |
| Sleep variables | | | | | | |
| Total sleep time, h | 9.5 | (0.7) | 9.5 | (0.6) | 0.16 | .23 |
| Sleep efficiency | 94.4 | (2.4) | 94.6 | (2.7) | 0.11 | .29 |
| Nocturnal awakenings | 19.6 | (5.9) | 15.5 | (7.8) | 0.40 | .03 |
| Stage 1 sleep (min) | 18.5 | (9.9) | 17.7 | (14.8) | 0.14 | .26 |
| Stage 2 sleep (min) | 263.2 | (41.8) | 248.4 | (35.9) | 0.41 | .03 |
| Slow wave sleep (min) | 139.6 | (32.0) | 150.0 | (31.3) | 0.42 | .02 |
| REM sleep (min) | 145.7 | (26.1) | 149.3 | (28.2) | 0.31 | .14 |
| REM latency (min) | 115.3 | (47.0) | 119.8 | (42.2) | 0.10 | .65 |
| Breathing problems (parent rating) | 0.7 | (1.5) | 0.3 | (0.5) | 0.34 | .10 |

*Note.*
SDQ = Strengths and Difficulties Questionnaire.
[a] Cohen's $d$, $P$-values: adjusted for first language, maternal education, children's age, and gender.

**Table 3**
Multiple regression with sleep and HPAA predicting behavioral and emotional problems assessed using the Strengths and Difficulties Questionnaire (SDQ).

| | Total behavioral/emotional difficulties | Emotional symptoms | Conduct problems | Hyper-activity-inattention | Peer problems |
|---|---|---|---|---|---|
| Sleep variables | | | | | |
| Total sleep time, h | .06 | .06 | .09 | .10 | −.12 |
| Sleep efficiency | .12 | .04 | .03 | .13 | .14 |
| Nocturnal awakenings | .02 | .12 | .05 | −.03 | −.09 |
| Stage 1 sleep (min) | −.02 | .02 | −.03 | −.03 | −.02 |
| Stage 2 sleep (min) | .21* | .16 | .15 | .23* | .01 |
| Slow wave sleep (min) | −.19* | −.12 | −.12 | −.12 | −.20* |
| REM sleep (min) | .04 | −.02 | .09 | −.03 | .09 |
| REM latency (min) | −.09 | −.06 | −.09 | .02 | −.16 |
| Breathing problems (parent rating) | .10 | .04 | .18* | .04 | .08 |
| Morning cortisol secretion | | | | | |
| AUCg | .05 | .13 | −.03 | −.02 | .06 |
| AUCi | −.08 | .05 | −.27** | −.06 | .00 |
| Evening cortisol secretion | | | | | |
| AUCg | −.10 | .00 | −.21* | −.12 | .05 |
| AUCi | −.01 | .05 | −.01 | .00 | −.08 |

*Note.* Data are standardized regression coefficients. All values adjusted for first language, maternal education, children's age, gender, prematurity status, and in analyses involving evening cortisol levels the clock time of saliva sampling was additionally controlled. AUCg = area-under-the-concentration-time-curve with respect to the ground; AUCi = area-under-the-concentration-time-curve with respect to the increase. *$p < 0.05$, **$p < 0.01$ (one-tailed).

More stage 2 sleep was associated with more SDQ total behavioral/emotional difficulties ($t = 2.09$, $\beta = .21$, $P = .02$) and more hyperactivity-inattention ($t = 2.28$, $\beta = .23$, $P = .01$). Less SWS was related to more SDQ total behavioral/emotional difficulties ($t = -1.88$, $\beta = -.19$, $P = .03$) and more peer problems ($t = -1.88$, $\beta = -.20$, $P = .03$). SDB was related to more conduct problems ($t = 1.80$, $\beta = .18$, $P = .04$). Total sleep time, sleep efficiency, nocturnal awakenings, stage 1 sleep, REM sleep, and REM latency were not related to behavioral and emotional problems. Lower morning cortisol secretion AUCi and lower evening cortisol secretion AUCg were associated with more conduct problems ($t = -2.81$, $\beta = -.27$, $P = .003$; $t = -2.11$, $\beta = -.21$, $P = .02$, respectively).

