# Biological Processes Related to Positive Development After Preterm Birth: The Interplay Between Sleep, Hypothalamic-Pituitary-Adrenal Axis Activity, and Autonomic Functioning, and the Role of Parental Insomnia Symptoms

**Inaugural Dissertation**

submitted to the Department of Psychology of the University of Basel
in partial fulfillment of the requirements for the degree of
Doctor of Philosophy
by

Natalie Urfer-Maurer

from Basel, BS

Basel, 2018

University of Basel

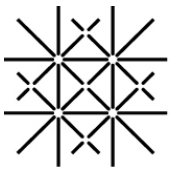
Approved by the Faculty of Psychology
at the request of

Prof. Dr. Alexander Grob
Prof. Dr. Sakari Lemola

Basel, _____

_____

Prof. Dr. Alexander Grob



University of Basel

# ACKNOWLEDGMENTS

I would like to thank the following people who supported me throughout my PhD:

Prof. Dr. Alexander Grob—for serving as my supervisor and for your guidance and support.

Prof. Dr. Sakari Lemola—for serving as my supervisor, for your endless support, and for giving me the chance to be a part of your interesting research project. Thank you for sharing your time and knowledge with me.

Prof. Dr. Rui Mata—for serving on the dissertation committee.

The Basel Study of Preterm Children team—for the time you have put into our research project. This study would not have been possible without you.

Coauthors and colleagues—for all your support, insightful and inspiring comments, and recommendations as well as for your motivation. Thank you for your contribution to a friendly working atmosphere.

My husband, Marco Urfer—for always believing in me. For making me laugh, even when I was stressed out, thank you.

My parents, Mireille Perusset and Marco Maurer—without you, I wouldn't be here! Thank you for all your love and your continuous, unconditional support.

# TABLE OF CONTENTS

ACKNOWLEDGMENTS III
ABSTRACT V
1. Introduction 1
2. Theoretical Background 3
2.1 Positive development according to the biodevelopmental framework 3
2.2 Sleep 3
2.3 The hypothalamic-pituitary-adrenocortical axis 4
2.3.1 HPA axis activity and sleep 4
2.4 The autonomic nervous system 5
2.4.1 ANS functioning and HPA axis activity 6
2.5 Very preterm birth 6
2.5.1 Sleep of children born very preterm 7
2.5.2 HPA axis activity of children born very preterm 7
2.5.3 ANS functioning of children born very preterm 8
2.6 Parental insomnia symptoms and children's sleep 9
2.7 Parental insomnia symptoms and parental perception of children's sleep 9
3. Research Questions 10
4. Method 11
4.1 Studies and Samples 11
4.2 Procedure and Measures 12
5. Synopsis of Results 13
5.1 The interplay between sleep, HPA axis activity, and ANS functioning 13
5.2 Sleep, HPA axis activity, and ANS functioning of children and adolescents born very preterm 13
5.3 Children's sleep and sleep assessment in the family context 13
6. General Discussion 14
6.1 The interplay between sleep, HPA axis activity, and ANS functioning 14
6.2 Sleep, HPA axis activity, and ANS functioning of children and adolescents born very preterm 15
6.3 Children's sleep and sleep assessment in the family context 16
6.4 Strengths and Limitations 17
6.5 Conclusions and Outlook 18
References 20
APPENDIX A: Study 1 32
APPENDIX B: Study 2 42
APPENDIX C: Study 3 51
APPENDIX D: Selbständigkeitserklärung 59
APPENDIX E: Curriculum Vitae 60

## ABSTRACT

Biological processes, including sleep, the hypothalamic-pituitary-adrenocortical (HPA) axis, and the autonomic nervous system (ANS), play an important role in positive development across the life-span. They are highly susceptible to early life experiences such as very preterm (VP) birth and to concurrent environmental factors such as parental sleep. Yet, research examining sleep, HPA axis activity, and ANS functioning in children and adolescents is rare. Therefore, the goal of this cumulative dissertation containing three studies is (a) to extend knowledge of the interplay between sleep, HPA axis activity, and ANS functioning during childhood and adolescence, (b) to examine the role of VP birth in these biological processes, and (c) to test whether parental insomnia symptoms are related to their children's sleep as well as to parental perception of children's sleep-related behavior. The samples included in the studies of this dissertation derived from the second wave of the Basel Study of Preterm Children investigating VP and full-term (FT) children and adolescents. Findings from Study 1 (Maurer[1] et al., 2016) showed an association between elevated post-awakening HPA axis activity and a later sleep onset time, shorter sleep duration, and shorter rapid eye movement latency across the whole sample. Additionally, Study 2 (Urfer-Maurer et al., 2018) showed that predominant sympathetic activity of the ANS at rest and during different sleep stages was related to increased post-awakening HPA axis activity across the whole sample. Further, Study 1 showed that VP children had an earlier sleep onset time and lower HPA axis activity compared to FT children. Mediation analyses showed that earlier sleep onset time partially accounted for lower post-awakening HPA axis activity in VP children. Moreover, Study 2 showed that VP children had a dominance of parasympathetic over sympathetic activity of the ANS when awake and during stage 2 sleep. The results of Study 3 (Urfer-Maurer et al., 2017) revealed that maternal but not paternal insomnia symptoms were related to less restorative sleep in children. Finally, parental insomnia symptoms were related to parents' reports of their children's sleep-related behavior, and maternal insomnia symptoms were additionally related to paternal reports of sleep-related behavior in children. Findings of the present dissertation highlight the important role VP birth plays in altered development of biological processes, especially HPA axis activity during childhood and adolescence. Additionally, they emphasize that parental sleep difficulties may affect the sleep of their own children as well as how they perceive their children's sleep. This dissertation outlines the practical implications of these results for the design of new treatments to foster positive development associated with sleep, HPA axis activity, and ANS functioning.


[1] Before I got married in December 2016, my surname was Maurer.

## 1. Introduction

There is growing interest in research examining biological processes associated with positive development (Beauchaine & Thayer, 2015; Clements, 2013; Dinges, 2014). Positive development is summarized as acquiring cognitive, behavioral, social, and emotional competencies in order to adapt successfully to challenges that could possibly lead to well-being and health (Weichold & Silbereisen, 2007). Shonkoff's (2010) biodevelopmental framework provides a theoretical underpinning by highlighting the importance of biological processes for positive development across the life-span. According to this framework, biological processes are influenced by gene–environment interactions during sensitive phases early in life; these processes are embedded during brain development (i.e., become biological "memories") and therefore provide the foundation for future health (Shonkoff, 2010). Biological processes such as sleep and the human stress system—further divided into the hypothalamic-pituitary-adrenocortical (HPA) axis and the autonomic nervous system (ANS)—serve critical roles in daytime functioning, physical and mental health, and survival (Adam et al., 2017; Cappuccio, D'Elia, Strazzullo, & Miller, 2010; Thayer & Lane, 2007). Sleep is a state of body and mind characterized by reduced motor as well as behavioral responsiveness and is important for brain development and functioning, including energy conservation, learning, memory consolidation, and restoration of cells (Mignot, 2008; Tononi, & Cirelli, 2006). Therefore, poor and short sleep is related to a number of physical and mental health impairments, such as cardiovascular diseases, cognitive decline, and depressed mood (Banks & Dinges, 2007). The HPA axis is the neuroendocrine branch of the human stress system and the ANS is part of the efferent division of the peripheral nervous system. The HPA axis and the ANS play key roles in stress adaptation by regulating various body systems to prevent homeostasis (Nicolaides, Charmandari, & Chrousos, 2015) as well as in emotion adaptability and regulation (Porges, 1995, 2007). Alterations in HPA axis activity and ANS functioning are associated with adverse health outcomes, such as obesity and depression (Adam et al., 2017; Koenig, Kemp, Beauchaine, Thayer, & Kaess, 2016). Although there is evidence that sleep, HPA axis activity, and ANS functioning are crucial for positive development, research examining the interplay between these biological processes is scarce.

According to the concept of developmental origins of health and disease, a nonoptimal environment (e.g., exposure to stress) during vulnerable periods of development in early life can lead to an altered predisposition for health and disease across the life-span (Barker, 1990, 2004). During their first weeks of life, children after very preterm (VP) birth (i.e., birth before 32 completed weeks of gestation) have to develop in a nonoptimal environment (i.e., outside of the mother's womb). Specifically, VP children are endowed with immature organs and are therefore exposed to many distressing and invasive medical procedures weeks and months after birth. Additionally, VP children are at higher risk for deficits in cognitive, social-emotional, and mental health outcomes (Lemola, 2015). To date, however, the idea of sleep, HPA axis activity, and ANS functioning as possible biological processes underlying altered development in children and adolescents born VP has rarely been studied.

Besides a nonoptimal environment during early life, concurrent environmental factors also play a central role in child development. The adapted version of El-Sheik and Sadeh's (2015) ecological systems theory of development (Bronfenbrenner, 1979) suggests that children's sleep is affected by, among other things, immediate context factors (e.g., family members). In this vein, previous research reported an association between parental sleep patterns and children's sleep (e.g., Bajoghli, Alipouri, Holsboer-Trachsler, & Brand, 2013). Yet, research examining the association between symptoms of parental insomnia, one of the most common sleep difficulties, and children's sleep is missing. Moreover, it remains unknown whether parental

insomnia symptoms are also related to parental perception of children's sleep. This is of great importance since parents are often the first to perceive their children's sleep problems and to seek help.

The present dissertation contains three studies and aims to expand current knowledge of the biological processes associated with positive development during childhood and adolescence. Specifically, the dissertation focuses on the interplay between sleep and HPA axis activity (Study 1: Maurer et al., 2016) as well as between HPA axis activity and ANS functioning (Study 2: Urfer-Maurer et al., 2018). Additionally, VP birth as an early life event possibly associated with these biological processes is considered (Maurer et al., 2016; Urfer-Maurer et al., 2018). Further, sleep, HPA axis activity, and ANS functioning are investigated during late childhood and early adolescence, a time when sleep problems are frequent (Fricke-Oerkermann et al., 2007) and sleep (Ohayon, Carskadon, Guilleminault, & Vitiello, 2004) as well as hormonal patterns (Kajantie & Phillips, 2006) change. Finally, the present dissertation examines parental insomnia symptoms as a concurrent environmental factor for children's sleep and parental perception of children's sleep (Study 3: Urfer-Maurer et al., 2017).

The following chapter provides an overview of the existing theoretical and empirical background relevant to this dissertation. Chapter 3 presents the research questions derived from the theoretical and empirical background. Chapter 4 gives a description of the studies, including the samples, procedure, and measures. Chapter 5 comprises a synopsis of the results. Finally, in Chapter 6 the results are discussed and an outlook for future research as well as practical implications are given.

## 2. Theoretical Background

Chapter 2 provides an overview of the existing theoretical and empirical background regarding positive development, biological processes (sleep, HPA axis, ANS), VP birth, and associations between parental insomnia symptoms and children's sleep as well as parental perception of children's sleep.

### 2.1 Positive development according to the biodevelopmental framework

Positive development is defined as cognitive, behavioral, social, and emotional competencies that children and adolescents may acquire and that may then result in adapted reactions to various life situations (Weichold & Silbereisen, 2007). Children and adolescents who develop these competencies are considered to be thriving (Lerner, Fisher, & Weinberg, 2000). Shonkoff's (2010) biodevelopmental framework suggests that the origin of positive development as well as of many impairments can be found among biological "memories" embedded in brain structures. These brain structures regulate various biological functions, such as stress management and neuroendocrine regulation. The biodevelopmental framework is based on findings from evolutionary biology, which suggests that the immature organism "prepares" itself for the environment that it "expects" to live in. While a nurturing, stable early environment can lead to a healthy development of the brain and subsequent biological processes, a threatening and uncertain environment can lead to a disrupted development of the brain and subsequent biological processes. Thus, early life experiences are incorporated into the human body through epigenetic mechanisms and may have lifelong consequences. Therefore, child and adolescent development has to be investigated, in order to develop new health-promoting programs to prevent problems that may arise later in life (Shonkoff, 2010). As previous research has already shown associations between biological processes and positive development, the present dissertation instead focuses on the relation among these biological processes, in particular, on the interplay of sleep, HPA axis activity, and ANS functioning.

### 2.2 Sleep

Sleep is an active brain process defined as a state of body and mind (Siegel, 2005). Sleep can be divided into rapid eye movement (REM) sleep and non-REM sleep (Carskadon & Dement, 2011). Non-REM sleep further consists of stage 1, stage 2, and slow wave sleep (SWS, stages 3 and 4; American Academy of Sleep Medicine & Iber, 2007; Rechtschaffen & Kales, 1968). Each sleep stage has its own distinct eye movement, muscle tone, and electrical brain activity, which can be measured by electroencephalography (EEG). Over the course of one night, there are five to seven repeating sleep cycles representing a person's sleep architecture, with non-REM sleep predominant in the first half of the night and REM sleep predominant during the second half (Carskadon & Dement, 2011). Different sleep stages are associated with specific functions (e.g., non-REM sleep restores glycogen stores in the brain; SWS and REM sleep optimize memory consolidation; Benington & Heller, 1995; Diekelmann & Born, 2010), which highlights the importance of investigating the detailed sleep architecture in research. The homeostatic process (Process S) and the circadian rhythm (Process C) regulate the sleep–wake cycle. While Process S increases throughout the day and runs down during the night, Process C receives information from the suprachiasmatic nucleus—the body's central pacemaker—in an approximately 24-h rhythm and is influenced by external *zeitgebers*, for example, light (Borbély & Achermann, 1999).

During the first months of life, infants' sleep is distributed across day and night, while at 1 year of age sleep preferably occurs during the night. Additionally, sleep duration decreases from approximately 14 h at 6 months of age to approximately 8 h at 16 years of age, and daytime napping generally disappears around 3 years of age (e.g., Iglowstein, Jenni, Molinari, & Largo, 2003). Regarding sleep architecture, SWS and REM sleep

decrease and stage 1 and stage 2 sleep increase by the transition from childhood to adolescence (Ohayon et al., 2004). Further, sleep disturbances are common during childhood and adolescence with 30–40% of school-age children suffering from sleep difficulties (Fricke-Oerkermann et al., 2007; Gradisar, Gardner, & Dohnt, 2011). Meta-analysis and reviews regarding sleep and positive development have reported an association between short and poor sleep and poor physical and mental health (Banks & Dinges, 2007; Gregory & Sadeh, 2012), impaired cognitive functioning (Dewald, Meijer, Oort, Kerkhof, & Bögels, 2010), as well as behavioral problems (Astill, Van der Heijden, Van IJzendoorn, & Van Someren, 2012).

**2.3 The hypothalamic-pituitary-adrenocortical axis**

The HPA axis is a neuroendocrine system that regulates stress reactions as well as many body processes. During acute stress, the HPA axis reacts within 10–20 min by secretion of corticotropin-releasing hormone from the paraventricular nucleus of the hypothalamus, which triggers the release of adrenocorticotropin hormone from the pituitary gland and finally releases the end product cortisol from the adrenal glands (Nicolaides, Kyratzi, Lamprokostopoulou, Chrousos, & Charmandari, 2015). To prevent an excessive or prolonged stress reaction, cortisol provides negative feedback on HPA axis activity to suppress corticotropin-releasing and adrenocorticotropin hormone production (Tsigos & Chousos, 2002). Whereas allostasis—a short-term alteration in HPA axis activity to achieve stability—is generally adaptive for the stress response and beneficial for survival, prolonged alterations called allostatic load can have harmful physiological and psychological consequences (Juster, McEwen, & Lupien, 2010). Besides responding to stressors, the HPA axis activity follows a circadian rhythm. Cortisol concentration increases in the morning and declines steadily throughout the day (Kalsbeek et al., 2012). Additionally, cortisol secretion rapidly increases across the first 30–45 min after morning awakening, which is termed the cortisol awakening response (CAR; Fries, Dettenborn, & Kirschbaum, 2009). Although the exact function of the CAR is still unclear, it has been suggested that it helps the individual regain arousal upon awakening (e.g., Thorn, Hucklebridge, Evans, & Clow, 2009) and prepares the individual for forthcoming demands (e.g., Kunz-Ebrecht, Kirschbaum, Marmot, & Steptoe, 2004). Salivary cortisol sampling of the CAR is a reliable noninvasive method to measure acute HPA axis activity (Stalder et al., 2016). Additionally, hair cortisol sampling and analysis is a novel and increasingly acknowledged method to measure long-term HPA axis activity for a period of up to 6 months (Stalder & Kirschbaum, 2012).

During the first year of life, children develop a circadian rhythm of cortisol (e.g., de Weerth, Zijl, & Buitelaar, 2003), and the CAR has been observed in infants as young as 2 months of age (e.g., Stalder et al., 2013). Additionally, older children and adolescents show higher diurnal cortisol levels than younger children (e.g., Gunnar, Wewerka, Frenn, Long, & Griggs, 2009). Recent meta-analyses showed an association between dysregulated HPA axis activity and cognitive impairments (Shields, Bonner, & Moons, 2015), behavioral problems (Alink et al., 2008), and physical as well as mental health issues (Adam et al., 2017; Chida & Steptoe, 2009).

**2.3.1 HPA axis activity and sleep.** HPA axis activity and sleep are connected in multiple ways and it is assumed that this relationship is bidirectional (for reviews, see Buckley & Schatzberg, 2005; Steiger, 2002). On one hand, the administration of cortisol decreases REM sleep and increases SWS in adults (e.g., Born, DeKloet, Wenz, Kern, & Fehm, 1991). On the other hand, SWS suppresses HPA axis activity (e.g., Steiger et al., 1992) and nocturnal awakening increases pulsatile cortisol release in adults (e.g., Späth-Schwalbe, Gofferje, Kern, Born, & Fehm, 1991). Additionally, morning awakening causes the CAR (e.g., Wilhelm, Born, Kudielka, Schlotz, & Wüst, 2007).