### *3.3. Mediation of the relationship between prematurity status and behavioral and emotional problems by sleep and/or HPAA*

Additionally, it was tested whether differences in sleep and/or HPAA characteristics accounted for the significant differences in behavioral and emotional problems between very preterm and full-term children. Based on the previous analyses, the preconditions for mediation were met by the amount of stage 2 sleep (which was positively associated with prematurity status and SDQ total behavioral/emotional difficulties) and amount of SWS (which was negatively associated with prematurity status and SDQ total behavioral/emotional difficulties). As indices of SWS and stage 2 sleep were negatively related to each other ($r = -.42$, $P < 0.001$) and as they were differentially related to SDQ total behavioral/emotional difficulties, the mediation analysis was conducted with the ratio between deep sleep (SWS) and light sleep (stages 1 and 2 together) as the mediator. The deep sleep to light sleep ratio represents an aggregate index of a favorable sleep-EEG pattern with higher values reflecting more restorative deep sleep compared to light sleep. The mediation analysis is displayed in Fig. 2. The ratio between deep sleep and light sleep partially mediated the relationship between prematurity status and SDQ total behavioral/emotional difficulties. When the mediator (deep sleep to light sleep ratio) was entered to the regression the effect of prematurity status on SDQ total behavioral/emotional difficulties dropped from $\beta = .20$; $t = 1.96$; $p = 0.03$ ($\Delta r^2 = .032$) to $\beta = .15$; $t = 1.42$; $p = 0.08$ ($\Delta r^2 = .018$).

## 4. Discussion

The aim of the present study was to shed light on underlying mechanism in the association between very preterm birth and psychosocial adjustment by examining the role of sleep and HPAA. The key finding of the study is that healthy school-aged very preterm children show less restorative sleep (more stage 2 sleep and less SWS) compared to full-term children and that less restorative sleep is related to more behavioral and emotional problems which partially accounts for the difference between very preterm and full-term children in behavioral and emotional problems.

### *4.1. Differences in behavioral and emotional problems, sleep, and HPAA between very preterm and full-term children*

First we hypothesized to find more behavioral and emotional problems, poorer sleep and an altered HPAA in very preterm compared to full-term children, which was partially supported by the data. We found that very preterm children had more total behavioral and emotional difficulties and emotional symptoms compared to full-term children which is consistent with previous research showing more internalizing behavior problems in very preterm compared to full-term children (Aarnoudse-Moens et al., 2009; Burnett et al., 2011). In contrast to previous research (Aarnoudse-Moens et al., 2009; Bhutta et al., 2002) we found no differences in hyperactivity and inattention symptoms between very preterm and full-term children, which may be due to limited statistical power to detect modest effects (the effect size for the difference regarding hyperactivity-inattention was $d = .28$).

Regarding sleep, results are consistent with the hypothesis that very preterm children show poorer sleep involving more nocturnal awakenings, more stage 2 sleep, and less SWS compared to full-term children. Our study did not replicate the finding that very preterm children show more SDB. In our study, SDB was rated by the parents, while e.g. in the study by Rosen et al. (2003) respiratory events were measured objectively. Though speculative, it is possible that PSG derived higher levels of stage 2 sleep, more nocturnal awakenings, and lower levels of SWS in our study are a reflection of breathing problems in the very preterm children, which were not detected by the parents. As a limitation to our study, we do not have objective measures of SDB. However, the present study expands upon previous research by showing that very preterm children show less restorative sleep objectively assessed using in-home PSG.

Our expectation to find altered HPAA in very preterm compared to full-term children was supported in that very preterm children showed a faster decline in evening cortisol compared to full-term children, which is in line with reports of a hypoactive HPAA in

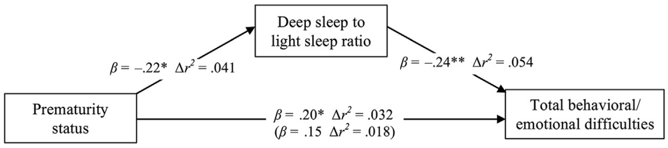


**Fig. 2.** Mediation of the relationship between prematurity status and behavioral/emotional difficulties by the deep sleep to light sleep ratio. Standardized regression coefficients are displayed. Prematurity status is coded 1 = very preterm birth and 0 = born at term. All analyses additionally control first language, maternal education, children's age, and gender. *$p < 0.05$, **$p < 0.01$ (one-tailed).

response to stress in very preterm born young adults (Kaseva et al., 2014). The faster decline in diurnal cortisol in very preterm children may be a sign of down-regulation of the HPAA due to excess exposure to glucocorticoids during the premature phase (cf. Karemaker et al., 2008). In line with Bäumler and colleagues (2013), the majority of the children in our study showed a marked increase in cortisol secretion upon awakening. However, the morning cortisol secretion did not differ between very preterm and full-term children, which is in contrast to results from Buske-Kirschbaum et al. (2007), who found an elevated cortisol awakening response in preterm children. In contrast to our study, Buske-Kirschbaum and colleagues studied older children (mean age of 10.5 years) who were born with gestational ages up to 36 weeks, which may explain differences in the findings.