In school-aged children, short and poor sleep assessed with actigraphy (i.e., a measurement method that measures proper acceleration of movement) and in a sleep laboratory was related to increased morning (Fernandez-Mendoza et al., 2014; Räikkönen et al., 2010), diurnal (El-Sheikh, Buckhalt, Keller, & Granger, 2008; Räikkönen et al., 2010), and evening (Fernandez-Mendoza et al., 2014) cortisol secretion. Additionally, in preschool children, poor in-home EEG sleep was associated with increased morning cortisol secretion (Hatzinger et al., 2008). However, to date, only one study (from our research team) has examined the relationship between sleep architecture assessed by in-home sleep-EEG and morning cortisol secretion in school-aged children (Lemola et al., 2015). In line with research with preschool children, findings for school-aged children also showed short sleep duration, less SWS, and more stage 2 sleep to be related to increased overall morning cortisol secretion the following morning (Lemola et al., 2015). The understanding of the interplay between sleep and HPA axis activity is a fundamental prerequisite for treatment of various physical and mental disorders related to altered sleep and HPA axis activity (Buckley & Schatzberg, 2005). Moreover, since sleep and HPA axis activity change during the transition to adolescence (Gradisar et al., 2011; Jenni & Carskadon, 2004; Ohayon et al., 2004; Kajantie & Phillips, 2006), examining this association during this time is of special interest. Therefore, Study 1 of the present dissertation examined the association between sleep measured by in-home sleep-EEG and salivary cortisol sampled the next morning during late childhood and early adolescence.

**2.4 The autonomic nervous system**

The ANS, consisting of the sympathetic (SNS), the parasympathetic (PNS), and the enteric nervous system, is part of the human stress system and follows a circadian rhythm (Jänig, 2006). Sympathetic activity increases during the day and decreases at night, while parasympathetic activity decreases during the day and increases at night (Guo & Stein, 2003). The SNS is involved in the so-called "fight or flight" response—the immediate reaction to a stressor within milliseconds—while the complementary PNS regulates "rest and digest" processes and enables the return to a baseline activity after a stress response. During acute stress, the ANS induces rapid bodily changes through modulation of noradrenergic and cholinergic neuronal communication and the quick release of adrenaline via the sympatho-adrenal medullary system (Charmandari, Tsigos, & Chrousos, 2005; Stratakis & Chrousos, 1995). Thereby SNS activity increases while PNS activity decreases, followed by increases in heart and breathing rate. Therefore, autonomic function can be measured noninvasively by the assessment of heart rate variability (HRV) by electrocardiogram (ECG). HRV describes the change in beat-to-beat intervals over time and can be separated into different frequency domain bands (Shaffer, McCraty, & Zerr, 2014). Just as for HPA axis activity, a prolonged stress reaction of the sympatho-adrenal medullary system can have negative consequences for the individual (Juster et al., 2010).

During gestation and the first months of life, the ANS matures and therefore HRV increases (David, Hirsch, Karin, Toledo, & Akselrod, 2007; Schneider et al., 2009). Increase in HRV continues until middle childhood and is then followed by a decrease (e.g., Acharya, Kannathal, Seng, Ping, & Chua, 2004). Previous reviews and meta-analyses regarding ANS functioning and positive development reported associations between predominant sympathetic activity of the ANS and poor physical and mental health (Acharya, Joseph, Kannathal, Lim, & Suri, 2006; Friedman, 2007). Additionally, predominant parasympathetic activity of the ANS is related to better emotion recognition and regulation (Quintana, Guastella, Outhred, Hickie, & Kemp, 2012). However, exaggerated parasympathetic activity of the ANS is also related to adverse health outcomes, for example, inefficient physiological functioning and energy utilization (Shaffer et al., 2014).

**2.4.1 ANS functioning and HPA axis activity.** Studies including animals have provided evidence of structural and functional associations between the ANS and the HPA axis (for a review, see Ulrich-Lai & Herman, 2009). Additionally, pharmacological blockade studies in humans have reported that by suppressing sympathetic activity of the ANS, cortisol levels increase, whereas in turn suppressing HPA axis activity elevates sympathetic activity of the ANS (e.g., Andrews, D'Aguiar, & Pruessner, 2012; Andrews & Pruessner, 2013). The polyvagal theory (Porges, 1995, 2007) explains how the two branches of the stress system may be interrelated from a theoretical perspective on emotion regulation, which has been partly supported by stress studies (e.g., Weber et al., 2010). The theory suggests an association via parasympathetic activity of the ANS. Specifically, the PNS moderates stress responses by either inhibiting or disinhibiting the SNS as well as the HPA axis depending on an individual's perception of a situation as safe or unsafe. When an individual feels safe, the parasympathetic activity of the ANS is elevated and social behavior and interaction are triggered. In contrast, when an individual feels threatened, the parasympathetic activity of the ANS is inhibited and the body fights for survival (Porges, 1995, 2007). Studies examining the association between ANS functioning and HPA axis activity aside from stress situations are scarce and only a few studies have investigated the relation in children and adolescents. In young adults, lower global HRV (i.e., low sympathetic and parasympathetic activity) in a laboratory setting as well as before and after awakening is associated with elevated post-awakening cortisol secretion (Stalder, Evans, Hucklebridge, & Clow, 2011). Additionally, one study reported more sympathetic activity to be associated with higher post-awakening cortisol secretion in children aged 5–10 years (Michels et al., 2013), whereas another study found no such association in children and adolescents aged 8–18 years (Rotenberg & McGrath, 2016). Thus, results regarding the association in daily life are heterogeneous, which can possibly be explained by the impact of daily experience on HRV measurement. Therefore, Study 2 of the present dissertation expanded on prior research by examining the association between ANS functioning and HPA axis activity across different psychophysiological states during late childhood and early adolescence, which may reduce the acute impact of daily experience on HRV measurement. Specifically, HRV was measured during a wake episode in a lying position as well as during different sleep stages, and salivary cortisol was assessed the next morning.

**2.5 Very preterm birth**

VP birth, defined as birth before 32 completed weeks of gestation, occurs worldwide in around 1.5% of all live births, with the number and survival rate increasing in the last decades (Child Trends, 2015; Rüegger, Hegglin, Adams, & Bucher, 2012). VP infants spend what would be the last trimester of gestation outside of their mother's womb and therefore have to develop in a markedly different environment. During this time, the cerebral cortex develops rapidly (Inder, Warfield, Wang, Hüppi, & Volpe, 2005) and programming of the neuroendocrine and biophysiological regulatory circuit takes place (Kajantie & Räikkönen, 2010). Due to immature functioning of the organs, for example, the lungs (Saigal & Doyle, 2008), VP infants are exposed to repeated distressing medical procedures during the first few weeks and months after birth, including painful treatments and administration of glucocorticoids (for a review, see Roberts & Dalziel, 2006). According to meta-analyses and reviews, VP children, adolescents, and adults are at higher risk for serious developmental problems, including developmental delays, decreased cognitive abilities, as well as psychosocial impairments (Aarnoudse-Moens, Weisglas-Kuperus, van Goudoever, & Oosterlaan, 2009; Burnett et al., 2011; Dempsey et al., 2015). Thus, VP birth is associated with long-term implications for the child, the parents, and the health service and is

therefore becoming a growing public health concern (Blencowe et al., 2012; McCormick, Litt, Smith, & Zupancic, 2011).

The concept of developmental origins of health and disease suggests that an altered environment during sensitive periods of pre- and postnatal development can have lifelong consequences (Barker, 1990, 2004). This process in which input during a sensitive period of development can permanently alter the brain and related body functions is called "programming" (Barker, 1990). According to the biodevelopmental framework, biological processes may mediate the association between early life events and later development (Shonkoff, 2010). Thus, sleep, HPA axis activity, and ANS functioning might be pathways that lead to differences in development between VP and full-term (FT; ≥37 weeks of gestation) children. Therefore, Studies 1 and 2 further investigated sleep, HPA axis activity, and ANS functioning in a sample of VP children and adolescents in comparison to a control group of FT children and adolescents.

**2.5.1 Sleep of children born very preterm.** The circadian rhythm, which develops during the fetal period and is programmed in the first months of life, is vulnerable to adverse events in early life (for reviews, see Brooks & Canal, 2013; Mirmiran, Maas, & Ariagno, 2003), which can be reflected in altered sleep. Accordingly, VP infants show longer actigraphic nighttime sleep during their first 3 months of life (Guyer et al., 2015). However, at around 12 months, preterm infants with very low birth weight (VLBW; ≤1500 g) have significantly shorter actigraphic sleep duration and more activity during nighttime than FT infants, which indicates less restful sleep (Asaka & Takada, 2010). A prospective study with preschool and school-aged children reported no differences in sleep patterns assessed with questionnaires between preterm and FT children (Iglowstein, Hajnal, Molinari, Largo, & Jenni, 2006). During adolescence and adulthood, preterm infants showed an advanced sleep phase (i.e., earlier bedtime and waking time) assessed by questionnaires and actigraphy (Björkqvist et al., 2014; Hibbs et al., 2014; Natale et al., 2005; Strang-Karlsson et al., 2010). Previous research in VP children generally used questionnaires or actigraphy to assess sleep, but research including sleep architecture as measured by sleep-EEG is scarce. As mentioned above (cf. Chapter 2, Section 2.2), investigating sleep architecture is of special interest, since different sleep stages are associated with specific functions (Benington & Heller, 1995; Diekelmann & Born, 2010). One prior study from our research team measured sleep with in-home sleep-EEG and found more nocturnal awakenings, more stage 2 sleep, and less SWS in VP children compared to FT children aged 6–10 years, which indicates poor sleep in VP children (Perkinson-Gloor et al., 2015b). However, to date, it remains unknown if VP children still vary from FT children in sleep architecture at an older age. Therefore, Study 1 expanded current knowledge by examining potential differences in in-home sleep-EEG between VP and FT children at an older age (i.e., approximately 2 years older).

**2.5.2 HPA axis activity of children born very preterm.** There is evidence that HPA axis activity is highly susceptible to pre- and postnatal programming (for a review, see Lupien, McEwen, Gunnar, & Heim, 2009). Animal and human studies showed altered HPA axis activity in the offspring after maternal depression, stress, or glucocorticoid exposure (Lupien et al., 2009). During the postnatal phase, neonatal "handling" (e.g., removing the offspring from their habitual environment) and maternal separation are related to altered HPA axis activity, resulting in up- or down-regulated HPA axis activity later in life (e.g., Levine & Wiener, 1988; Tyrka et al., 2008). In a similar vein, some studies found lower diurnal cortisol levels (Wadsby, Nelson, Ingemansson, Samuelsson, & Leijon, 2014), faster decreasing cortisol levels in the evening (Perkinson-Gloor et al., 2015b), lower hair cortisol levels (Grunau et al., 2013), and decreased salivary cortisol responses to social stress (Kaseva et al., 2014) in children born VP, preterm (<37 completed weeks of gestation), or with VLBW (≤1500 g).

However, other studies reported higher salivary cortisol levels right at awakening (Buske-Kirschbaum et al., 2007), similar diurnal cortisol levels (Brummelte et al., 2015), and an increased cortisol response to psychosocial stress (Quesada, Tristão, Pratesi, & Wolf, 2014) in VP and preterm children compared to FT children. Regarding the CAR, no differences (Buske-Kirschbaum et al., 2007; Perkinson-Gloor et al., 2015b) or lower cortisol levels in VP and preterm children have been found (Quesada et al., 2014). Thus, studies including preterm and VP children often showed down-regulated HPA axis activity; however, results of studies with VP and FT children are mixed. This inconsistency in results is possibly due to differences in methodology (i.e., timing of measurement, measurement method) and inclusion criteria (e.g., degree of prematurity, age). Therefore, Study 1 of the present dissertation examined potential differences in post-awakening salivary cortisol secretion as well as hair cortisol and cortisone between VP and FT children during late childhood and early adolescence, using gold-standard measurements (i.e., CAR assessment following expert consensus guidelines; Stalder et al., 2016) and analyses (i.e., liquid chromatography tandem mass spectrometry; Gao, Kirschbaum, Grass, & Stalder, 2016). Moreover, while prior research showed that poor and short sleep are generally related to increased HPA axis activity, VP birth is generally related to poor sleep as well as down-regulated HPA axis activity. Therefore, Study 1 additionally examined the link between VP birth, post-awakening salivary cortisol secretion, and sleep alterations during the preceding night.

**2.5.3 ANS functioning of children born very preterm.** ANS maturation occurs during the fetal period and the first months after birth (David et al., 2007; Schneider et al., 2009). Various studies including animals and humans support the assumption of a relation between adverse intrauterine and early postnatal environment and altered ANS functioning later in life (e.g., Card, Levitt, Gluhovsky, & Rinaman, 2005; Herlenius & Lagercrantz, 2004). Experimental studies on rats, for example, showed exaggerated cardiovascular activation and heightened sympathetic reactivity to stressors after exposure to prenatal stress (e.g., Igosheva, Klimova, Anishchenko, & Glover, 2004; Weinstock, Poltyrev, Schorer-Apelbaum, Men, & McCarty, 1998). However, research in human fetuses exposed to stress is limited. Intrauterine growth retardation as a sign of fetus stress exposure is related to higher heart rate and lower HRV in fetuses and newborns (e.g., Nijhuis et al., 2000; Spassov et al., 1994). In a similar vein, infants born preterm show decreased autonomic function right after birth as well as at theoretical term age (i.e., calculated date of birth) compared to FT children (Landrot et al., 2007; Patural et al., 2008), indicating reduced regulatory capacity in responding to environmental stressors (Shaffer et al., 2014). However, evidence is heterogeneous regarding differences in autonomic functioning between VP and FT children at a later age up to 7 years. Whereas some studies reported either lower sympathetic activity (Yiallourou, Witcombe, Sands, Walker, & Horne, 2013) or lower parasympathetic activity (Fyfe et al., 2015; Yiallourou et al., 2013) of the ANS in children born preterm, others failed to reveal any differences in HRV (Fyfe et al., 2015; Landrot et al., 2007; Yiallourou et al., 2013). To date, only one study investigated HRV differences in older children and found decreased overall activity of the ANS (i.e., lower sympathetic and parasympathetic activity) in VP and small-for-gestational-age FT children aged 9 years old compared to FT children of appropriate size for gestational age (Rakow, Katz-Salamon, Ericson, Edner, & Vanpée, 2013). Thus, findings regarding HRV differences between VP and FT school-aged children are rare and inconsistent. Again, differences in results are possibly due to differences in measurement methods and inclusion criteria. While HRV in studies with younger children during infancy has generally been measured with ECG during sleep (Fyfe et al., 2015; Yiallourou et al., 2013), HRV in studies with older school-aged children was measured with ECGs over a 24-h period, but these studies did not consider HRV during sleep in their analyses (Landrot et al., 2007; Rakow et al. 2013). Hence,

research in school-aged children with HRV assessments during different sleep stages is missing but would be essential to determine if differences between VP and FT children are consistent across different psychophysiological states. Therefore, Study 2 examined potential differences in HRV at rest and during different sleep stages between VP and FT children during late childhood and early adolescence.

**2.6 Parental insomnia symptoms and children's sleep**

Besides a nonoptimal environment during early life, concurrent environmental factors do play an important role for child development. According to the adapted version of El-Sheik and Sadeh's (2015) ecological systems theory of development (Bronfenbrenner, 1979), children's sleep is strongly affected by agents in their immediate context (e.g., family members). Therefore, it seems likely that parents' sleep plays an important role in their children's sleep. Previous research found a positive relation between children's and parents' sleep duration, assessed with parental questionnaires (e.g., Bajoghli et al., 2013; Li et al., 2010). Additionally, there is evidence for a positive relation between parents' and children's sleep–wake patterns. However, this association is stronger for the mother–child relationship than the father–child relationship (Zhang, Wang, & Huang, 2010). A recent study including parents and their adolescent children showed that children's and parents' objective sleep patterns are positively related. This association, again, is stronger for the mother–child relationship than the father–child relationship (Kalak et al., 2012). Thus, previous research showed an association between children's and parents' sleep, but this association is more salient when sleep is measured with the same method (Kalak et al., 2012; Kouros & El-Sheik, 2017). Hence, associations of sleep across family members could possibly be overestimated when sleep assessment is conducted with the same measurement method. Therefore, Study 3 of the present dissertation investigated whether self-reported insomnia symptoms of mothers and fathers are related to the objectively measured sleep of their children using in-home sleep-EEG.

**2.7 Parental insomnia symptoms and parental perception of children's sleep**

Children's sleep and sleep problems are most commonly assessed with parent or self-report questionnaires since such measures are practical and inexpensive (Sadeh, 2015). However, previous research showed that parents often overestimate total sleep time (TST) and underestimate sleep disturbances when compared to children's sleep measured objectively by actigraphy (e.g., Iwasaki et al., 2010). Thus, parent reports are error prone and might be distorted by biased perception, for instance, due to their own sleep difficulties (Sadeh, Mindell, & Rivera, 2011). Because parents are often the first to perceive their children's sleep problems and seek help, it is important to examine the association between parental sleep and parental perception of their children's sleep. Yet to date, only one study has examined this association: Rönnlund, Elovainio, Virtanen, Matomäki, and Lapinleimu (2016) found that parents who themselves suffer from poor sleep more often reported sleep problems in their 2- to 6-year-old children. Further, this association was not attenuated after analyses were additionally controlled for actigraphic measures of children's sleep. Thus, the association between parental sleep problems and parental perception of their children's sleep was unexplained by objective measures of children's sleep. To date, the most common sleep difficulty during adulthood is insomnia (i.e., difficulty initiating and/or maintaining sleep or waking up too early) with 25 to 37% of adults frequently experiencing at least one insomnia symptom (Mai & Buysse, 2008). Therefore, Study 3 further investigated whether a parent's insomnia symptoms are associated with his or her own as well as his or her partner's perception of children's sleep-related behavior.

## 3. Research Questions

The present dissertation addresses the following research questions derived from the theoretical and empirical background. Figure 1 offers a schematic overview of the dissertation concept:

1. The interplay between HPA axis activity and sleep (Study 1, Maurer et al., 2016): Is increased HPA axis activity associated with poor sleep?
2. The interplay between ANS functioning and HPA axis activity (Study 2, Urfer-Maurer et al., 2018): Is HRV associated with HPA axis activity?
3. Sleep, HPA axis activity, and ANS functioning of VP children and adolescents (Studies 1 and 2):
   a. Is VP birth associated with earlier sleep times and poor sleep?
   b. Is VP birth associated with decreased HPA axis activity?
   c. Does sleep mediate the relationship between VP birth and HPA axis activity?
   d. Is VP birth associated with altered HRV?
4. Children's sleep and sleep assessment in the family context (Study 3, Urfer-Maurer et al., 2017):
   a. Are parental insomnia symptoms associated with children's sleep?
   b. Are parental insomnia symptoms associated with parents' perception of their children's sleep-related behavior?

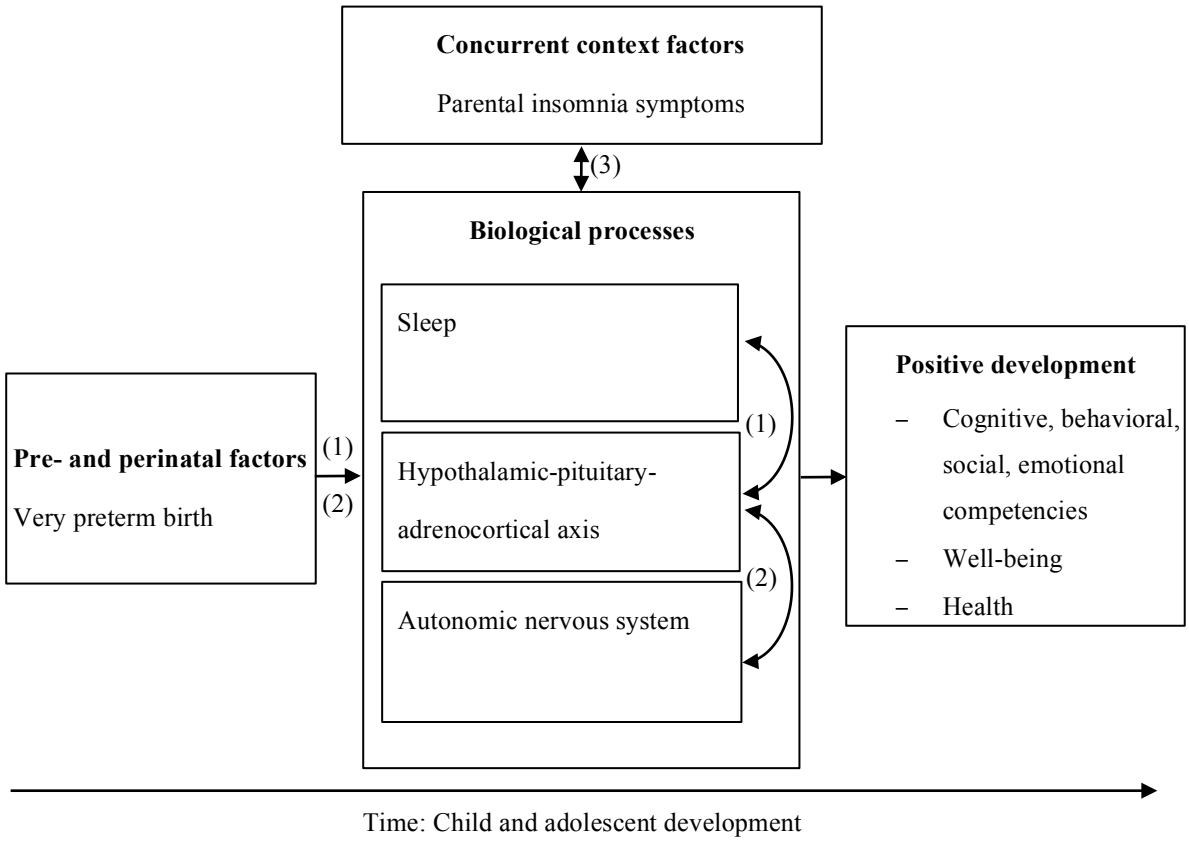



*Figure 1.* Dissertation concept. Numbers in parentheses refer to the studies included in the present dissertation: Study 1, Maurer, Perkinson-Gloor, Stalder, Hagmann-von Arx, Brand, Holsboer-Trachsler, Wellmann, Grob, Weber, & Lemola, 2016, *Psychoneuroendocrinology*. Study 2, Urfer-Maurer, Ludyga, Stalder, Brand, Holsboer-Trachsler, Gerber, Grob, Weber, & Lemola, 2018, *Psychoneuroendocrinology*. Study 3, Urfer-Maurer, Weidmann, Brand, Holsboer-Trachsler, Grob, Weber, & Lemola, 2017, *Sleep Medicine*.

## 4. Method

Sections 4.1 and 4.2 provide an overview of the samples, procedures, and measures of the studies included in this dissertation.

### 4.1 Studies and Samples

Data included in the present dissertation were derived from the second wave of the Basel Study of Preterm Children. Healthy VP children were recruited from an initial cohort of 260 prematurely born children treated at the University Children's Hospital Basel in Switzerland between June 2001 and December 2006. Of the 260 children, 90 (34.6%) had to be excluded because of no information on neurobehavioral development until the age of 2 years, severe developmental delay, insufficient German language skills of the parents to give informed consent, or place of residence outside of Switzerland or too distant from the study center (i.e., >100 km). Of the remaining 170 eligible children, families of 148 (87.1% of the eligible children) could be contacted by phone to ask for participation and 100 (58.8% of the eligible children) agreed to participate. FT children were recruited from official birth notifications and were comparable regarding age and sex.

**Study 1 (Maurer, Perkinson-Gloor, Stalder, Hagmann-von Arx, Brand, Holsboer-Trachsler, Wellmann, Grob, Weber, & Lemola, 2016).** In Study 1, we investigated whether higher levels of post-awakening cortisol secretion would be negatively associated with sleep duration, sleep continuity, and SWS and positively associated with stage 2 and REM sleep, using multiple regression analyses. Additionally, we examined whether VP children differ in their sleep patterns (earlier sleep times, more nocturnal awakenings, more stage 2 sleep, less SWS) as well as in their HPA axis activity (decreased post-awakening cortisol secretion, hair cortisol, and cortisone) from FT children, using analyses of covariance (ANCOVAs). Further, we tested whether sleep mediates the relationship between prematurity status and post-awakening cortisol secretion, using the bootstrapped indirect procedure (cf., Preacher & Hayes, 2008). The sample of Study 1 consisted of 85 VP children (age: $M$ = 9.5 years, $SD$ = 1.4; range: 7.4–12.4 years; gestational age: $M$ = 29.7 weeks, $SD$ = 2.0; birth weight: $M$ = 1325.1 g, $SD$ = 407.4; sex: 51 male) and 91 FT children (age: $M$ = 9.6 years, $SD$ = 1.4 years; range: 6.9–13.0 years; gestational age: $M$ = 39.5 weeks, $SD$ = 1.5; birth weight: $M$ = 3307.5 g, $SD$ = 443.9; sex: 51 male).

**Study 2 (Urfer-Maurer, Ludyga, Stalder, Brand, Holsboer-Trachsler, Gerber, Grob, Weber, & Lemola, 2018).** In Study 2, we investigated whether and how HRV is related to HPA axis activity, using multiple regression analyses. Further, we examined whether VP children differ in their HRV from FT children, using ANCOVAs. The sample of Study 2 consisted of 54 VP children (age: $M$ = 9.6 years, $SD$ = 1.4; range: 7.3–12.3 years; gestational age: $M$ = 30.0 weeks, $SD$ = 1.9; birth weight: $M$ = 1383.5 g, $SD$ = 401.7; sex: 32 male) and 67 FT children (age: $M$ = 9.7 years, $SD$ = 1.5; range: 7.5–12.9 years; gestational age: $M$ = 39.6 weeks, $SD$ = 1.5; birth weight: $M$ = 3321.9 g, $SD$ = 441.2; sex: 40 male).

**Study 3 (Urfer-Maurer, Weidmann, Brand, Holsboer-Trachsler, Grob, Weber, & Lemola, 2017).** In Study 3, we investigated whether maternal and paternal insomnia symptoms are related to children's sleep as well as parents' perception of their children's sleep-related behavior, using actor–partner interdependence models (Kenny & Cook, 1999; Kenny, Kashy, & Cook, 2006). Specifically, the interdependence of maternal and paternal perception was examined: Actor effects are the associations between one parent's insomnia symptoms and his or her perception of children's sleep-related behavior, and partner effects are the associations between one parent's insomnia symptoms and the other parent's perception of children's sleep-related behavior. In an additional step, associations between parental insomnia symptoms and parental perception of children's sleep-

related behavior were controlled for children's EEG sleep. Hence, it was possible to examine the degree to which the associations can be explained by children's objectively measured sleep. The sample of Study 3 consisted of 96 VP children (age: *M* = 9.3 years, *SD* = 1.4; range: 7.2–12.3 years; gestational age: *M* = 29.8 weeks, *SD* = 2.1; birth weight: *M* = 1312.8 g, *SD* = 406.3; sex: 54 male) and 95 FT children (age: *M* = 9.8 years, *SD* = 1.5; range: 7.5–12.9 years; gestational age: *M* = 39.4 weeks, *SD* = 1.7; birth weight: *M* = 3303.9 g, *SD* = 455.2; sex: 55 male).

**4.2 Procedure and Measures**

Trained study personnel visited the children at home on a regular school day to administer one night of in-home sleep-EEG, including ECG (HRV was measured during a wake episode in a lying position at rest before sleep onset as well as during stage 2 sleep, SWS, and REM sleep), and to collect hair samples. The following morning, parents collected saliva samples of their children at 0, 10, 20, and 30 min after awakening. The methods and measures of the studies included in the present dissertation are displayed in Table 1.

Table 1
*Description of methods and corresponding measures and scales*

| Method | Measure/Scale | Study |
|---|---|---|
| Sleep | | |
| EEG (Compumedics Somté PSG; Singen, Germany; American Academy of Sleep Medicine & Iber, 2007; Rechtschaffen & Kales, 1968) | Sleep duration (TST; time in bed minus time in bed spent awake in hours)<br>Sleep continuity: sleep efficiency (SE; TST/time in bed × 100), nocturnal awakenings (number of arousals from sleep)<br>Sleep architecture: stage 1 sleep (%), stage 2 sleep (%), SWS (%; stages 3 and 4 sleep), REM sleep (%), REM latency (min) | 1, 2, 3 |
| CSHQ-DE (Schlarb, Schwerdtle, & Hautzinger, 2010) | Bedtime resistance, sleep onset delay, sleep duration problems, sleep anxiety, night wakings, parasomnias, sleep-disordered breathing, daytime sleepiness, overall sleep disturbances | 3 |
| ISI (Bastien, Vallières, & Morin, 2001) | Insomnia symptoms | 3 |
| HPA axis activity | | |
| Free salivary cortisol concentration (Pruessner, Kirschbaum, Meinlschmid, & Hellhammer, 2003) | S1: the level of cortisol on awakening<br>$AUC_I$ : CAR<br>$AUC_G$ : the overall post-awakening cortisol secretion | 1, 2 |
| LC–MS/MS (Gao et al., 2016) | Hair cortisol<br>Hair cortisone | 1 |
| ANS | | |
| ECG (Compumedics Somté PSG; Singen, Germany; Acharya et al., 2006; Stein & Pu, 2012) | LF power: 0.04–0.15 Hz; combination of sympathetic and parasympathetic nervous system inputs<br>HF power: 0.15–0.4 Hz; parasympathetic activity<br>LF/HF power ratio: relative power of the frequency bands<br>Total spectral power: absolute power of the frequency bands | 2 |

*Note.* EEG = Electroencephalography. PSG = Polysomnography. CSHQ-DE = German version of the Children's Sleep Habits Questionnaire. ISI = Insomnia Severity Index. HPA axis = Hypothalamic-pituitary-adrenocortical axis. LC–MS/MS = Liquid chromatography tandem mass spectrometry. ANS = Autonomic nervous system. ECG = Electrocardiogram. TST = total sleep time. SE = sleep efficiency. SWS = Slow wave sleep. REM = rapid eye movement. S1 = the first sample, synchronized with the moment of awakening. $AUC_I$ = the area-under-the-curve with respect to increase. CAR = the cortisol awakening response. $AUC_G$ = the area-under-the-curve with respect to ground. LF = low frequency. HF = high frequency.

## 5. Synopsis of Results

The following sections summarize the results of the studies included in the present dissertation.

### 5.1 The interplay between sleep, HPA axis activity, and ANS functioning

Results of Study 1 revealed that post-awakening $AUC_G$ (the area-under-the-curve with respect to ground) was positively related to sleep onset time and negatively related to TST and REM latency. Awakening time, sleep efficiency (SE), nocturnal awakenings, stage 1 sleep, stage 2 sleep, SWS, and REM sleep were unrelated to post-awakening $AUC_G$. None of the sleep variables were significantly associated with the level of cortisol on awakening (S1) and post-awakening CAR (the area-under-the-curve with respect to increase, $AUC_I$). Study 2 showed that higher low-frequency (LF) power during the awake state, stage 2 sleep, and REM sleep, a higher LF/HF (low-frequency/high-frequency) power ratio during the awake state, and higher total spectral power during REM sleep were related to more post-awakening $AUC_G$. Additionally, higher LF and total spectral power during stage 2 sleep were related to more post-awakening CAR ($AUC_I$), and a higher LF/HF ratio during the awake state was related to more S1. No association was found between high-frequency (HF) power and post-awakening cortisol secretion.

### 5.2 Sleep, HPA axis activity, and ANS functioning of children and adolescents born very preterm

Study 1 and Study 2 showed that VP children had a trend toward longer TST, significantly earlier sleep onset time, and lower S1, post-awakening $AUC_G$, and hair cortisone concentrations (Study 1) as well as a lower LF/HF ratio during wake and stage 2 sleep (Study 2) compared to FT children. There were no mean differences in SE, sleep architecture, post-awakening CAR ($AUC_I$), hair cortisol, and HRV parameters during SWS and REM sleep between VP and FT children. Regarding the mediation of the relationship between prematurity status and post-awakening cortisol secretion, sleep onset time (i.e., mediator) was the only sleep variable that was significantly associated with both the independent variable (i.e., prematurity status) and the dependent variable (i.e., post-awakening cortisol secretion). The association of prematurity status with post-awakening $AUC_G$ was partially attenuated when sleep onset time was additionally controlled for.

### 5.3 Children's sleep and sleep assessment in the family context

Results of Study 3 showed that increased maternal insomnia symptoms were related to less children's sleep-EEG TST, more stage 2 sleep, less SWS, later sleep onset time, and later awakening time, but not with children's sleep continuity. Paternal insomnia symptoms were unrelated to children's sleep-EEG. Further, results revealed significant actor and partner effects. For mothers, their insomnia levels predicted their perception of children's bedtime resistance, sleep anxiety, night wakings, and overall sleep disturbances. For fathers, insomnia symptoms were positively related to their perception of children's sleep duration problems, daytime sleepiness, and overall sleep disturbances. Additionally, maternal insomnia symptoms were positively linked to paternal perception of children's bedtime resistance, sleep anxiety, sleep-disordered breathing, and overall sleep disturbances. These associations remained significant when analyses were additionally controlled for children's sleep-EEG. Paternal insomnia symptoms were unrelated to maternal perception of children's sleep-related behavior. A significant relation between paternal insomnia symptoms and maternal perception of children's daytime sleepiness appeared after analyses were additionally controlled for children's sleep-EEG.

## 6. General Discussion

In this chapter, results are discussed and an outlook for future research, as well as practical implications, is given.

### 6.1 The interplay between sleep, HPA axis activity, and ANS functioning

Results of Study 1 showed that more overall post-awakening cortisol ($AUC_G$) was related to shorter sleep duration and a later sleep onset time during late childhood and early adolescence. Thus, our findings are in line with prior studies showing a negative association between sleep duration and morning (Fernandez-Mendoza et al., 2014; Hatzinger et al., 2008; Lemola et al., 2015; Räikkönen et al., 2010), diurnal (El-Sheikh et al., 2008; Räikkönen et al., 2010), and evening HPA axis activity (Fernandez-Mendoza et al., 2014). The sleep–wake cycle and HPA axis activity are both under the influence of the suprachiasmatic nucleus, which is a possible factor leading to a relation between the two processes (Buckley & Schatzberg, 2005). Anticipation of the upcoming day is another possible factor associated with both biological processes. In particular, anticipating a stressor is associated with shorter sleep duration (e.g., Wuyts et al., 2012) as well as higher levels of morning cortisol secretion (e.g., Kunz-Ebrecht et al., 2004). However, and in contrast to previous research including a prior study of our research team (Hatzinger et al., 2008; Lemola et al., 2015), no association between post-awakening cortisol secretion and non-REM sleep or REM sleep was found. It is possible that these differences may be due to the older age of the children in the present study, since sleep (Ohayon et al., 2004) and hormonal patterns (Kajantie & Phillips, 2006) change with age and pubertal maturation.

Study 2 was the first to report that higher sympathetic activity of the ANS during wake, stage 2 sleep, and REM sleep is associated with more post-awakening cortisol secretion during school age, which is in line with prior findings showing a co-occurrence of sympathetic dominance in the ANS in the afternoon and an increased CAR (Michels et al., 2013). The association between the two stress systems can be traced back to brainstem and hypothalamic structures, since they initiate ANS and HPA axis reactivity during stress (Ulrich-Lai & Herman, 2009). Additionally, the ANS and the HPA axis follow a circadian rhythm (Jänig, 2006; Kalsbeek et al., 2012), which may align their activity. Further, the ANS and the HPA axis are both involved in emotion regulation, which again could be a further possible explanation for the association, since the PNS either inhibits or disinhibits the SNS as well as the HPA axis depending on the individual perception of a situation (Porges, 1995, 2007). Moreover, results of Study 2 coincide with the assumption that the ANS and the HPA axis are relatively stable biological markers of a stress reaction (e.g., increased sympathetic and HPA axis activity are related to general life stress). In a similar vein, predominant sympathetic activity and elevated HPA axis activity are associated with poor physical and mental health (for reviews, see Acharya et al., 2006; Chida & Steptoe, 2009; Friedman, 2007). However, findings from our study are also in contrast to previous studies: For example, Rotenberg and McGrath (2016) found no association between ANS functioning and HPA axis activity. Further, Stalder et al. (2011) found no association between HRV and cortisol levels right at awakening (S1) and reported lower sympathetic and parasympathetic activity of the ANS to be associated with a higher CAR. However, these results are not directly comparable as we used HRV measurement at rest and during different sleep stages, whereas Stalder et al. (2011) measured HRV during the day in a laboratory and before and after awakening. Additionally, Stalder et al. (2011) studied young adults, whereas our study included children and adolescents aged 7–12 years, which could also lead to differences in results. In sum, findings of the present dissertation support and expand the knowledge on the interplay between biological processes, by showing an association between short sleep and increased post-awakening HPA axis activity as well as between elevated sympathetic

activity during wake and sleep and increased post-awakening HPA axis activity during late childhood and early adolescence.