### *4.2. Association of sleep indices and HPAA with behavioral and emotional problems*

Second, we hypothesized that poor sleep and an altered HPAA are associated with more behavioral and emotional problems. The data supported this assumption in that poor sleep involving more stage 2 sleep and less SWS was associated with more total behavioral and emotional difficulties, more hyperactivity and inattention symptoms, as well as more peer problems, respectively. This is consistent with other PSG-studies reporting that alterations in objective sleep are associated with more behavioral and emotional problems in preschoolers and adolescents (Brand et al., 2010, 2014; Hatzinger et al., 2013). Importantly and beyond what was known from previous research, the present study also indicates that differences in stage 2 sleep and SWS between preterm and full-term children (as represented by the ratio between deep sleep and light sleep) may partially account for increased behavioral and emotional problems in very preterm children.

Regarding HPAA, we found that lower levels of evening cortisol secretion AUCg and a blunted morning cortisol secretion AUCi is related to conduct problems, which is in line with previous research showing that a hypoactive HPAA is associated with more behavioral problems (Hartman et al., 2013). However and in contrast to our hypothesis we found no associations of cortisol secretion and emotional problems. This finding reflects research indicating that the size of the association between cortisol secretion and emotional problems may be rather modest (Dietrich et al., 2013).

### *4.3. Limitations*

We think our study has four limitations. First, due to the correlative design of the study, no conclusions on causal relations among the studied variables may be drawn. Second, sleep and HPAA were only assessed on a single night and day, which may reduce reliability of sleep and HPAA variables. However, sleep assessment was conducted at the children's home in familiar surroundings which we consider as an advantage compared to laboratory PSG as it improves the ecological validity of the sleep assessment (Frölich and Lehmkuhl, 2004). Third, we did not assess HPAA in response to a standardized psychosocial stressor, which would have shed further light on the HPAA of very preterm and full-term children. We did assess evening cortisol levels during assessment of cognitive functions during a home-visit, which may have been a minor social stressor for some of the children. Overall, the cognitive testing situation appeared not to have been stressful for the children as on average the cortisol levels declined steadily over the course of 90 min of testing. Last, while the current study was sufficiently powered to detect medium size effects, the statistical power was insufficient to detect small size effects.

## 5. Conclusions

The present study indicates that very preterm children remain at higher risk for behavioral and emotional problems as well as poor sleep during middle childhood. Poor sleep partially accounts for the increases in behavioral and emotional problems in very preterm children. Thus, it is possible that perinatal adversities related to very preterm birth affect behavioral and emotional development by altering sleep patterns. Moreover, very preterm children show a faster decline in evening cortisol levels, which may indicate a hypoactive HPAA. The present study points to the importance of sleep in very preterm born children. Clinicians who are concerned with behavioral and emotional problems of very preterm born children during middle childhood may put greater emphasis on good sleep quality.

## Role of the funding source

This research was financially supported by the Swiss National Science Foundation (Project: Sleep, cognitive, and socio-emotional development in preterm children during middle and late childhood, Grant number: 143962), and the Research Fund of the University of Basel. The sponsor had no role in study design, data collection, data analysis, data interpretation, or in the writing of the report.

## Contributors

NPG, PHvA, SB, EHT, AG, PW, and SL contributed to the conception and design of the study and all of them managed the literature searches and analyses. NPG collected a large subset of the data, undertook the statistical analysis and prepared and revised the manuscript. PW contributed in the acquisition interpretation of data and revised the manuscript. PHvA, SB, EHT, and AG, contributed in the interpretation of data and revised the manuscript. SL, as the principal investigator, obtained funding and supervised all stages of the study, participated in the acquisition and interpretation of data, contributed to the drafting of the manuscript, revised the manuscript, and approved the final manuscript as submitted. All authors contributed to and have approved the final manuscript.

### Conflict of interests

The authors declare no conflicts of interest.