**6.2 Sleep, HPA axis activity, and ANS functioning of children and adolescents born very preterm**

In line with previous research, Studies 1 and 2 found earlier sleep onset times, a trend toward longer sleep duration (Björkqvist et al., 2014), decreased HPA axis activity (Grunau et al., 2013; Quesada et al., 2014), and altered ANS functioning (Rakow et al., 2013) in VP children compared to FT children. Our results regarding sleep differences are in line with previous studies reporting earlier sleep onset times as well as an advanced sleep phase in adolescents and adults born preterm or with VLBW (Björkqvist et al., 2014; Hibbs et al., 2014; Natale et al., 2005; Strang-Karlsson et al., 2010). A possible explanation derives from animal research that has reported adult phase advances in animals that underwent prenatal adversities (Kennaway, 2002). Additionally, previous studies (e.g., Hibbs et al., 2014) have suggested that the phase advances in preterm adolescents is related to the increased compliance from preterm children and adolescents with parental instructions regarding earlier bedtimes, which is in line with decreased risk-taking behavior in children and adolescents born preterm (e.g., Hack, Cartar, Schluchter, Klein, & Forrest, 2007). In contrast to previous findings from the prior wave of our study (Perkinson-Gloor et al., 2015b), we found no differences between VP and FT children in sleep continuity and sleep architecture. A possible explanation might be the older age of our sample, since sleep architecture develops to a great extent during the transition to adolescence. Specifically, SWS and REM sleep decrease while stage 1 and stage 2 sleep increase (Ohayon et al., 2004). Thus, it is possible that FT children and adolescents reach the same level of sleep patterns that VP children already show during early and middle childhood and that these changes in sleep architecture may lead to the convergence of the sleep architecture between VP and FT children. This assumption is also in line with a prior study that found an earlier emergence of a 24-h sleep–wake rhythm in VP compared to FT infants (Guyer et al., 2015).

Differences in HPA axis activity between VP and FT children are in line with prior studies reporting down-regulation of HPA axis activity in VP children (Kaseva et al., 2014; Grunau et al., 2013; Perkinson-Gloor et al., 2015b; Quesada et al., 2014; Wadsby et al., 2014). There are a number of possible explanations for blunted HPA axis activity in children born preterm: First, there may be long-term habituation related to prolonged exposure to stress during the pre- and postnatal phase (Lemola, 2015; Roberts & Dalziel, 2006); early life stress may lead to increased HPA axis activity in the short term, which may then result in overall down-regulated HPA axis activity. This assumption is in line with the decrease in HPA axis activity occurring in response to a repeated stressor (for a review, see Grissom & Bhatnagar, 2009). Second, it is possible that pre- and neonatal therapeutic exposure to glucocorticoids may lead to down-regulation of HPA axis activity in VP children (e.g., Karemaker et al., 2008). Third, blunted HPA axis activity might be associated with immaturity of the adrenal gland in VP children, leading to adrenal insufficiency (for a review, see Fernandez & Watterberg, 2009). Fourth, pregnancy-related issues, such as maternal infections or maternal depression, might increase the risk of preterm birth and neurodevelopmental alterations (for reviews, see Goldenberg, Culhane, Iams, & Romero, 2008; Van den Bergh et al., in press). However, our results are also in contrast to previous research, including a prior study by our research team, which found similar cortisol levels or even higher cortisol levels in VP and preterm children compared to FT children (Buske-Kirschbaum et al., 2007; Perkinson-Gloor et al., 2015b). Possible explanations for divergent findings between our study and the study by Buske-Kirschbaum et al. (2007) may be differences in gestational age (VP children vs. moderately preterm children), birth weight (small for gestational age vs. appropriate for gestational age), and different treatment regimens in the prenatal

and early postnatal phase across the samples. Regarding the prior study by our research team (Perkinson-Gloor et al., 2015b), age might again explain differences in results.

Further, Study 1 showed that the association between prematurity status and post-awakening cortisol secretion is partially mediated by sleep onset time. This relation may be through a shared common etiology early in life, since sleep and HPA axis activity are both highly susceptible to pre- and postnatal programming (Brooks & Canal, 2013; Lupien et al., 2009).

Results of Study 2 regarding differences in the LF/HF ratio during wake and stage 2 sleep between VP and FT children are in line with Rakow et al. (2013), who reported a shift to parasympathetic dominance (i.e., lower LF/HF ratio) in 9-year-old VP children and FT children born small for gestational age. Differences in the LF/HF ratio between VP and FT children might be explained by the timing of maturation of the ANS branches. While the SNS develops during early gestation, the PNS begins to increase rapidly between 25 and 32 weeks of gestation (David et al., 2007; Schneider et al., 2009). However, VP children spend this crucial period in the neonatal intensive care unit instead of the mother's womb and therefore, PNS may develop differently. Additionally, prior studies reported a general increase of the autonomic function with age, which is more pronounced in parasympathetic than sympathetic activity (Landrot et al., 2007; Patural et al., 2008). In this vein, Landrot et al. (2007) found sympathetic predominance right after birth in VP infants, which, however, disappeared at age 2–3 years. The initial sympathetic predominance, as a reaction to excessive stress, may then lead to long-term sympathetic down-regulation by habituation (Landrot et al., 2007). In contrast to Rakow et al. (2013), we found no differences in the other frequency domain parameters between VP and FT children. A possible explanation for these results may be differences in gestational age, birth weight, and measurement methods across the samples. While our study sample included only VP and FT children and measured HRV parameters at rest as well as during different sleep stages, Rakow et al. (2013) included VP children, FT children born small for gestational age, and FT children born appropriate for gestational age and conducted a 24-h ECG. In sum, findings of the present dissertation support and expand the knowledge of the role of VP birth in altered development of biological processes by showing earlier sleep onset times, decreased HPA axis activity, and a slight shift toward parasympathetic predominance of the ANS in VP children and adolescents compared to FT children and adolescents.

**6.3 Children's sleep and sleep assessment in the family context**

To the best of my knowledge, Study 3 was the first to report an association between maternal, but not paternal, insomnia symptoms and children's sleep-EEG patterns. Thus, our findings are in line with prior studies reporting associations between maternal and children's sleep but not between paternal and children's sleep (Bajoghli et al., 2013; Kalak et al., 2012; Li et al., 2010; Zhang et al., 2010). Several mechanisms may explain the association between children's and parental sleep. First, young children with sleep problems can prevent parents from achieving a good night's sleep (Gay, Lee, & Lee, 2004); second, children may learn sleep habits from their parents (Reid, Huntley, & Lewin, 2009); third, sleep of all family members may, for instance, be affected by poor family functioning (El-Sheikh, Buckhalt, Mize, & Acebo, 2006) or environmental stress (Muzet, 2007). Additionally, children share genes with their parents and therefore, it is possible that they also share genetic variation, which might be related to poor sleep (Barclay & Gregory, 2013). It is possible that the stronger association between maternal insomnia symptoms and children's objective sleep patterns are due to differences between parents in spending time with their children. In Switzerland, mothers spend more time with their children and are more often involved in basic child care tasks (e.g., putting children to bed) than fathers

(Craig, 2006; Swiss Federal Statistical Office, 2009, 2013). Therefore, sleep of mothers and their children may influence each other more strongly.

The results that parental insomnia symptoms are related to parental perception of children's sleep are in line with our hypothesis and results from Rönnlund et al. (2016). Parents with more insomnia symptoms also reported more sleep-related behavior problems in their children. However, the aforementioned associations could not be explained by children's objectively measured sleep. A possible explanation might be that parents with more insomnia symptoms over-report their children's sleep problems, since they have a cognitive negativity bias caused by sleep loss (Gobin, Banks, Fins, & Tartar, 2015; Harris et al., 2015). Thereby, they show increased attention to and more often remember negative stimuli related to their children's sleep. Additionally, it is possible that parents with more insomnia symptoms monitor their children's sleep more frequently and therefore may even trigger their children's sleep problems. This assumption is in line with Harvey's cognitive model of insomnia, which suggests that excessive negative cognition regarding sleep and related health problems may result in anxiety, which triggers autonomic arousal and emotional distress, which in turn may lead to sleep problems (Harvey, 2002). Moreover, our study was the first to report partner effects according to actor–partner interdependence models—an association between maternal insomnia symptoms and paternal perception of children's sleep-related behavior. However, paternal insomnia symptoms were not related to maternal perception of children's sleep-related behavior. Given that mothers spend more time with their children than fathers (Swiss Federal Statistical Office, 2009, 2013), it is possible that mothers report their perception of children's sleep problems to their partners more often than vice versa. Hence, these reports can be influenced by maternal sleep difficulties. In sum, findings of the present dissertation support and expand previous research by showing an association between maternal but not paternal insomnia symptoms and children's sleep as well as between parental insomnia symptoms and parental perception of children's sleep-related behavior.

### 6.4 Strengths and Limitations

The present dissertation has several strengths. First, biological processes were measured by multiple methods: Sleep was measured objectively by unattended in-home sleep-EEG, the gold-standard to measure sleep duration, continuity, and architecture (Frölich & Lehmkuhl, 2004). Thereby, the differences between children's usual sleep conditions and the conditions during the study night were minimized and the ecological validity of sleep assessment was improved compared to laboratory-based sleep assessment. Additionally, information from both parents regarding perception of children's sleep was available, whereas prior research generally included information only from mothers. HPA axis activity was assessed with salivary cortisol samples, which provides information on acute HPA axis activity, and with cortisol and cortisone in hair, which shows the cumulative HPA axis activity of the preceding months. Further, in our salivary cortisol sampling and statistical analysis we strove to follow published guidelines on post-awakening cortisol assessment (Stalder et al., 2016). Not only the overall ANS functioning but also the individual ANS functioning across different psychophysiological states was measured. Thus, measurement situation was more standardized across participants compared to 24-h assessments, since HRV was assessed during the same circadian phase and sleep stages, which may have reduced the acute impact of daily experiences. Further, HRV recording and interpretation adhered to existing methodological guidelines (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). Moreover, measurements of all biological processes were at about the same time. Second, a new statistical analysis was used: Study 3 was the first study to use actor–partner interdependence models in sleep research, which allowed us to examine actor and partner effects. Finally, the

sample included VP children: Biological processes were investigated in VP children, as they represent a population at increased risk for lifelong consequences.

Although the present dissertation has a number of strengths, it also has some limitations. First, the measurement methods used in the studies included in the present dissertation have their limitations: Biological processes were measured only during one night/day, a practice that may reduce reliability compared to assessment across multiple nights/days. Relatedly, there was no EEG-adaptation night and therefore, "first-night effects" could not be ruled out. However, prior studies showed that one night of in-home sleep-EEG could be regarded as a reliable method to assess children's habitual sleep (Perkinson-Gloor et al., 2015a; Pesonen et al., 2014). However, while children's sleep was measured during one night, the parent questionnaires referred to 1 and 2 weeks, respectively, which could lead to discrepancies between children's sleep measured objectively and parental perception of children's sleep. Additionally, post-awakening cortisol assessment did not include sampling-time verification and objective information on participants' compliance regarding the instructions for saliva collection. However, we did control for objectively assessed sleep-EEG awakening time to estimate sampling time. Second, the study design is limited: The studies in the present dissertation are cross-sectional and do not allow causal conclusions. Finally, generalizability is restricted: By including VP children in the samples of the studies, findings apart from differences between VP and FT children may not necessarily apply to the general population.

**6.5 Conclusions and Outlook**

Taken together, results of the present dissertation support and extend the understanding of the interplay between sleep, HPA axis activity, and ANS functioning in children and adolescents. Specifically, later sleep onset time and shorter sleep duration are associated with increased HPA axis activity. Mental diseases such as depression are associated with both short and poor sleep as well as increased HPA axis activity (Buckley & Schatzberg, 2005). Therefore, future research would benefit from further examination of these associations across the life-span to develop new therapy and treatment approaches for diseases associated with sleep and HPA axis activity. One possibility might be that by enhancing one biological process (e.g., sleep) the other biological process (e.g., HPA axis activity) as well as related psychological symptoms could improve, as has, for example, already been found for sleep and related mental problems (e.g., Freeman et al., 2017). Moreover, while we found increased sympathetic activity at wake and during different sleep stages to be associated with increased post-awakening HPA axis activity, research is still very limited and findings need to be replicated. Future studies should also attempt to extend our findings by assessing ANS functioning and HPA axis activity concurrently at different stages of the diurnal cycle and during different situations (e.g., stress vs. relaxation) to unravel their diurnal covariation. Additionally, while we assumed a connection between biological processes and positive development as outlined in prior research, future research would benefit from further examinations of these associations during childhood and adolescence.

Moreover, findings showed that VP birth, a stress-related factor early in life, is associated with altered HPA axis activity and to some extent with altered sleep and ANS functioning during childhood and adolescence. Hence, the present dissertation expands the concept of developmental origins of health and disease and shows to what extent an early life indicator is associated with altered biological processes during later daily life. Future research would benefit from longitudinal assessment of sleep, HPA axis activity, and ANS functioning and their interplay from infancy to childhood and adolescence in VP children and in children with other stress-related factors early in life. Thus, differential trajectories of biological processes in children with different levels of

early risk exposure should be examined. Additionally, by showing alterations of sleep, HPA axis activity, and ANS functioning in VP children, we unraveled potential biological underpinnings of long-term consequences for VP children. Therefore, findings of the present dissertation might be valuable for the development of new treatment approaches for mental problems that frequently occur in VP children (e.g., depression and anxiety) and are associated with altered sleep, HPA axis activity, and ANS functioning. Treatment of biological processes may lead to improved mental health and well-being in VP children. One future goal should be to further investigate possible causes of VP birth and to decrease the number of VP births, for example, by specialized care of women before and after birth (e.g., education on the risks of premature birth, depression, posttraumatic stress disorder) or by optimizing the neonatal intensive care unit environment (e.g., light, noise; van den Hoogen, et al., 2017). In 2011, for example, our research team released practice guidelines for midwives on screening and counseling for women during and after pregnancy, including recommendations on issues related to premature birth (e.g., smoking, stress) in collaboration with the Swiss Association of Midwives (Schweizerischer Hebammenverband, 2011). Additionally, future research should investigate possible protective factors after preterm birth across the life-span to create new promotion schemes, which could possibly reverse long-term consequences of adverse pre-and postnatal environments (Shonkoff, 2010).

Finally, the present dissertation provides important evidence that parental insomnia is an immediate context factor for children's sleep and children's sleep assessment. Thus, it is important for practitioners to consider children's sleep in the family context and to take sleep patterns of the family members, especially maternal sleep patterns, into account when assessing children's sleep problems. Additionally, findings of the present dissertation point out the importance of sleep hygiene interventions across all family members and education of parents regarding sleep to improve children's sleep (Mindell, Sedmak, Boyle, Butler, & Williamson, 2016). Further, it is essential to use adequate and objective sleep assessment in research and clinically, since the most frequently used measure to detect children's sleep problems (i.e., parent reports) might be biased by parental sleep difficulties. Future studies would benefit from examining further immediate context factors as well as social and cultural context factors possibly associated with children's sleep (El-Sheikh & Sadeh, 2015). Additionally, this dissertation's findings await replication and extension, by assessing several consecutive nights of in-home sleep-EEG or by including a broader range of parental sleep difficulties.

In sum, the present dissertation emphasizes that sleep, HPA axis activity, and ANS functioning are related to each other during late childhood and early adolescence, are susceptible to early life factors such as VP birth, and are influenced by concurrent environmental factors such as parental insomnia. Additionally, this dissertation outlines the practical implications of the results for the development of new therapeutic interventions to foster positive development associated with altered sleep, HPA axis activity, and ANS functioning as well as for practitioners regarding the assessment of children's sleep and children's sleep problems.

**References**

Aarnoudse-Moens, C. S. H., Weisglas-Kuperus, N., van Goudoever, J. B., & Oosterlaan, J. (2009). Meta-analysis of neurobehavioral outcomes in very preterm and/or very low birth weight children. *Pediatrics, 124*, 717-728. doi:10.1542/peds.2008-2816

Acharya, U. R., Joseph, K. P., Kannathal, N., Lim, C. M., & Suri, J. S. (2006). Heart rate variability: A review. *Medical & Biological Engineering & Computing*, *44*, 1031-1051. doi:10.1007/s11517-006-0119-0

Acharya, U. R., Kannathal, N., Sing, O. W., Ping, L. Y., & Chua, T. (2004). Heart rate analysis in normal subjects of various age groups. *Biomedical Engineering Online, 3*. doi:10.1186/1475-925X-3-24

Adam, E. K., Quinn, M. E., Tavernier, R., McQuillan, M. T., Dahlke, K. A., & Gilbert, K. E. (2017). Diurnal cortisol slopes and mental and physical health outcomes: A systematic review and meta-analysis. *Psychoneuroendocrinology, 83*, 25-41. doi:10.1016/j.psyneuen.2017.05.018

Alink, L. R., van IJzendoorn, M. H., Bakermans-Kranenburg, M. J., Mesman, J., Juffer, F., & Koot, H. M. (2008). Cortisol and externalizing behavior in children and adolescents: Mixed meta-analytic evidence for the inverse relation of basal cortisol and cortisol reactivity with externalizing behavior. *Developmental Psychobiology, 50*, 427-450. doi:10.1002/dev.20300

American Academy of Sleep Medicine, & Iber, C. (2007). *The AASM manual for the scoring of sleep and associated events: Rules, terminology and technical specifications.* Westchester, IL: American Academy of Sleep Medicine.

Andrews, J., D'Aguiar, C., & Pruessner, J. C. (2012). The combined dexamethasone/TSST paradigm—A new method for psychoneuroendocrinology. *PLoS ONE, 7*. doi:10.1371/journal.pone.0038994

Andrews, J., & Pruessner, J. C. (2013). The combined propranolol/TSST paradigm—a new method for psychoneuroendocrinology. *PLoS ONE, 8*. doi:10.1371/journal.pone.0057567

Asaka, Y., & Takada, S. (2010). Activity-based assessment of the sleep behaviors of VLBW preterm infants and full-term infants at around 12 months of age. *Brain & Development, 32*, 150-155. doi:10.1016/j.braindev.2008.12.006

Astill, R. G., Van der Heijden, K. B., Van IJzendoorn, M. H., & Van Someren, E. J. (2012). Sleep, cognition, and behavioral problems in school-age children: A century of research meta-analyzed. *Psychological Bulletin, 138*, 1109-1138. doi:10.1037/a0028204

Bajoghli, H., Alipouri, A., Holsboer-Trachsler, E., & Brand, S. (2013). Sleep patterns and psychological functioning in families in northeastern Iran; evidence for similarities between adolescent children and their parents. *Journal of Adolescence, 36*, 1103-1113. doi:10.1016/j.adolescence.2013.08.016

Banks, S., & Dinges, D. F. (2007). Behavioral and physiological consequences of sleep restriction. *Journal of Clinical Sleep Medicine, 3*, 519-528.

Barclay, N. L., & Gregory, A. M. (2013). Quantitative genetic research on sleep: A review of normal sleep, sleep disturbances and associated emotional, behavioural, and health-related difficulties. *Sleep Medicine Reviews*, *17*, 29-40. doi:10.1016/j.smrv.2012.01.008

Barker, D. J. (1990). The fetal and infant origins of adult disease. *BMJ: British Medical Journal, 301*, 1111.

Barker, D. J. P. (2004). The developmental origins of adult disease. *Journal of the American College of Nutrition, 23*, 588S-595S. doi:10.1080/07315724.2004.10719428

Bastien, C. H., Vallières, A., & Morin, C. M. (2001). Validation of the Insomnia Severity Index as an outcome measure for insomnia research. *Sleep Medicine*, *2*, 297-307. doi:10.1016/s1389-9457(00)00065-4

Beauchaine, T. P., & Thayer, J. F. (2015). Heart rate variability as a transdiagnostic biomarker of psychopathology. *International Journal of Psychophysiology, 98*, 338-350. doi:10.1016/j.ijpsycho.2015.08.004

Benington, J. H., & Heller, H. C. (1995). Restoration of brain energy metabolism as the function of sleep. *Progress in Neurobiology*, *45*, 347-360. doi:10.1016/0301-0082(94)00057-o

Björkqvist, J., Paavonen, J., Andersson, S., Pesonen, A. K., Lahti, J., Heinonen, K., ... Strang-Karlsson, S. (2014). Advanced sleep–wake rhythm in adults born prematurely: Confirmation by actigraphy-based assessment in the Helsinki Study of Very Low Birth Weight Adults. *Sleep Medicine*, *15*, 1101-1106. doi:10.1016/j.sleep.2014.04.016

Blencowe, H., Cousens, S., Oestergaard, M. Z., Chou, D., Moller, A. B., Narwal, R., … Lawn, J. E. (2012). National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: A systematic analysis and implications. *The Lancet*, *379*, 2162-2172. doi:10.1097/01.aoa.0000432360.25014.c3

Borbély, A. A., & Achermann, P. (1999). Sleep homeostasis and models of sleep regulation. *Journal of Biological Rhythms, 14*, 559-570. doi:10.1177/074873099129000894

Born, J., DeKloet, E. R., Wenz, H., Kern, W., & Fehm, H. L. (1991). Gluco- and antimineralocorticoid effects on human sleep: A role of central corticosteroid receptors. *American Journal of Physiology-Endocrinology & Metabolism*, *260*, E183-E188. doi:10.1152/ajpendo.1991.260.2.e183

Bronfenbrenner, U. (1979). *The ecology of human development.* Cambridge, MA: Harvard University Press.

Brooks, E., & Canal, M. M. (2013). Development of circadian rhythms: Role of postnatal light environment. *Neuroscience & Biobehavioral Reviews*, *37*, 551-560. doi:10.1016/j.neubiorev.2013.02.012

Brummelte, S., Chau, C. M., Cepeda, I. L., Degenhardt, A., Weinberg, J., Synnes, A. R., & Grunau, R. E. (2015). Cortisol levels in former preterm children at school age are predicted by neonatal procedural pain-related stress. *Psychoneuroendocrinology, 51*, 151-163. doi:10.1016/j.psyneuen.2014.09.018

Buckley, T. M., & Schatzberg, A. F. (2005). On the interactions of the hypothalamic-pituitary-adrenal (HPA) axis and sleep: Normal HPA axis activity and circadian rhythm, exemplary sleep disorders. *The Journal of Clinical Endocrinology & Metabolism*, *90*, 3106-3114. doi:10.1210/jc.2004-1056

Burnett, A. C., Anderson, P. J., Cheong, J., Doyle, L. W., Davey, C. G., & Wood, S. J. (2011). Prevalence of psychiatric diagnoses in preterm and full-term children, adolescents and young adults: A meta-analysis. *Psychological Medicine*, *41*, 2463-2474. doi:10.1017/S003329171100081X

Buske-Kirschbaum, A., Krieger, S., Wilkes, C., Rauh, W., Weiss, S., & Hellhammer, D. H. (2007). Hypothalamic-pituitary-adrenal axis function and the cellular immune response in former preterm children. *The Journal of Clinical Endocrinology & Metabolism, 92*, 3429-3435. doi:10.1210/jc.2006-2223

Cappuccio, F. P., D'Elia, L., Strazzullo, P., & Miller, M. A. (2010). Sleep duration and all-cause mortality: A systematic review and meta-analysis of prospective studies. *Sleep, 33*, 585-592. doi:10.1093/sleep/33.5.585

Card, J. P., Levitt, P., Gluhovsky, M., & Rinaman, L. (2005). Early experience modifies the postnatal assembly of autonomic emotional motor circuits in rats. *Journal of Neuroscience*, *25*, 9102-9111. doi:10.1523/JNEUROSCI.2345-05.2005

Carskadon, M. A., & Dement, W. C. (2011). Monitoring and staging human sleep. In M. H. Kryger, T. Roth, & W. C. Dement (Eds.), *Principles and practice of sleep medicine* (5th ed., pp. 16-26). St. Louis, MO: Elsevier Saunders.

Charmandari, E., Tsigos, C., & Chrousos, G. (2005). Endocrinology of the stress response. *Annual Review of Physiology*, *67*, 259-284. doi:10.1146/annurev.physiol.67.040403.120816

Chida, Y., & Steptoe, A. (2009). Cortisol awakening response and psychosocial factors: A systematic review and meta-analysis. *Biological Psychology*, *80*, 265-278. doi:10.1016/j.biopsycho.2008.10.004

Child Trends. (2015). *Preterm births – indicators of child and youth well-being*. Retrieved from http://www.childtrends.org/?indicators=preterm-births

Clements, A. D. (2013). Salivary cortisol measurement in developmental research: Where do we go from here? *Developmental Psychobiology, 55*, 205-220. doi:10.1002/dev.21025

Craig, L. (2006). Does father care mean fathers share? A comparison of how mothers and fathers in intact families spend time with children. *Gender & Society*, *20*, 259-281. doi:10.1177/0891243205285212

David, M., Hirsch, M., Karin, J., Toledo, E., & Akselrod, S. (2007). An estimate of fetal autonomic state by time-frequency analysis of fetal heart rate variability. *Journal of Applied Physiology*, *102*, 1057-1064. doi:10.1152/japplphysiol.00114.2006

Dempsey, A. G., Keller-Margulis, M., Mire, S., Abrahamson, C., Dutt, S., Llorens, A., & Payan, A. (2015). School-aged children born preterm: Review of functioning across multiple domains and guidelines for assessment. *Advances in School Mental Health Promotion, 8*, 17-28. doi:10.1080/1754730x.2014.978117

Dewald, J. F., Meijer, A. M., Oort, F. J., Kerkhof, G. A., & Bögels, S. M. (2010). The influence of sleep quality, sleep duration and sleepiness on school performance in children and adolescents: A meta-analytic review. *Sleep Medicine Reviews*, *14*, 179-189. doi:10.1016/j.smrv.2009.10.004

De Weerth, C., Zijl, R. H., & Buitelaar, J. K. (2003). Development of cortisol circadian rhythm in infancy. *Early Human Development, 73*, 39-52. doi:10.1016/s0378-3782(03)00074-4

Diekelmann, S., & Born, J. (2010). The memory function of sleep. *Nature Reviews Neuroscience*, *11*, 114-126. doi:10.1038/nrn2762

Dinges, D. F. (2014). The growth of sleep science and the role of sleep. *Sleep, 37*, 7-8. doi:10.5665/sleep.3296

El-Sheikh, M., Buckhalt, J. A., Keller, P. S., & Granger, D. A. (2008). Children's objective and subjective sleep disruptions: Links with afternoon cortisol levels. *Health Psychology*, *27*, 26-33. doi:10.1037/0278-6133.27.1.26

El-Sheikh, M., Buckhalt, J. A., Mize, J., & Acebo, C. (2006). Marital conflict and disruption of children's sleep. *Child Development*, *77*, 31-43. doi:10.1111/j.1467-8624.2006.00854.x

El-Sheikh, M., & Sadeh, A. (2015). I. Sleep and development: Introduction to the monograph. *Monographs of the Society for Research in Child Development, 80*, 1-14. doi:10.1111/mono.12141

Fernandez, E. F., & Watterberg, K. L. (2009). Relative adrenal insufficiency in the preterm and term infant. *Journal of Perinatology*, *29*, S44-S49. doi:10.1038/jp.2009.24

Fernandez-Mendoza, J., Vgontzas, A. N., Calhoun, S. L., Vgontzas, A., Tsaoussoglou, M., Gaines, J., … Bixler, E. O. (2014). Insomnia symptoms, objective sleep duration and hypothalamic-pituitary-adrenal activity in children. *European Journal of Clinical Investigation*, *44*, 493-500. doi:10.1111/eci.12263

Freeman, D., Sheaves, B., Goodwin, G. M., Yu, L. M., Nickless, A., Harrison, P. J., … Hinds, C. (2017). The effects of improving sleep on mental health (OASIS): A randomised controlled trial with mediation analysis. *The Lancet Psychiatry, 4*, 749-758. doi:10.1016/s2215-0366(17)30328-0

Fricke-Oerkermann, L., Plück, J., Schredl, M., Heinz, K., Mitschke, A., Wiater, A., & Lehmkuhl, G. (2007). Prevalence and course of sleep problems in childhood. *Sleep, 30*, 1371-1377. doi:10.1093/sleep/30.10.1371

Friedman, B. H. (2007). An autonomic flexibility–neurovisceral integration model of anxiety and cardiac vagal tone. *Biological Psychology*, *74*, 185-199. doi:10.1016/j.biopsycho.2005.08.009

Fries, E., Dettenborn, L., & Kirschbaum, C. (2009). The cortisol awakening response (CAR): Facts and future directions. *International Journal of Psychophysiology*, *72*, 67-73. doi:10.1016/j.ijpsycho.2008.03.014

Frölich, J., & Lehmkuhl, G. (2004). Home polysomnography in children—A complementary assessment method of sleep disorders in children. *Somnologie*, *8*, 61-64. doi:10.1111/j.1439-054x.2004.00013.x

Fyfe, K. L., Yiallourou, S. R., Wong, F. Y., Odoi, A., Walker, A. M., & Horne, R. S. (2015). The effect of gestational age at birth on post-term maturation of heart rate variability. *Sleep*, *38*, 1635-1644. doi:10.5665/sleep.5064

Gao, W., Kirschbaum, C., Grass, J., & Stalder, T. (2016). LC–MS based analysis of endogenous steroid hormones in human hair. *The Journal of Steroid Biochemistry & Molecular Biology*, *162*, 92-99. doi:10.1016/j.jsbmb.2015.12.022

Gay, C. L., Lee, K. A., & Lee, S. Y. (2004). Sleep patterns and fatigue in new mothers and fathers. *Biological Research for Nursing*, *5*, 311-318. doi:10.1177/1099800403262142

Gobin, C. M., Banks, J. B., Fins, A. I., & Tartar, J. L. (2015). Poor sleep quality is associated with a negative cognitive bias and decreased sustained attention. *Journal of Sleep Research*, *24*, 535-542. doi:10.1111/jsr.12302

Goldenberg, R. L., Culhane, J. F., Iams, J. D., & Romero, R. (2008). Epidemiology and causes of preterm birth. *The Lancet*, *371*, 75-84. doi10.1016/s0140-6736(08)60074-4

Gunnar, M. R., Wewerka, S., Frenn, K., Long, J. D., & Griggs, C. (2009). Developmental changes in hypothalamus–pituitary–adrenal activity over the transition to adolescence: Normative changes and associations with puberty. *Development and Psychopathology, 21*, 69-85. doi:10.1017/s0954579409000054

Guo, Y. F., & Stein, P. K. (2003). Circadian rhythm in the cardiovascular system: Chronocardiology. *American Heart Journal*, *145*, 779-786. doi:10.1016/s0002-8703(02)94797-6

Guyer, C., Huber, R., Fontijn, J., Bucher, H. U., Nicolai, H., Werner, H., … Jenni, O. G. (2015). Very preterm infants show earlier emergence of 24-hour sleep–wake rhythms compared to term infants. *Early Human Development*, *91*, 37-42. doi:10.1016/j.earlhumdev.2014.11.002

Gradisar, M., Gardner, G., & Dohnt, H. (2011). Recent worldwide sleep patterns and problems during adolescence: A review and meta-analysis of age, region, and sleep. *Sleep Medicine, 12,* 110-118. doi:10.1016/j.sleep.2010.11.008

Gregory, A. M., & Sadeh, A. (2012). Sleep, emotional and behavioral difficulties in children and adolescents. *Sleep Medicine Reviews*, *16*, 129-136. doi:10.1016/j.smrv.2011.03.007

Grissom, N., & Bhatnagar, S. (2009). Habituation to repeated stress: Get used to it. *Neurobiology of Learning & Memory*, *92*, 215-224. doi:10.1016/j.nlm.2008.07.001

Grunau, R. E., Cepeda, I. L., Chau, C. M., Brummelte, S., Weinberg, J., Lavoie, P. M., … Van Uum, S. (2013). Neonatal pain-related stress and NFKBIA genotype are associated with altered cortisol levels in preterm boys at school age. *PLoS ONE*, *8*. doi:10.1371/journal.pone.0073926

Hack, M., Cartar, L., Schluchter, M., Klein, N., & Forrest, C. B. (2007). Self-perceived health, functioning and well-being of very low birth weight infants at age 20 years. *The Journal of Pediatrics, 151*, 635-641. doi:10.1016/j.jpeds.2007.04.063

Harris, K., Spiegelhalder, K., Espie, C. A., MacMahon, K. M., Woods, H. C., & Kyle, S. D. (2015). Sleep-related attentional bias in insomnia: A state-of-the-science review. *Clinical Psychology Review*, *42*, 16-27. doi:10.1016/j.cpr.2015.08.001

Harvey, A. G. (2002). A cognitive model of insomnia. *Behaviour Research & Therapy*, *40*, 869-893. doi:10.1016/s0005-7967(01)00061-4

Hatzinger, M., Brand, S., Perren, S., Stadelmann, S., von Wyl, A., von Klitzing, K., & Holsboer-Trachsler, E. (2008). Electroencephalographic sleep profiles and hypothalamic–pituitary–adrenocortical (HPA)-activity in kindergarten children: Early indication of poor sleep quality associated with increased cortisol secretion. *Journal of Psychiatric Research*, *42*, 532-543. doi:10.1016/j.jpsychires.2007.05.010

Herlenius, E., & Lagercrantz, H. (2004). Development of neurotransmitter systems during critical periods. *Experimental Neurology*, *190*, 8-21. doi:10.1016/j.expneurol.2004.03.027

Hibbs, A. M., Storfer-Isser, A., Rosen, C., Ievers-Landis, C. E., Taveras, E. M., & Redline, S. (2014). Advanced sleep phase in adolescents born preterm. *Behavioral Sleep Medicine*, *12*, 412-424. doi:10.1080/15402002.2013.825838

Iglowstein, I., Jenni, O. G., Molinari, L., & Largo, R. H. (2003). Sleep duration from infancy to adolescence: Reference values and generational trends. *Pediatrics, 111*, 302-307. doi:10.1542/peds.111.2.302

Iglowstein, I., Hajnal, B. L., Molinari, L., Largo, R. H., & Jenni, O. G. (2006). Sleep behaviour in preterm children from birth to age 10 years: A longitudinal study. *Acta Paediatrica, 95*, 1691-1693. doi:10.1080/08035250600686938

Igosheva, N., Klimova, O., Anishchenko, T., & Glover, V. (2004). Prenatal stress alters cardiovascular responses in adult rats. *The Journal of Physiology*, *557*, 273-285. doi:10.1113/jphysiol.2003.056911

Inder, T. E., Warfield, S. K., Wang, H., Hüppi, P. S., & Volpe, J. J. (2005). Abnormal cerebral structure is present at term in premature infants. *Pediatrics, 115*, 286-294. doi:10.1542/peds.2004-0326

Iwasaki, M., Iwata, S., Iemura, A., Yamashita, N., Tomino, Y., Anme, T., ... Matsuishi, T. (2010). Utility of subjective sleep assessment tools for healthy preschool children: A comparative study between sleep logs, questionnaires, and actigraphy. *Journal of Epidemiology*, *20*, 143-149. doi:10.2188/jea.je20090054

Jänig, W. (2006). *The integrative action of the autonomic nervous system: Neurobiology of homeostasis*. New York, NY: Cambridge University Press.