### Acknowledgment

We thank Marielle Koenig and Vladimir Djurdjevic, Center for Affective, Stress and Sleep Disorders, Psychiatric Clinics of the University of Basel, Basel, Switzerland, for scoring polysomnographic data and the Swiss National Science Foundation (Grant number: 143962) and the University of Basel (Grant number: DPE2083) for funding the research.

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# APPENDIX C

Study 3

Perkinson-Gloor, N., Hagmann-von Arx, P., Brand, S., Holsboer-Trachsler, E., Grob, A., Weber, P., & Lemola, S. Intra-individual long-term stability of the sleep-EEG in school-age children. *Manuscript submitted for publication to Sleep Medicine.*

Draft of March 18, 2015

**Intra-individual long-term stability of the sleep-EEG in school-age children**

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**Financial support:** This research was financially supported by the Swiss National Science Foundation (Project: Sleep, cognitive, and socio-emotional development in preterm children during middle and late childhood, Grant number: 143962), and the Research Fund of the University of Basel.

**Conflict of interest:** none.

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Abstract (206/250)

**Objective:** To examine the long-term stability of sleep duration, sleep continuity, and sleep architecture assessed via unattended home sleep-EEG during middle childhood.

**Methods:** 69 healthy children (18 girls) aged 8.2 years (*SD* = 1.3) at T1 underwent unattended home sleep-EEG on two nights separated by 18.5 months (*SD* = 3.9 months). Thirty-four (49.3%) children were born premature (<32 gestational weeks; mean birth weight = 1367g) and 35 (50.7%) children were born at term (mean birth weight = 3275g).

**Results:** We found moderate to substantial stability (all $P < 0.001$) for total sleep time (TST; $ICC = 0.65$), slow wave sleep (SWS; min, %: $ICC = 0.49$), and stage 2 sleep (min; $ICC = 0.47$), and fair stability (all $P < 0.013$) for sleep efficiency ($ICC = 0.28$), nocturnal awakenings ($ICC = 0.33$), stage 2 sleep (%; $ICC = 0.32$, $P = 0.004$), and rapid eye movement (REM) sleep (min: $ICC = 0.33$, $P = 0.003$; %: $ICC = 0.27$).

**Conclusions:** Long-term follow-up of one night of unattended home sleep-EEG during middle childhood reveals that TST, stage 2 sleep, and SWS are relatively stable, trait-like characteristics. This applies less strongly for sleep efficiency, nocturnal awakenings, and REM sleep. Stage 1 sleep and REM latency showed no stability.

**Keywords:** Sleep-EEG; sleep architecture; middle childhood; long-term stability

Polysomnography (PSG) is the gold standard for sleep assessment, providing objective measures of sleep duration, sleep continuity, and sleep architecture. Although a growing body of research has applied PSG with childhood samples, surprisingly little is known regarding psychometric properties of these PSG-derived sleep measures, such as the intra-individual stability, often also referred to as test-retest reliability. It is of particular importance to appraise the intra-individual stability of PSG-derived sleep measures in children to unravel if these measures reflect trait-like characteristics or simply a snapshot of children's sleep that is not representative of their habitual sleep patterns. To our knowledge, only two studies have addressed this question with regard to childhood samples to date. One laboratory study including 14 children aged 9-12-years found a high short-term stability of sleep architecture across two nights separated by one to two weeks, but not for sleep duration and continuity.[1] The small sample size, however, makes generalization from these findings difficult and the confidence intervals around the stability coefficients are large. Long-term stability of PSG sleep in children has, to our knowledge, only been examined in one study with preschoolers, who were grouped into poor, normal and good sleepers based on one night of sleep assessment with PSG at the children's home. Twelve months later, the formerly poor sleepers were still more likely to show poorer sleep patterns compared to good/normal sleepers.[2] Thus, in preschoolers, sleep assessed during one night with unattended PSG showed significant stability over 12 months. However, due to the group level approach of this study, the intra-individual long-term stability coefficients of the PSG-derived sleep indices remain unknown.

Further evidence that sleep indices are likely to show high long-term stability stems from behavioral-genetic research. In twin studies with adolescents and young adults sleep continuity[3] and sleep architecture were strongly influenced by genetic factors, indicating trait-

[1] Abbreviations: TST, total sleep time; SWS, slow wave sleep; REM, rapid eye movement

like (and therefore probably highly stable) characteristics of the sleep parameters.[4,5] The strongest heritability concerning sleep stages was found for SWS with heritability estimates ranging between .50 and .90.[4] However, particularly during childhood, high heritability does not necessarily indicate that individual characteristics are unchangeable.[6] Thus, although behavioral-genetic studies suggest that sleep continuity and architecture are heritable characteristics and should therefore remain highly stable, none of these studies examined the long-term stability which is a prerequisite for PSG-derived sleep indices being trait-like characteristics.

To fill the gap in research regarding the stability of sleep-EEG indices, the present study examined the stability coefficients of sleep-EEG parameters during middle childhood across one and a half years. We expected high stability coefficients for sleep duration, sleep continuity, and sleep architecture, which would also indicate that one night of sleep-EEG can be regarded as a reliable measure of children's habitual sleep. In particular, we assessed sleep with unattended home sleep-EEG, allowing the children to sleep in their usual surroundings and according to their usual schedule, which, compared to laboratory-assessed sleep, results in better sleep quality[7,8] and provides a more convenient and cost-effective method to assess sleep in children.[9]

## 2. Methods

### *2.1. Study population and procedure*

The study included 69 healthy school-age children (age: $M$ = 8.2 years, $SD$ = 1.3; range: 6.0 to 10.9; 18 girls), who underwent one night of unattended home sleep-EEG assessment between June 2011 and September 2012 and again between May 2013 and February 2014 (9.6 to 27.5 months later; $M$ = 18.5 months, $SD$ = 3.9). At the follow-up, children were on average 9.8 years old ($SD$ = 1.3). Thirty-four (49.3%) children were born very premature (<32 weeks of gestation; mean birth weight = 1367g) and 35 (50.7%) were born at term (mean birth weight = 3275g). Very preterm children were recruited from a cohort of prematurely born children treated at the University Children's Hospital Basel (Switzerland), which has been described elsewhere in detail.[10] (REF Perkinson-Gloor et al. 2015). All children attended primary school in Switzerland. Parents gave written informed consent for the children to participate and assent was obtained from the child. The study was approved by the Ethics Committee of Basel.

*2.2. Sleep assessment*

Sleep was assessed using the ambulatory Compumedics Somté PSG device (Melbourne, Australia) for one night at T1 and one night at T2 on a regular school day (i.e., Monday to Thursday). Polysomnogram signals C3/A2 and C4/A1 EEG, right and left electrooculogram and bipolar submental electromyogram were obtained. Sleep-EEGs were scored by experienced raters according to the standard procedures.[11] Sleep indices included: Total sleep time (TST; time in bed minus time spent awake in hours), sleep efficiency (TST/time in bed × 100), nocturnal awakenings (number of arousals from sleep), and sleep architecture (stage 1 sleep, stage 2 sleep, SWS (stages 3 and 4), REM sleep and REM latency).

*2.5. Statistical analysis*

Paired-sample t-tests were conducted to examine changes in the sleep-EEG indices from T1 to T2. To test the longitudinal stability of sleep-EEG measures, a series of regression analyses was conducted with sleep parameters at T1 predicting the corresponding sleep parameters at T2, controlling for children's age and prematurity status. Supplementary analysis included the time period between T1 and T2 as a covariate. As an additional measure of stability, we calculated the intraclass correlation coefficients (ICCs), defined as the error-free between subject variance, divided by the sum of the error-free between- and within-subject variances,[12] and interpreted according to the following benchmarks: "slight" (0.0-0.2), "fair" (0.2-0.4), "moderate" (0.4-0.6), "substantial" (0.6-0.8), and "almost perfect" (0.8-1.0).[13] Statistical computations were performed with IBM® SPSS® Statistics 20 (IBM Corporation, Armonk NY, USA) for Apple Mac®.