Jenni, O. G., & Carskadon, M. A. (2004). Spectral analysis of the sleep electroencephalogram during adolescence. *Sleep, 27*, 774-783. doi:10.1093/sleep/27.4.774

Juster, R. P., McEwen, B. S., & Lupien, S. J. (2010). Allostatic load biomarkers of chronic stress and impact on health and cognition. *Neuroscience & Biobehavioral Reviews, 35*, 2-16. doi:10.1016/j.neubiorev.2009.10.002

Kajantie E., & Phillips, D. I. (2006). The effects of sex and hormonal status on the physiological response to acute psychosocial stress. *Psychoneuroendocrinology, 31*, 151-178. doi:10.1016/j.psyneuen.2005.07.002

Kajantie, E., & Räikkönen, K. (2010). Early life predictors of the physiological stress response later in life. *Neuroscience & Biobehavioral Reviews*, *35*, 23-32. doi:10.1016/j.neubiorev.2009.11.013

Kalak, N., Gerber, M., Kirov, R., Mikoteit, T., Pühse, U., Holsboer-Trachsler, E., & Brand, S. (2012). The relation of objective sleep patterns, depressive symptoms, and sleep disturbances in adolescent children and their parents: A sleep-EEG study with 47 families. *Journal of Psychiatric Research, 46*, 1374-1382. doi:10.1016/j.jpsychires.2012.07.006

Kalsbeek, A., Van der Spek, R., Lei, J., Endert, E., Buijs, R. M., & Fliers, E. (2012). Circadian rhythms in the hypothalamo–pituitary–adrenal (HPA) axis. *Molecular and Cellular Endocrinology, 349*, 20-29. doi:10.1016/j.mce.2011.06.042

Karemaker, R., Karemaker, J. M., Kavelaars, A., Tersteeg-Kamperman, M., Baerts, W., Veen, S., … Heijnen, C. J. (2008). Effects of neonatal dexamethasone treatment on the cardiovascular stress response of children at school age. *Pediatrics*, *122*, 978-987. doi:10.1542/peds.2007-3409

Kaseva, N., Wehkalampi, K., Pyhälä, R., Moltchanova, E., Feldt, K., Pesonen, A. K., ... Kajantie, E. (2014). Blunted hypothalamic-pituitary-adrenal axis and insulin response to psychosocial stress in young adults born preterm at very low birth weight. *Clinical Endocrinology, 80*, 101-106. doi:10.1111/cen.12251

Kennaway, D. J. (2002). Programming of the fetal suprachiasmatic nucleus and subsequent adult rhythmicity. *Trends in Endocrinology & Metabolism, 13*, 398-402. doi:10.1016/s1043-2760(02)00692-6

Kenny, D. A., & Cook, W. (1999). Partner effects in relationship research: Conceptual issues, analytic difficulties, and illustrations. *Personal Relationships, 6*, 433-448. doi:10.1111/j.1475-6811.1999.tb00202.x

Kenny, D. A., Kashy, D. A., & Cook, W. L. (2006). *Dyadic data analysis*. New York, NY: Guilford Press.

Koenig, J., Kemp, A. H., Beauchaine, T. P., Thayer, J. F., & Kaess, M. (2016). Depression and resting state heart rate variability in children and adolescents—A systematic review and meta-analysis. *Clinical Psychology Review, 46*, 136-150. doi:10.1016/j.cpr.2016.04.013

Kouros, C. D., & El-Sheikh, M. (2017). Within-family relations in objective sleep duration, quality, and schedule. *Child Development*, *88*, 1983-2000. doi:10.1111/cdev.12667

Kunz-Ebrecht, S. R., Kirschbaum, C., Marmot, M., & Steptoe, A. (2004). Differences in cortisol awakening response on work days and weekends in women and men from the Whitehall II cohort. *Psychoneuroendocrinology*, *29*, 516-528. doi:10.1016/s0306-4530(03)00072-6

Landrot, I. D. R., Roche, F., Pichot, V., Teyssier, G., Gaspoz, J. M., Barthelemy, J. C., & Patural, H. (2007). Autonomic nervous system activity in premature and full-term infants from theoretical term to 7 years. *Autonomic Neuroscience: Basic & Clinical*, *136*, 105-109. doi:10.1016/j.autneu.2007.04.008

Lemola, S. (2015). Long-term outcomes of very preterm birth: Mechanisms and interventions. *European Psychologist, 20*, 128-137. doi:10.1027/1016-9040/a000207

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

Lerner, R. M., Fisher, C. B. & Weinberg, R.A. (2000). Toward a science for and of the people: Promoting civil society through the application of developmental science. *Developmental Psychology, 71*, 11-20. doi:10.1111/1467-8624.00113

Levine, S. & Wiener, S. G. (1988). Psychoendocrine aspects of mother-infant relationships in nonhuman primates. *Psychoneuroendocrinology 13*, 143-154. doi:10.1016/0306-4530(88)90011-x

Li, S., Zhu, S., Jin, X., Yan, C., Wu, S., Jiang, F., & Shen, X. (2010). Risk factors associated with short sleep duration among Chinese school-aged children. *Sleep Medicine*, *11*, 907-916. doi:10.1016/j.sleep.2010.03.018

Lupien, S. J., McEwen, B. S., Gunnar, M. R., & Heim, C. (2009). Effects of stress throughout the lifespan on the brain, behaviour and cognition. *Nature Reviews Neuroscience*, *10*, 434-445. doi:10.1038/nrn2639

Mai, E., & Buysse, D. J. (2008). Insomnia: Prevalence, impact, pathogenesis, differential diagnosis, and evaluation. *Sleep Medicine Clinics*, *3*, 167-174. doi:10.1016/j.jsmc.2008.02.001

McCormick, M. C., Litt, J. S., Smith, V. C., & Zupancic, J. A. (2011). Prematurity: An overview and public health implications. *Annual Review of Public Health*, *32*, 367-379. doi:10.1146/annurev-publhealth-090810-182459

Michels, N., Sioen, I., Clays, E., De Buyzere, M., Ahrens, W., Huybrechts, I., … De Henauw, S. (2013). Children's heart rate variability as stress indicator: Association with reported stress and cortisol. *Biological Psychology*, *94*, 433-440. doi:10.1016/j.biopsycho.2013.08.005

Mignot, E. (2008). Why we sleep: The temporal organization of recovery. *PLoS Biology, 6*. doi:10.1371/journal.pbio.0060106

Mindell, J. A., Sedmak, R., Boyle, J. T., Butler, R., & Williamson, A. A. (2016). Sleep well!: A pilot study of an education campaign to improve sleep of socioeconomically disadvantaged children. *Journal of Clinical Sleep Medicine, 12*, 1593-1599. doi:10.5664/jcsm.6338

Mirmiran, M., Maas, Y. G., & Ariagno, R. L. (2003). Development of fetal and neonatal sleep and circadian rhythms. *Sleep Medicine Reviews*, *7*, 321-334. doi:10.1053/smrv.2002.0243

Muzet, A. (2007). Environmental noise, sleep and health. *Sleep Medicine Reviews*, *11*, 135-142. doi:10.1016/j.smrv.2006.09.001

Natale, V., Sansavini, A., Trombini, E., Esposito, M. J., Alessandroni, R., & Faldella, G. (2005). Relationship between preterm birth and circadian typology in adolescence. *Neuroscience Letters*, *382*, 139-142. doi:10.1016/j.neulet.2005.03.004

Nicolaides, N. C., Charmandari, E., & Chrousos, G. P. (2015). The hypothalamic-pituitary-adrenal axis in human health and disease. In D. V. Cokkinos (Ed.), *Introduction to translational cardiovascular research* (pp. 91-107). Cham, Switzerland: Springer. doi:10.1007/978-3-319-08798-6_6

Nicolaides, N. C., Kyratzi, E., Lamprokostopoulou, A., Chrousos, G. P., & Charmandari, E. (2015). Stress, the stress system and the role of glucocorticoids. *Neuroimmunomodulation, 22*, 6-19. doi:10.1159/000362736

Nijhuis, I. J., ten Hof, J., Mulder, E. J., Nijhuis, J. G., Narayan, H., Taylor, D. J., & Visser, G. H. (2000). Fetal heart rate in relation to its variation in normal and growth retarded fetuses. *European Journal of Obstetrics & Gynecology and Reproductive Biology*, *89*, 27-33. doi:10.1016/s0301-2115(99)00162-1

Ohayon, M. M., Carskadon, M. A., Guilleminault, C., & Vitiello, M. V. (2004). Meta-analysis of quantitative sleep parameters from childhood to old age in healthy individuals: Developing normative sleep values across the human lifespan. *Sleep, 27*, 1255-1273. doi:10.1093/sleep/27.7.1255

Patural, H., Pichot, V., Jaziri, F., Teyssier, G., Gaspoz, J. M., Roche, F., & Barthelemy, J. C. (2008). Autonomic cardiac control of very preterm newborns: A prolonged dysfunction. *Early Human Development*, *84*, 681-687. doi:10.1016/j.earlhumdev.2008.04.010

Perkinson-Gloor, N., Hagmann-von Arx, P., Brand, S., Holsboer-Trachsler, E., Grob, A., Weber, P., & Lemola, S. (2015a). Intraindividual long-term stability of sleep electroencephalography in school-aged children. *Sleep Medicine, 16*, 1348-1351. doi:10.1016/j.sleep.2015.07.025

Perkinson-Gloor, N., Hagmann-von Arx, P., Brand, S., Holsboer-Trachsler, E., Grob, A., Weber, P., & Lemola, S. (2015b). 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

Pesonen, A. K., Martikainen, S., Heinonen, K., Wehkalampi, K., Lahti, J., Kajantie, E., & Räikkönen, K. (2014). Continuity and change in poor sleep from childhood to early adolescence. *Sleep*, *37*, 289-297. doi:10.5665/sleep.3400

Porges, S. W. (1995). Cardiac vagal tone: A physiological index of stress. *Neuroscience & Biobehavioral Reviews, 19*, 225–233. doi:10.1016/0149-7634(94)00066-a

Porges, S. W. (2007). The polyvagal perspective. *Biological Psychology, 74*, 116-143. doi:10.1016/j.biopsycho.2006.06.009

Preacher, K. J., & Hayes, A. F. (2008). Asymptotic and resampling strategies for assessing and comparing indirect effects in multiple mediator models. *Behavior Research Methods, 40*, 879-891. doi:10.3758/BRM.40.3.879

Pruessner, J. C., Kirschbaum, C., Meinlschmid, G., & Hellhammer, D. H. (2003). Two formulas for computation of the area under the curve represent measures of total hormone concentration versus time-dependent change. *Psychoneuroendocrinology*, *28*, 916-931. doi:10.1016/s0306-4530(02)00108-7

Quesada, A. A., Tristão, R. M., Pratesi, R., & Wolf, O. T. (2014). Hyper-responsiveness to acute stress, emotional problems and poorer memory in former preterm children. *Stress, 17*, 389-399. doi:10.3109/10253890.2014.949667

Quintana, D. S., Guastella, A. J., Outhred, T., Hickie, I. B., & Kemp, A. H. (2012). Heart rate variability is associated with emotion recognition: Direct evidence for a relationship between the autonomic nervous system and social cognition. *International Journal of Psychophysiology*, *86*, 168-172. doi:10.1016/j.ijpsycho.2012.08.012

Räikkönen, K., Matthews, K. A., Pesonen, A. K., Pyhälä, R., Paavonen, E. J., Feldt, K., … Lahti, J. (2010). Poor sleep and altered hypothalamic-pituitary-adrenocortical and sympatho-adrenal-medullary system activity in children. *The Journal of Clinical Endocrinology & Metabolism*, *95*, 2254-2261. doi:10.1210/jc.2009-0943

Rakow, A., Katz-Salamon, M., Ericson, M., Edner, A., & Vanpée, M. (2013). Decreased heart rate variability in children born with low birth weight. *Pediatric Research*, *74*, 339-343. doi:10.1038/pr.2013.97

Rechtschaffen, A., & Kales, A. (1968). *A manual for standardized terminology, techniques and scoring system for sleep stages of human subjects*. In: Brain Information Service. Los Angeles: Brain Research Institute.

Reid, G. J., Huntley, E. D., & Lewin, D. S. (2009). Insomnias of childhood and adolescence. *Child & Adolescent Psychiatric Clinics*, *18*, 979-1000. doi:10.1016/j.chc.2009.06.002

Roberts, D., & Dalziel S. R. (2006). Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. *Cochrane Database Systematic Reviews, 3*, CD004454.

Rönnlund, H., Elovainio, M., Virtanen, I., Matomäki, J., & Lapinleimu, H. (2016). Poor parental sleep and the reported sleep quality of their children. *Pediatrics*, *137*. doi:10.1542/peds.2015-3425

Rotenberg, S., & McGrath, J. J. (2016). Inter-relation between autonomic and HPA axis activity in children and adolescents. *Biological Psychology*, *117*, 16-25. doi:10.1016/j.biopsycho.2016.01.015

Rüegger, C., Hegglin, M., Adams, M., & Bucher, H. U. (2012). Population based trends in mortality, morbidity and treatment for very preterm- and very low birth weight infants over 12 years. *BMC Pediatrics, 12*. doi:10.1186/1471-2431-12-17

Sadeh, A. (2015). III. Sleep assessment methods. *Monographs of the Society for Research in Child Development, 80*, 33-48. doi:10.1111/mono.12143

Sadeh, A., Mindell, J., & Rivera, L. (2011). "My child has a sleep problem": A cross-cultural comparison of parental definitions. *Sleep Medicine*, *12*, 478-482. doi:10.1016/j.sleep.2010.10.008

Saigal, S., & Doyle, L. W. (2008). An overview of mortality and sequelae of preterm birth from infancy to adulthood. *The Lancet*, *371*, 261-269. doi:10.1016/S0140-6736(08)60136-1

Schlarb, A. A., Schwerdtle, B., & Hautzinger, M. (2010). Validation and psychometric properties of the German version of the Children's Sleep Habits Questionnaire (CSHQ-DE). *Somnologie-Schlafforschung und Schlafmedizin, 14*, 260-266. doi:10.1007/s11818-010-0495-4

Schneider, U., Schleussner, E., Fiedler, A., Jaekel, S., Liehr, M., Haueisen, J., & Hoyer, D. (2009). Fetal heart rate variability reveals differential dynamics in the intrauterine development of the sympathetic and parasympathetic branches of the autonomic nervous system. *Physiological Measurement*, *30*, 215-226. doi:10.1088/0967-3334/30/2/008

Schweizerischer Hebammenverband. (2011). Guideline zu Screening und Beratung bei Zigaretten-und Alkoholkonsum vor, während und nach der Schwangerschaft [Guideline on screening and advice on cigarettes and alcohol consumption before, during and after pregnancy].
Retrieved from http://www. hebamme.ch/de/heb/lit/index. cfm

Shaffer, F., McCraty, R., & Zerr, C. L. (2014). A healthy heart is not a metronome: An integrative review of the heart's anatomy and heart rate variability. *Frontiers in Psychology*, *5*. doi:10.3389/fpsyg.2014.01040

Shields, G. S., Bonner, J. C., & Moons, W. G. (2015). Does cortisol influence core executive functions? A meta-analysis of acute cortisol administration effects on working memory, inhibition, and set-shifting. *Psychoneuroendocrinology*, *58*, 91-103. doi:10.1016/j.psyneuen.2015.04.017

Shonkoff, J. P. (2010). Building a new biodevelopmental framework to guide the future of early childhood policy. *Child Development, 81*, 357-367. doi:10.1111/j.1467-8624.2009.01399.x

Siegel, J. M. (2005). Clues to the functions of mammalian sleep. *Nature*, *437*, 1264-1271. doi:10.1038/nature04285

Spassov, L., Curzi-Dascalova, L., Clairambault, J., Kauffmann, F., Eiselt, M., Medigue, C., & Peirano, P. (1994). Heart rate and heart rate variability during sleep in small-for-gestational age newborns. *Pediatric Research*, *35*, 500-504. doi:10.1203/00006450-199404000-00022

Späth-Schwalbe, E., Gofferje, M., Kern, W., Born, J., & Fehm, H. L. (1991). Sleep disruption alters nocturnal ACTH and cortisol secretory patterns. *Biological Psychiatry*, *29*, 575-584. doi:10.1016/0006-3223(91)90093-2

Stalder, T., Bäumler, D., Miller, R., Alexander, N., Kliegel, M., & Kirschbaum, C. (2013). The cortisol awakening response in infants: Ontogeny and associations with development-related variables. *Psychoneuroendocrinology, 38*, 552-559. doi:10.1016/j.psyneuen.2012.07.015

Stalder, T., Evans, P., Hucklebridge, F., & Clow, A. (2011). Associations between the cortisol awakening response and heart rate variability. *Psychoneuroendocrinology, 36*, 454-462. doi:10.1016/j.psyneuen.2010.07.020

Stalder, T., & Kirschbaum, C. (2012). Analysis of cortisol in hair—State of the art and future directions. *Brain, Behavior, & Immunity*, *26*, 1019-1029. doi:10.1016/j.bbi.2012.02.002

Stalder, T., Kirschbaum, C., Kudielka, B. M., Adam, E. K., Pruessner, J. C., Wüst, S., … Clow, A. (2016). Assessment of the cortisol awakening response: Expert consensus guidelines. *Psychoneuroendocrinology, 63*, 414–432. doi:10.1016/j.psyneuen.2015.10.010

Steiger, A. (2002). Sleep and the hypothalamo–pituitary–adrenocortical system. *Sleep Medicine Reviews*, *6*, 125-138. doi:10.1053/smrv.2001.0159

Steiger, A., Guldner, J., Hemmeter, U., Rothe, B., Wiedemann, K., & Holsboer, F. (1992). Effects of growth hormone-releasing hormone and somatostatin on sleep EEG and nocturnal hormone secretion in male controls. *Neuroendocrinology*, *56*, 566-573. doi:10.1159/000126275

Stein, P. K., & Pu, Y. (2012). Heart rate variability, sleep and sleep disorders. *Sleep Medicine Reviews*, *16*, 47-66. doi:10.1016/j.smrv.2011.02.005

Strang-Karlsson, S., Kajantie, E., Pesonen, A. K., Räikkönen, K., Hovi, P., Lahti, J., … Paavonen, E. J. (2010). Morningness propensity in young adults born prematurely: The Helsinki Study of Very Low Birth Weight Adults. *Chronobiology International*, *27*, 1829-1842. doi:10.3109/07420528.2010.512689