3. Results

Table 1 shows the descriptive statistics of the sleep-EEG indices at T1 and T2, including the analysis of mean value change (paired-sample t-test). TST, sleep efficiency, SWS (min, %) and REM sleep (min) decreased over time, while stage 1 sleep (min, %) and stage 2 sleep (%) increased between T1 and T2. Further, analyses showed that TST (*ICC* = 0.65, Figure 1a), sleep continuity (sleep efficiency (*ICC* = 0.28, Figure 1b), nocturnal awakenings (*ICC* = 0.33, Figure 1c), and sleep architecture (stage 2 sleep %: *ICC* = 0.33, Figure 1d; stage 2 sleep min: *ICC* = 0.47; SWS %: *ICC* = 0.49, Figure 1e; SWS min: *ICC* = 0.49; REM sleep %: *ICC* = 0.27, Figure 1f; REM sleep min: *ICC* = 0.33) showed fair to substantial stability over 18.5 months with regard to the individuals' position in the distribution, after controlling for children’s age and prematurity status. No significant associations between T1 and T2 sleep parameters were found for stage 1 sleep (stage 1 sleep %: $t = 1.55, \beta = 0.20, P = .13$; $ICC = 0.16$; stage 1 sleep min: $t = 1.70, \beta = 0.21, P = .09$; $ICC = 0.17$) and REM latency ($t = 0.36, \beta = 0.05, P = .72$; $ICC = 0.02$).

Children’s age was associated with TST ($t = -2.48$, $\beta = -0.25$, $P = 0.02$), such that sleep duration decreased with age, while prematurity status was not associated with any sleep variables. Results remained very similar when additionally controlling for the time span that elapsed between T1 and T2.

4. Discussion

The present study shows for the first time, that in school-age children, TST, sleep continuity, i.e. sleep efficiency and nocturnal awakenings, and the sleep architecture, i.e., the amount and percentage of time spent in stage 2 sleep, SWS and REM sleep, assessed via unattended home sleep-EEG, showed fair to substantial intra-individual stability over a time period of one and a half years. The results confirm our hypothesis, which was based on behavioral-genetic studies indicating strong trait-like characteristics of sleep architecture in adults.[4]

In the present study, stage 1 sleep did not show significant stability over time, while the strongest stability concerning sleep architecture was found for SWS, which is in line with studies on sleep architecture in adults, that show no or weak trait-like characteristics for stage 1 sleep and the strongest trait-like inter-individual variability for SWS.[4,14] In line with Quan and colleagues,[15] the results of the present study suggest that SWS, along with the time spent in stage 2 sleep, may be the most reliable measures of one night of unattended home PSG also in children.

As a limitation to the present study we are not able to distinguish between short-term test-retest reliability and long-term stability of sleep measures. Only the assessment of sleep-EEG on several consecutive nights, repeated after a long interval, would allow disentangling short-term fluctuations (i.e. reliability across several consecutive nights) from long-term developmental patterns (i.e. the stability of the aggregated measures across a longer period), which may be addressed in future research.

In conclusion, our study shows that in school-age children TST, stage 2 sleep, and SWS show moderate to substantial stability, while sleep efficiency, nocturnal awakenings, and REM sleep show only fair stability when assessed via one night of unattended home sleep-EEG across a time period of one and a half years. No stability was found for stage 1 sleep and REM latency. We conclude that one night of unattended home sleep-EEG can be regarded as a reliable method to assess children's habitual sleep patterns, especially concerning the TST, stage 2 sleep, and SWS.

## Acknowledgements

We thank Marielle Koenig and Vladimir Djurdjevic, Center for Affective, Stress and Sleep Disorders, Psychiatric Clinics of the University of Basel, Basel, Switzerland, for scoring polysomnographic data and the Swiss National Science Foundation (Grant number: 143962) and the University of Basel for funding the research.

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*Table 1*

*Descriptive statistics of total sleep time, sleep continuity, and sleep architecture*.

| | T1 | | T2 | | | |
|---|---|---|---|---|---|---|
| | M | (SD) | M | (SD) | *t* | *P* |
| TST (hours) | 9.5 | (0.7) | 9.0 | (0.8) | 6.20 | <0.001 |
| Sleep efficiency (%) | 94.5 | (2.5) | 93.3 | (3.0) | 2.89 | 0.01 |
| Nocturnal awakenings | 17.2 | (7.3) | 16.2 | (7.3) | 1.00 | 0.32 |
| Stage 1 sleep (min) | 18.6 | (13.9) | 23.5 | (14.3) | -2.24 | 0.03 |
| Stage 1 sleep (%) | 2.8 | (2.6) | 3.9 | (2.6) | -2.53 | 0.01 |
| Stage 2 sleep (min) | 253.1 | (43.1) | 256.0 | (35.9) | -0.58 | 0.56 |
| Stage 2 sleep (%) | 44.1 | (6.0) | 46.7 | (5.0) | -3.27 | 0.002 |
| SWS (Stages 3 and 4; min) | 148.7 | (33.9) | 122.4 | (27.8) | 6.82 | <0.001 |
| SWS (Stages 3 and 4; %) | 25.3 | (5.8) | 21.7 | (5.3) | 5.32 | <0.001 |
| REM sleep (min) | 146.8 | (27.2) | 139.4 | (25.5) | 2.01 | 0.05 |
| REM sleep (%) | 25.4 | (4.5) | 25.2 | (3.9) | 0.28 | 0.78 |
| REM latency (min) | 113.5 | (43.9) | 114.3 | (41.8) | -0.11 | 0.91 |