Stratakis, C. A., & Chrousos, G. P. (1995). Neuroendocrinology and pathophysiology of the stress system. *Annals of the New York Academy of Sciences*, *771*, 1-18. doi:10.1111/j.1749-6632.1995.tb44666.x

Swiss Federal Statistical Office. (2009). Veränderungen beim Zeitaufwand für Haus- und Familienarbeit: 1997-2007 [Changes in time expenditure for housework and family work: 1997-2007]. Retrieved from https://www.bfs.admin.ch/bfs/de/home/statistiken/querschnittsthemen/wohlfahrtsmessung/nutzung-gueter/nutzung-gueter/haus-familienarbeit.assetdetail.346965.html

Swiss Federal Statistical Office. (2013). Das Engagement der Väter in Haushalt und Familie [The commitment of fathers in household and family]. Retrieved from https://www.bfs.admin.ch/bfs/de/home/statistiken/querschnittsthemen/wohlfahrtsmessung/nutzung-gueter/nutzung-gueter/haus-familienarbeit.assetdetail.348982.html

Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. (1996). Heart rate variability: Standards of measurement, physiological interpretation, and clinical use. C*irculation*, *93*, 1043-1065. doi:10.1161/01.cir.93.5.1043

Thayer, J. F., & Lane, R. D. (2007). The role of vagal function in the risk for cardiovascular disease and mortality. *Biological Psychology, 74*, 224-242. doi:10.1016/j.biopsycho.2005.11.013

Thorn, L., Hucklebridge, F., Evans, P., & Clow, A. (2009). The cortisol awakening response, seasonality, stress and arousal: A study of trait and state influences. *Psychoneuroendocrinology, 3*4, 299-306. doi:10.1016/j.psyneuen.2008.11.005

Tononi, G., & Cirelli, C. (2006). Sleep function and synaptic homeostasis. *Sleep Medicine Reviews, 10*, 49-62. doi:10.1016/j.smrv.2005.05.002

Tsigos, C., & Chrousos, G. P. (2002). Hypothalamic–pituitary–adrenal axis, neuroendocrine factors and stress. *Journal of Psychosomatic Research*, *53*, 865-871. doi:10.1016/s0022-3999(02)00429-4

Tyrka, A. R., Wier, L., Price, L. H., Ross, N., Anderson, G. M., Wilkinson, C. W., & Carpenter, L. L. (2008). Childhood parental loss and adult hypothalamic-pituitary-adrenal function. *Biological Psychiatry*, *63*, 1147-1154. doi:10.1016/j.biopsych.2008.01.011

Ulrich-Lai, Y. M., & Herman, J. P. (2009). Neural regulation of endocrine and autonomic stress responses. *Nature Reviews Neuroscience, 10*, 397-409. doi:10.1038/nrn2647

Van den Bergh, B. R., van den Heuvel, M. I., Lahti, M., Braeken, M., de Rooij, S. R., Entringer, S., … Schwab, M. (in press). Prenatal developmental origins of behavior and mental health: The influence of maternal stress in pregnancy. *Neuroscience & Biobehavioral Reviews*. doi:10.1016/j.neubiorev.2017.07.003

Van den Hoogen, A., Teunis, C. J., Shellhaas, R. A., Pillen, S., Benders, M., & Dudink, J. (2017). How to improve sleep in a neonatal intensive care unit: A systematic review. *Early Human Development, 113*, 78-86. doi:10.1016/j.earlhumdev.2017.07.002

Wadsby, M., Nelson, N., Ingemansson, F., Samuelsson, S., & Leijon, I. (2014). Behaviour problems and cortisol levels in very-low-birth-weight children. *Nordic Journal of Psychiatry*, *68*, 626-632. doi:10.3109/08039488.2014.907341

Weber, C. S., Thayer, J. F., Rudat, M., Wirtz, P. H., Zimmermann-Viehoff, F., Thomas, A., … Deter, H. C. (2010). Low vagal tone is associated with impaired post stress recovery of cardiovascular, endocrine, and immune markers. *European Journal of Applied Physiology*, 109, 201-211. doi:10.1007/s00421-009-1341-x

Weichold, K., & Silbereisen, R. K. (2007). Positive Jugendentwicklung und Prävention [Positive adolescent development and prevention]. In B. Röhrle (Ed.), *Prävention und Gesundheitsförderung für Kinder und Jugendliche* [Prevention and health promotion for children and adolescents] (pp. 103-125). Tübingen, Germany: dgtv.

Weinstock, M., Poltyrev, T., Schorer-Apelbaum, D., Men, D., & McCarty, R. (1998). Effect of prenatal stress on plasma corticosterone and catecholamines in response to footshock in rats. *Physiology & Behavior*, *64*, 439-444. doi:10.1016/s0031-9384(98)00056-0

Wilhelm, I., Born, J., Kudielka, B. M., Schlotz, W., & Wüst, S. (2007). Is the cortisol awakening rise a response to awakening? *Psychoneuroendocrinology, 32*, 358-366. doi:10.1016/j.psyneuen.2007.01.008

Wuyts, J., De Valck, E., Vandekerckhove, M., Pattyn, N., Exadaktylos, V., Haex, B., … Cluydts, R. (2012). Effects of pre-sleep simulated on-call instructions on subsequent sleep. *Biological Psychology, 91*, 383-388. doi:10.1016/j.biopsycho.2012.09.003

Yiallourou, S. R., Witcombe, N. B., Sands, S. A., Walker, A. M., & Horne, R. S. (2013). The development of autonomic cardiovascular control is altered by preterm birth. *Early Human Development*, *89*, 145-152. doi:10.1016/j.earlhumdev.2012.09.009

Zhang, L. J., Wang, H. S., & Huang, X. N. (2010). Sleep patterns amongst Chinese children. *Biological Rhythm Research, 41*, 203-215. doi:10.1080/09291011003687965

# APPENDIX A: Study 1

Maurer, N., Perkinson-Gloor, N., Stalder, T., Hagmann-von Arx, P., Brand, S., Holsboer-Trachsler, E., Wellmann, S., Grob, A., Weber, P., & Lemola, S. (2016). Salivary and hair glucocorticoids and sleep in very preterm children during school age. *Psychoneuroendocrinology, 72*, 166-174.

Psychoneuroendocrinology 72 (2016) 166–174

Contents lists available at ScienceDirect

Psychoneuroendocrinology

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

# Salivary and hair glucocorticoids and sleep in very preterm children during school age

Natalie Maurer[a], Nadine Perkinson-Gloor[a], Tobias Stalder[b], Priska Hagmann-von Arx[a], Serge Brand[c,d], Edith Holsboer-Trachsler[c], Sven Wellmann[e], Alexander Grob[a], Peter Weber[f], Sakari Lemola[g,*]

[a] University of Basel, Department of Psychology, Basel, Switzerland
[b] Technische Universität Dresden, Department of Psychology, Dresden, Germany
[c] Psychiatric Clinics of the University of Basel, Center for Affective, Stress, and Sleep Disorders, Basel, Switzerland
[d] University of Basel, Faculty of Medicine, Department of Sport, Exercise and Health, Division Sport and Psychosocial Health, Basel, Switzerland
[e] University Children's Hospital Basel, Fetal and Neonatal Stress Research Group, Basel, Switzerland
[f] University Children's Hospital Basel, Division of Neuropediatrics and Developmental Medicine, Basel, Switzerland
[g] University of Warwick, Department of Psychology, University Road, Coventry CV4 7AL, United Kingdom

ARTICLE INFO

*Article history:*
Received 19 February 2016
Received in revised form 5 July 2016
Accepted 5 July 2016

*Keywords:*
Preterm birth
HPA axis activity
Glucocorticoids
Cortisol
Sleep electroencephalography
Sleep architecture

ABSTRACT

Very preterm birth involves increased stress for the child, which may lead to programming of the hypothalamic-pituitary-adrenal (HPA) axis activity and poor sleep in later life. Moreover, there is evidence for a relationship between HPA axis activity and sleep. However, research with objective sleep measures in very preterm children during school-age is rare. Eighty-five healthy children born very preterm (<32nd gestational week) and 91 full-term children aged 7–12 years were recruited for the present study. To assess HPA axis activity, salivary cortisol was measured at awakening, 10, 20, and 30 min later. In addition, hair cortisol and cortisone concentrations were quantified using liquid chromatography tandem mass spectrometry to assess cumulative endocrine activity over the preceding months. One night of in-home polysomnographic sleep assessment was conducted to assess sleep duration, sleep continuity, and sleep architecture. Children born very preterm showed significantly lower levels of cortisol at awakening and lower overall post-awakening cortisol secretion, lower cortisone in hair, and earlier sleep onset than full-term children. Across the whole sample, overall post-awakening cortisol secretion was positively related to sleep onset time and negatively to sleep duration. The association between prematurity status and post-awakening cortisol secretion was partially mediated by earlier sleep onset time. In conclusion, this study provides evidence for a possible down-regulation of the HPA axis activity and slightly earlier sleep phase in very preterm children during school age.



## 1. Introduction

The hypothalamic-pituitary-adrenal (HPA) axis controls adaptive reactions of the organism to stressors by managing the secretion of glucocorticoids including cortisol (Clements, 2013). Early life events may be involved in long-term programming of the HPA axis during fetal and early postnatal development (Kajantie and Räikkönen, 2010). One such early life event is very preterm birth, defined as live birth before 32 weeks of gestation are completed, which occurs in approximately 1–2% of all births world-wide (Child Trends, 2015) and involves increased risk for cognitive and psychosocial impairments across the life span (Aarnoudse-Moens et al., 2009; Lemola, 2015). Very preterm birth involves several adversities that could induce HPA axis programming: First, pregnancy-related aspects, such as maternal infections, inflammations, and prenatal stress, may influence both the risk of preterm birth and children's brain development (Buss et al., 2012; Goldenberg et al., 2008; Monk et al., 2016). Second, children born very preterm suffer from the immature functioning of the lungs, often leading to hypoxia (Saigal and Doyle, 2008) and the adrenal gland leading to potential adrenal insufficiency (Fernandez and Watterberg, 2009). Third, children born very preterm are exposed to many distressing medical procedures including blood draws

* Corresponding author.
*E-mail address:* s.lemola@warwick.ac.uk (S. Lemola).

http://dx.doi.org/10.1016/j.psyneuen.2016.07.003
0306-4530/

and mechanical ventilation (Anand, 2001; Brummelte et al., 2015; Grunau et al., 2007).

Studies with children born very preterm and animal models of early life adversities show similar HPA axis alterations – often involving persistent down-regulation of HPA axis activity (Feng et al., 2011; Kaseva et al., 2014). School aged children born very preterm or with very-low-birth-weight (VLBW; <1500 g) show lower diurnal cortisol profiles (Wadsby et al., 2014), faster decreasing cortisol levels in the evening (Perkinson-Gloor et al., 2015), and decreased salivary cortisol responses to social stress (Buske-Kirschbaum et al., 2007), which is also consistent with findings in adults (Kaseva et al., 2014). Relatedly, boys born very preterm exposed to more distressing medical procedures had lower diurnal cortisol levels at age 7 (Brummelte et al., 2015). Moreover, Grunau et al. (2013) reported lower hair cortisol levels in very preterm compared to full-term children. However, there are also conflicting data. For example, preterm born children were found to exhibit no differences regarding morning (Brummelte et al., 2015; Perkinson-Gloor et al., 2015), evening (Quesada et al., 2014), and diurnal cortisol profiles (Buske-Kirschbaum et al., 2007; Kaseva et al., 2014) and salivary cortisol responses to social stress (Brummelte et al., 2015; Buske-Kirschbaum et al., 2007), or even higher salivary cortisol levels at awakening (Buske-Kirschbaum et al., 2007; Quesada et al., 2014).

Beside trait factors, there are also more transient state factors that affect HPA axis function (Stalder et al., 2016). An important state factor affecting cortisol secretion after morning awakening is the duration and quality of sleep the preceding night (Elder et al., 2014; Lemola et al., 2015). Children with short and poor sleep had increased HPA axis activity after awakening (Fernandez-Mendoza et al., 2014; Pesonen et al., 2014; Räikkönen et al., 2010). Two studies examining the relationship between sleep architecture assessed by sleep-electroencephalography (EEG) and morning cortisol secretion showed increased morning cortisol secretion in children with short sleep duration, shorter relative amounts of slow wave sleep (SWS), longer relative amounts of light sleep (including stage 1 sleep and stage 2 sleep), and rapid-eye-movement (REM) sleep (Hatzinger et al., 2013; Lemola et al., 2015). Importantly, there is also evidence that sleep regulation is altered after preterm birth (Brooks and Canal, 2013) possibly leading to differences compared to term born peers during adolescence and young adulthood involving earlier bedtimes and circadian preference (Björkqvist et al., 2014; Hibbs et al., 2014; Strang-Karlsson et al., 2010). Moreover, poor sleep is also more prevalent in children born very preterm compared to full term peers including more sleep disordered breathing (Rosen et al., 2003), nocturnal awakenings, light sleep, and less SWS (Perkinson-Gloor et al., 2015).

Taken together, children born very preterm are at an increased risk for HPA axis alterations and poor sleep, which, in turn, are also likely to be interrelated. However, there are important gaps in knowledge and existing research is characterized by heterogeneous findings. Part of this may be due to methodological factors related to saliva sampling, which may be addressed by adhering to recent methodological recommendations (see Stalder et al., 2016). Applying a multi-method assessment strategy by additionally using the recently introduced method of hair steroid analysis, providing a stable and trait-like measure of integrated long-term cortisol secretion (Stalder and Kirschbaum, 2012) may further allow to examine whether findings from saliva measures can be corroborated. In addition, research examining the complex links between very preterm birth, morning cortisol secretion, and sleep alterations during the preceding night is important for resolving the apparent paradox that poor sleep was related to increased HPA axis activity (e.g. Fernandez-Mendoza et al., 2014), while children born very preterm often showed both poor sleep and decreased HPA axis activity (e.g. Wadsby et al., 2014).

The present study thus tested the following hypotheses: First, we hypothesized that HPA axis activity, assessed through post-awakening cortisol and hair cortisol and cortisone, is decreased in children born very preterm compared to full-term children. Moderation of these associations by sex was also examined, given previous findings on sex differences in HPA axis activity. Further, additional analyses tested associations of birth weight and gestational age with HPA axis activity within the group of very preterm children expecting decreasing HPA axis activity the earlier gestation children were born. Second, we hypothesized that earlier sleep times and poorer sleep (more nocturnal awakenings, more light sleep, and less SWS) would be found in children born very preterm compared to full-term children. Third, we hypothesized that post-awakening cortisol would be negatively associated with sleep duration, sleep continuity (including higher sleep efficiency and less nocturnal awakenings), and SWS and positively associated with light sleep and REM-sleep. Finally, we examined whether differences in sleep of the preceding night accounted for differences in post-awakening cortisol secretion between children born very preterm and full-term.

## 2. Methods

### 2.1. Study population

Between May 2013 and August 2014, 85 healthy very preterm children (<32nd gestational week; age: $M = 9.5$ years, $SD = 1.4$; range: 7.4–12.4) and 91 full-term children (age: $M = 9.6$, $SD = 1.4$; range: 6.9–13.0) were recruited for the present study, which was the second wave of a longitudinal study on very preterm birth, HPA axis activity, and sleep (see e.g. Perkinson-Gloor et al., 2015; Lemola et al., 2015 for reports on the first study wave). Due to dropout

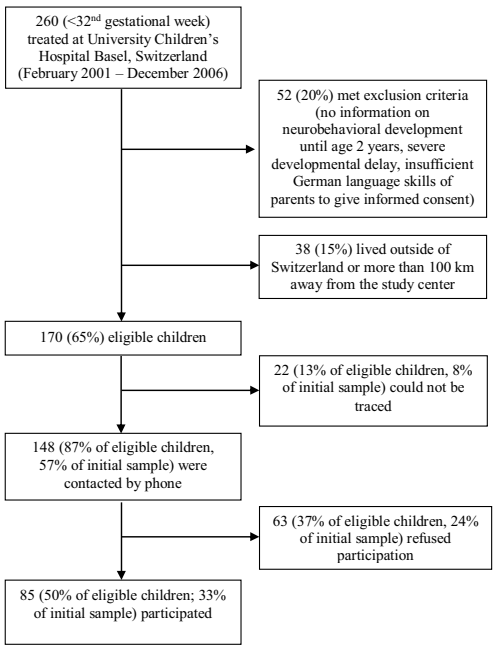



**Fig. 1.** Inclusion procedure of very preterm children.

from and resampling after the first study wave the present sample was only partially overlapping with the sample of the first wave. In the present sample 46 (54.1%) of the very preterm children and 43 (47.3%) of the full-term children already participated in the first study wave, while 39 (45.9%) of the very preterm and 48 (52.7%) of the full-term children were newly recruited for the second wave.

Very preterm children were recruited from an initial cohort of 260 prematurely born children treated at the University Children's Hospital Basel (Switzerland) between June 2001 and December 2006. Fifty-two (20.0%) of the 260 very preterm children met the exclusion criteria; no information on neurobehavioral development until age 2 years ($n = 39$), severe developmental delay ($n = 7$), insufficient German language skills of parents to give informed consent ($n = 6$). Further 38 (14.6%) very preterm children lived outside of Switzerland or too distant from the study center (>100 km). Of the remaining 170 eligible very preterm children, 22 (12.9% of eligible children) could not be traced. Thus, 148 (87.1% of the eligible children, 56.9% of the initial sample) were contacted by phone and 85 (50.0% of eligible children, 32.7% of initial cohort) agreed to participate in the current study (Fig.1). Participating preterm children did not differ from non-participants with regard to birth weight (1325 g vs. 1260 g, $F(1,257) = 1.52$, $p = 0.219$), gestational age (29.7 weeks vs. 29.5 weeks, $F(1,258) = 0.98$, $p = 0.323$), and length of hospital stay (51.8 days vs. 53.3 days, $F(1,224) = 0.21$, $p = 0.649$). Four (4.7%) out of 85 children born very preterm were born small for gestational age (SGA). The sample characteristics are presented in Table 1.