*Note*. P-value of the paired-sample t-test

Figure 1

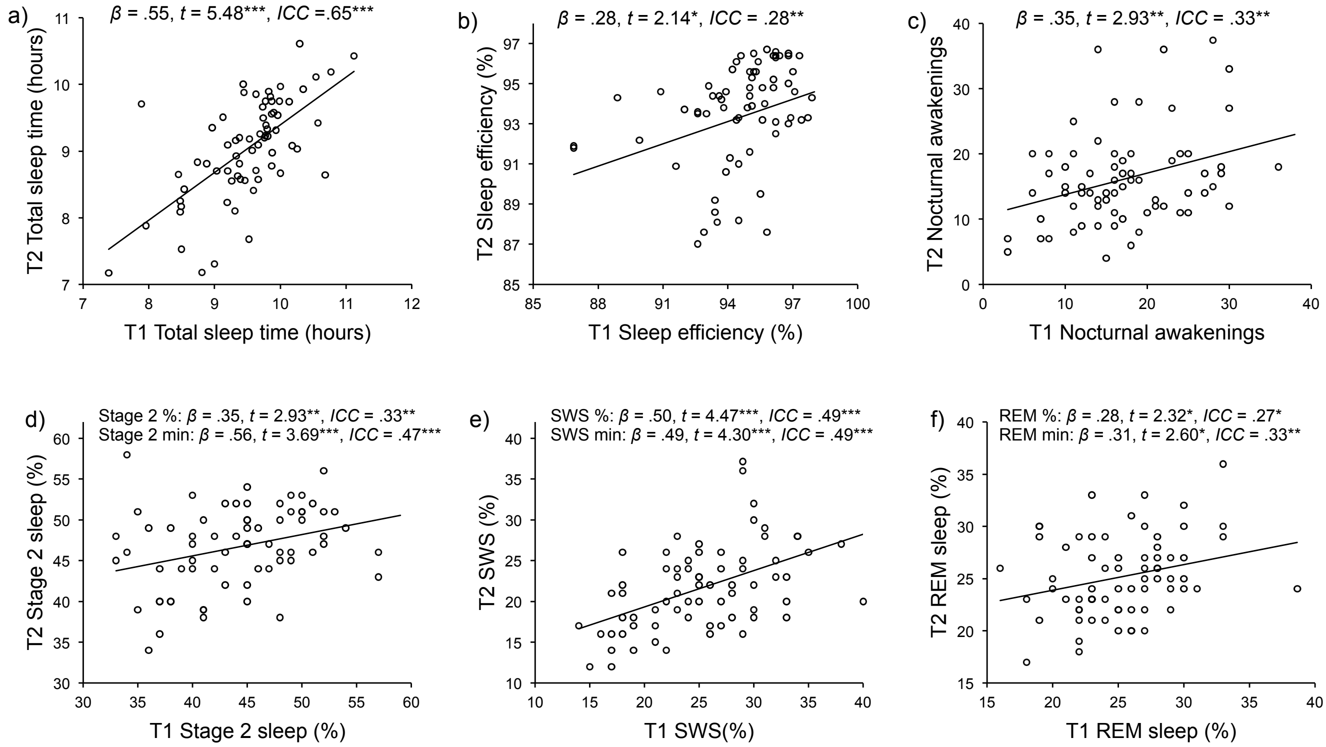
a)
β = .55, t = 5.48***, ICC =.65***
T2 Total sleep time (hours)
T1 Total sleep time (hours)
b)
β = .28, t = 2.14*, ICC = .28**
T2 Sleep efficiency (%)
T1 Sleep efficiency (%)
c)
β = .35, t = 2.93**, ICC = .33**
T2 Nocturnal awakenings
T1 Nocturnal awakenings
d)
Stage 2 %: β = .35, t = 2.93**, ICC = .33**
Stage 2 min: β = .56, t = 3.69***, ICC = .47***
T2 Stage 2 sleep (%)
T1 Stage 2 sleep (%)
e)
SWS %: β = .50, t = 4.47***, ICC = .49***
SWS min: β = .49, t = 4.30***, ICC = .49***
T2 SWS (%)
T1 SWS(%)
f)
REM %: β = .28, t = 2.32*, ICC = .27*
REM min: β = .31, t = 2.60*, ICC = .33**
T2 REM sleep (%)
T1 REM sleep (%)

Figure Legend

Figure 1

Intra-individual stability of sleep parameters. Associations of TST (a), sleep efficiency (b), nocturnal awakenings (c), stage 2 sleep (d), SWS (e) and REM sleep (f) at T1 with corresponding sleep parameters at T2. Scatterplots show unadjusted values. ICCs are based on z-standardized unadjusted values. Regression analyses are based on z-standardized values adjusted for children's age and prematurity status. Extreme values were truncated to ± 3 SD.

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$

# APPENDIX D

## Selbständigkeitserklärung

Hiermit erkläre ich, dass ich die Dissertation „Sleep and the Hypothalamic-Pituitary-Adrenocortical Activity: Biological Processes Associated with Psychosocial Adjustment During Childhood and Adolescence“ selbständig verfasst und nur unter Verwendung der angegebenen Quellen und Hilfsmittel angefertigt habe. Alle wörtlichen oder sinngemässen Zitate sind als solche gekennzeichnet. Die zur Promotion eingereichten Zeitschriftenbeiträge wurden in Zusammenarbeit mit den jeweiligen Co-Autorinnen und Co-Autoren angefertigt.

Lausen, im April, 2015

Nadine Perkinson-Gloor

# APPENDIX E

## List of Publications

Hagmann-von Arx, P., Perkinson-Gloor, N., Brand, S., Albert, D., Holsboer-Trachsler, E., Grob, A., ... Lemola, S. (2014). In school-age children who were born very preterm sleep efficiency is associated with cognitive function. *Neuropsychobiology*, *70*, 244-252. doi:10.1159/000369026

Lemola, S., Brand, S., Vogler, N., Perkinson-Gloor, N., Allemand, M. & Grob, A. (2011). Habitual computer game playing at night is related to depressive symptoms. *Personality and Individual Differences, 51,* 117–122. doi:10.1016/j.paid.2011.03.024

Lemola, S., Perkinson-Gloor, N., Brand, S., Dewald-Kaufmann, J., & Grob, A. (2014). Adolescents' electronic media use at night, sleep disturbance, and depressive symptoms in the smartphone age. *Journal of Youth and Adolescence,* doi:10.1007/s10964-014-0176-x.

Lemola, S., Perkinson-Gloor, N., Hagmann-von Arx, P., Brand, S., Holsboer-Trachsler, E., Grob, A., & Weber, P. (2015). Morning cortisol secretion in school-age children is related to the sleep pattern of the preceding night. *Psychoneuroendocrinology, 52,* 297–301. doi:10.1016/j.psyneuen.2014.12.007

Perkinson-Gloor, N., Hagmann-von Arx, P., Brand, S. Holsboer-Trachsler, E., Grob, A., Weber, P., Lemola, S. (2015). The role of sleep and the hypothalamic-pituitary-adrenal axis for behavioral and emotional problems in very preterm children during middle childhood. *Journal of Psychiatric Research, 60,* 141–147. doi:10.1016/j.jpsychires.2014.10.005

Perkinson-Gloor, N., Hagmann-von Arx, P., Brand, S., Holsboer-Trachsler, E., Grob, A., Weber, P., & Lemola, S. Intra-individual long-term stability of the sleep-EEG in school-age children. *Manuscript submitted for publication to Sleep Medicine.*

Perkinson-Gloor, N., Lemola, S., & Grob, A. (2013). Sleep duration, positive attitude towards life, and academic achievement: The role of daytime tiredness, behavioral persistence, and school start times. *Journal of Adolescence, 36,* 311–318. doi:10.1016/j.adolescence.2012.11.008

Vogler, N.*, Perkinson-Gloor, N.*, Brand, S., Grob, A., & Lemola, S. (2014). Sleep, aggression, and psychosocial adjustment in male prisoners. *Swiss Journal of Psychology, 73,* 167-176. doi:10.1024/1421-0185/a000137 (*shared first authorship)