The 91 full-term children (>37 weeks of gestation) were recruited from official birth notifications. The samples were comparable regarding age and sex. All children attended primary or secondary school in Switzerland. Five very preterm children and one full-term child received additional support at school (e.g. by a remedial teacher) or visited small group classes.

Post-hoc power analysis using G*Power was performed to evaluate the statistical power given the sample size of the study (Faul et al., 2007). Regarding mean differences between very preterm and full-term children the chance of detecting effects of medium size ($d = 0.50$) was 91% at a 0.05 alpha level (two-sided). Regarding correlations between two variables, the power analyses indicated a 99% chance of detecting effects of medium size ($r = 0.30$) at a 0.05 alpha level (two-sided; based on the total sample size). Therefore, we considered the study to be sufficiently powered to detect medium size effects (Cohen, 1988).

### 2.2. Procedure

Trained study personnel visited the children at home on a regular school day to administer in-home sleep-EEG, collect hair samples, and instruct parents on how to collect saliva samples the following morning. Parents completed questionnaires to assess demographic data. From the medical files of the University Children's Hospital Basel information on neonatal health of the very preterm children was obtained. Assent was obtained from the children and parents gave written informed consent for the children to participate. 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.

### 2.3. Variables

#### 2.3.1. Assessment of post-awakening cortisol secretion

To assess post-awakening cortisol secretion, parents were instructed to collect four saliva samples from their children at 0, 10, 20, and 30 min after the child's awakening. Parents were instructed that their children were not allowed to eat or drink and brush their teeth until saliva sampling was completed. Awakening times ranged from 0501 h to 0730 h ($M = 0635$ h, $SD = 22$ min). Due to home visits being conducted on a Friday in four children, these had later awakening times on the following Saturday morning. However, analyses examining salivary cortisol and sleep did not differ when these children were excluded, therefore they were included in the sample used for analyses. Saliva samples were collected using the "Salivette" device (Sarstedt, Nümbrecht/Germany). 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).

The statistical analyses strived to follow published guidelines on post-awakening cortisol assessment (Stalder et al., 2016). Specifically, three measures were computed to quantify different aspects of post-awakening cortisol secretion: the level of cortisol on awakening (S1), the area-under-the-curve with respect to increase ($AUC_I$) and with respect to ground ($AUC_G$; Pruessner et al., 2003). To deal with outliers, salivary variables were log-transformed before building $AUC_G$ and $AUC_I$. S1 was interpreted as the endpoint of the pre-awakening cortisol increase and the $AUC_I$ was interpreted as reflecting the cortisol awakening response (CAR; the CAR is viewed as a normal part of the human circadian rhythm in which cor-

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

| | Very preterm (n = 85) | | Full-term (n = 91) | | *P* |
|---|---|---|---|---|---|
| | M/N | (SD/%) | M/N | (SD/%) | |
| Age, years | 9.5 | (1.4) | 9.6 | (1.4) | 0.755 |
| Sex, male | 51 | (60.0) | 51 | (56.0) | 0.595 |
| Gestational age, weeks | 29.7 | (2.0) | 39.5 | (1.5) | <0.001 |
| Birth weight, grams | 1325.1 | (407.4) | 3307.5 | (443.9) | <0.001 |
| Prenatal treatment with glucocorticoids | 57 | (67.1) | 0 | (0.0) | <0.001 |
| Postnatal treatment with glucocorticoids | 7 | (8.2) | 0 | (0.0) | 0.005 |
| Ventilation | 33 | (38.8) | 0 | (0.0) | <0.001 |
| Intubation | 25 | (29.4) | 0 | (0.0) | <0.001 |
| Continuous positive airway pressure | 63 | (74.1) | 0 | (0.0) | <0.001 |
| Infant respiratory distress syndrome | 69 | (81.2) | 0 | (0.0) | <0.001 |
| Apnea of Prematurity | 66 | (77.6) | 0 | (0.0) | <0.001 |
| Bronchopulmonary Dysplasia | 7 | (8.2) | 0 | (0.0) | 0.005 |
| First language (German) | 56 | (72.7) | 78 | (86.7) | 0.024 |
| Maternal education | | | | | <0.001 |
| No vocational training | 9 | (10.6) | 1 | (1.1) | |
| Vocational training | 52 | (62.4) | 40 | (44.0) | |
| University | 19 | (22.4) | 47 | (51.6) | |

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

tisol levels increase across the first 30–40 min after awakening; Stalder et al., 2016). The $AUC_G$ was viewed as an additional estimate of overall post-awakening cortisol secretion (Stalder et al., 2016). Cortisol values were skewed and data were thus log-transformed before computing composite measures. Finally, as suggested by the guidelines, additional analyses were run in which available PSG data were utilized to compare parent-reported light-on-times to objectively measured awakening times. In these additional analyses, the main analytical strategy (see below) was repeated after exclusion of children with a discrepancy between parent-reported cortisol sampling time and objective PSG-based awakening time of more than 5 min ('parent reported light-on-time' – 'in-home PSG awakening time' >5 min; Stalder et al., 2016). After exclusion of these children, the findings of the additional analyses were equal regarding significance and effect size (data not shown).

#### 2.3.2. Assessment of hair glucocorticoids

Trained study personnel cut hair strands (3 mm diameter, minimum: 3 cm length) with fine scissors at the base of the hair shaft from a *posterior vertex* position from 2 small spots. Hair samples were labeled, secured on aluminum foil and stored in a dark and dry cupboard at room temperature until analyses. A first part of 38 hair samples (23.3% of the cohort) were sent to and analyzed in the laboratory of TU Dresden, Germany in autumn 2013, the other 125 hair samples (76.7% of the cohort) in autumn 2014. Hair cortisol and cortisone concentrations were determined from scalp-near 3 cm hair segments using liquid chromatography tandem mass spectrometry (LC–MS/MS), which is considered the current gold standard method for hair steroid analysis (Gao et al., 2016). Wash and steroid extraction procedures followed the protocol described in Stalder et al. (2012 with minor adaptations. Briefly, samples were washed twice in 3 ml isopropanol for 3 min. For glucocorticoid extraction 7.5 mg of hair were incubated with 1.8 ml of methanol for 18 h at room temperature. The methanol was evaporated at 50 °C under a constant stream of nitrogen until the samples were completely dried. The dry residue was resuspended using 175 μl double-distilled water. 100 μl were used for analysis by a Shimadzu HPLC-tandem mass spectrometry system (Shimadzu, Canby, Oregon, USA) coupled to an ABSciex API 5000 Turboion-spray triple quadrupole tandem mass spectrometer (AB Sciex, Foster City, California) with purification by on-line solid-phase extraction. Intra and interassay coefficients of variance for hair cortisol and cortisone have been shown to be between 3.7–8.8% (Gao et al., 2013). Outliers in hair glucocorticoid variables were truncated to a value of 2 interquartile ranges above the median.

#### 2.3.3. Sleep assessment

Sleep was assessed using in-home PSG during a single night at the children's home. In-home EEG was used to minimize the differences between the child's usual sleep conditions and the conditions during the study night. Using the Compumedics Somté PSG, polysomnogram signals C3/A2 and C4/A1 EEG, right and left electrooculogram and bipolar submental electromyogram were obtained. Two experienced raters visually analyzed the EEG reports according to the standard procedures (Rechtschaffen and Kales, 1968). The following sleep indices were evaluated: Sleep continuity: Sleep duration (the total sleep time, i.e., the time in bed minus time spent awake in hours), sleep efficiency (sleep duration/time in bed × 100), and nocturnal awakenings (number of arousals from sleep). Sleep architecture (%): Stage 1 sleep, stage 2 sleep, SWS (SWS: Stages 3 and 4 sleep), REM sleep, and REM latency (min). In addition parents completed a short sleep questionnaire for the night of the EEG assessment and reported the child's awakening time. After one outlier of bedtime was winsorized to a value of 2 interquartile ranges above the median, bedtime ranged from 1940 h to 2310 h ($M$ = 2119 h, $SD$ = 39 min). Polysomnographic sleep data was available for 58 (68.2%) very preterm and 85 (93.4%) full-term children. As there were no differences in salivary cortisol measures between participants and non-participants of the PSG-sleep assessment (all $p$-values > 0.10) participation on the PSG should not have strongly affected our findings. For 126 (71.6%) children both sleep and post-awakening cortisol was available (very preterm: 51 (60.0%); full-term: 75 (82.4%)).

### 2.4. Control variables

All analyses were controlled for first language, maternal education, children's age, and sex if not stated otherwise. Analyses involving salivary cortisol were additionally controlled for awakening time as measured by polysomnography and analyses involving hair cortisol variables were additionally controlled for the time point of the lab analyses (i.e., if the analysis took place in autumn 2013 or in autumn 2014). Due to the extended time period of the study assessment, analyses with HPA axis activity were additionally controlled for season (Stalder et al., 2016). All statistical analyses were performed with IBM® SPSS® Statistics 22 (IBM Corporation, Armonk NY, USA) for Apple Mac®.

## 3. Results

### 3.1. Preliminary analyses

First, preliminary analyses were conducted to describe the CAR and to assess associations of salivary and hair glucocorticoids and sleep measures with trait and state factors that possibly affect HPA axis activity and sleep including age, sex, familial demographic background, season of assessment, and pre- and postnatal treatments.

An increase in cortisol secretion over the post-awakening period (i.e. defined as 'fourth salivary sample' – 'first salivary sample' >1.5 nmol/L; Miller et al., 2013), indicating a cortisol awakening response, was observed in 107 (69.9%) children. The first sample on awakening (S1) was positively related to child age ($r$ = 0.17, $p$ = 0.037) and female sex ($F(1,138)$ = 4.52, $p$ = 0.035, $d$ = 0.36). Moreover, the post-awakening $AUC_G$ was positively related to child age ($r$ = 0.19, $p$ = 0.020). The examination of associations with hair glucocorticoid concentrations revealed a negative association between hair cortisone and child age ($r$ = −0.16, $p$ = 0.041) and boys had significantly higher hair cortisol ($F(1,149)$ = 5.14, $p$ = 0.025, $d$ = 0.37) and cortisone levels ($F(1,149)$ = 11.29, $p$ < 0.001, $d$ = 0.54) than girls. No associations between familial demographic background (i.e., maternal education and language) and HPA axis variables were found. Regarding season of assessment, a higher CAR ($AUC_I$) was found in children tested during the winter season compared to the other seasons ($F(1,120)$ = 8.28, $p$ = 0.005, $d$ = 0.83). Regarding pre- and postnatal treatments, 57 out of 85 (67.1%) very preterm infants had received prenatal steroids (e.g. dexamethasone, betamethasone, prednisone) and only 7 out of 85 (8.2%) very preterm infants had received postnatal steroids (budesonide). We did not observe significant correlations of prenatal steroid treatments, ventilation, intubation, and continuous positive airway pressure (CPAP) with any salivary or hair glucocorticoid measure (all p-values > 0.10). As only 7 children were exposed to postnatal steroid treatment, this variable was not analyzed.

Sleep duration was negatively associated with child age ($r$ = −0.47, $p$ < 0.001) and boys showed longer REM sleep latency than girls ($t(141)$ = 2.43, $p$ = 0.016, $d$ = 0.41). No other significant relations between sleep measures and child age and sex and familial demographic background were observed (all $p$-values > 0.10).

**Table 2**
Salivary cortisol, hair glucocorticoids, and sleep in very preterm and full-term children.

| | Very preterm | | Full-term | | *d* | *P* |
|---|---|---|---|---|---|---|
| | M | (SD) | M | (SD) | | |
| Salivary morning cortisol secretion[a] | | | | | | |
| $AUC_G$ | 0.5 | (0.1) | 0.5 | (0.1) | 0.45 | 0.011 |
| $AUC_I$ | 0.6 | (0.1) | 0.6 | (0.1) | 0.02 | 0.927 |
| First sample (S1) | 0.8 | (0.2) | 0.9 | (0.2) | 0.35 | 0.049 |
| Second sample | 0.9 | (0.2) | 1.0 | (0.2) | 0.38 | 0.031 |
| Third sample | 1.0 | (0.2) | 1.1 | (0.2) | 0.48 | 0.008 |
| Fourth sample | 1.0 | (0.4) | 1.1 | (0.2) | 0.21 | 0.228 |
| Hair variables[b] | | | | | | |
| Cortisol | 2.0 | (2.1) | 1.9 | (1.8) | 0.07 | 0.672 |
| Cortisone | 8.7 | (6.7) | 10.9 | (7.7) | 0.52 | 0.002 |
| Sleep variables[c] | | | | | | |
| Sleep onset time | 21:11 | (0:40) | 21:24 | (0:38) | 0.44 | 0.013 |
| Awakening time | 6:34 | (0:26) | 6:35 | (0:21) | 0.03 | 0.872 |
| Sleep duration (h) | 9.0 | (0.7) | 8.9 | (0.7) | 0.33 | 0.066 |
| Sleep efficiency (%) | 93.1 | (3.0) | 93.6 | (2.8) | 0.03 | 0.849 |
| Nocturnal awakenings (number) | 17.2 | (7.7) | 15.0 | (6.2) | 0.23 | 0.194 |
| Stage 1 sleep (%) | 3.9 | (2.4) | 3.3 | (2.3) | 0.17 | 0.327 |
| Stage 2 sleep (%) | 46.8 | (5.1) | 48.0 | (4.9) | 0.19 | 0.275 |
| Slow wave sleep (%) | 21.3 | (5.1) | 21.5 | (4.6) | 0.05 | 0.781 |
| REM sleep (%) | 25.5 | (4.1) | 24.7 | (3.7) | 0.20 | 0.257 |
| REM latency (min) | 116.7 | (45.0) | 108.1 | (40.7) | 0.25 | 0.159 |

*Note*: $AUC_G$: area-under-the-concentration-time-curve with respect to the ground, $AUC_I$: area-under-the-concentration-time-curve with respect to the increase, REM: rapid eye movement.

[a] Log-transformed before building $AUC_G$/$AUC_I$; adjusted for first language, maternal education, children's age, sex, season, and awakening time.

[b] Truncated to a value of 2 interquartile ranges above the median; adjusted for first language, maternal education, children's age, sex, season, and time point of the lab analyses.

[c] Cohen's *d*, *P*-values: z-standardized data; adjusted for first language, maternal education, children's age, and sex.

### *3.2. Differences in salivary and hair glucocorticoids between very preterm and full-term children and associations with birth weight and gestational age*

To test our first hypothesis that children born very preterm show decreased HPA axis activity compared to full-term children, we performed analyses of covariance (ANCOVA) with salivary morning cortisol and hair cortisol and cortisone as dependent variables. Table 2 shows the results of these ANCOVAs. Children born very preterm showed a lower S1 ($F(1,140) = 3.93$, $p = 0.049$, $d = 0.35$) and $AUC_G$ ($F(1,138) = 6.58$, $p = 0.011$, $d = 0.45$) than full-term children. There were no mean differences in the CAR ($AUC_I$) between very preterm and full-term children. Fig. 2 depicts the patterns of post-awakening cortisol secretion for the two groups. Very preterm children showed lower hair cortisone concentrations ($F(1,149) = 9.52$, $p = 0.002$, $d = 0.52$) than full-term children. There were no mean differences in hair cortisol between very preterm and full-term children. Moreover, there was no evidence for moderation of the relationship between prematurity status and HPA axis variables by sex (data not shown).

In additional analyses we tested whether birth weight and gestational age were positively related to salivary and hair glucocorticoids within the group of very preterm children applying multiple regression analyses. Neither birth weight nor gestational age were related to salivary cortisol (all *p*-values > 0.10). Higher birth weight was at trend level related to higher hair cortisol ($\beta = 0.21$, $t = 1.95$, $p = 0.055$) and hair cortisone concentrations ($\beta = 0.20$, $t = 1.96$, $p = 0.055$), while higher gestational age was at trend level associated with higher cortisone levels in hair ($\beta = 0.18$, $t = 1.79$, $p = 0.078$).

### *3.3. Differences in sleep measures between very preterm and full-term children and associations with birth weight and gestational age*

To test our second hypothesis that very preterm children show earlier sleep onset and poorer sleep compared to full-term children, we performed ANCOVA with objective sleep measures assessed by PSG as dependent variables. Table 2 shows the results of these ANCOVAs. Very preterm children had a significantly earlier sleep onset time compared to full-term children (very preterm children: $M = 2111$ h; full-term children: $M = 2124$ h; $F(1,134) = 6.29$, $p = 0.013$, $d = 0.44$), while there were no significant differences in awakening times (very preterm children: $M = 0634$ h; full-term children: $M = 0635$ h; $F(1,134) = 0.03$, $p = 0.872$, $d = 0.03$) and a trend towards longer sleep duration ($F(1,134) = 3.44$, $p = 0.066$, $d = 0.33$). There were no mean differences in sleep efficiency and sleep architecture between very preterm and full-term children (all p-values > 0.10). Moreover, we tested if sex moderated the relationship between prematurity status and sleep variables. More nocturnal awakenings were found in very preterm girls compared to full-term girls but not between very preterm and full-term boys (girls: $F(1,51) = 4.09$, $p = 0.048$, $d = 0.56$; boys: $F(1,76) = 0.06$, $p = 0.801$, $d = 0.06$); prematurity status × sex interaction: $F(1,133) = 4.49$, $p = 0.036$.

In additional analyses we tested whether birth weight and gestational age were related to sleep variables within the group of very preterm children applying multiple regression analyses. Within the subsample of very preterm children, neither birth weight nor gestational age were significantly related to sleep variables, although higher birth weight and gestational age tended to be related to higher sleep efficiency (birth weight: $\beta = 0.266$, $t = 1.80$, $p = 0.078$; gestational age: $\beta = 0.255$, $t = 1.75$, $p = 0.087$).

### *3.4. Associations of post-awakening cortisol with objective sleep measures*

To test our third hypothesis that salivary post-awakening cortisol secretion is associated with objective sleep measures, hierarchical regression analyses were conducted with post-awakening cortisol secretion measures as dependent variables. Table 3 shows the results of these analyses. The post-awakening $AUC_G$ was positively associated with sleep onset time ($\beta = 0.36$, $t = 3.57$, $p < 0.001$) and negatively associated with sleep duration ($\beta = -0.34$, $t = -3.42$,

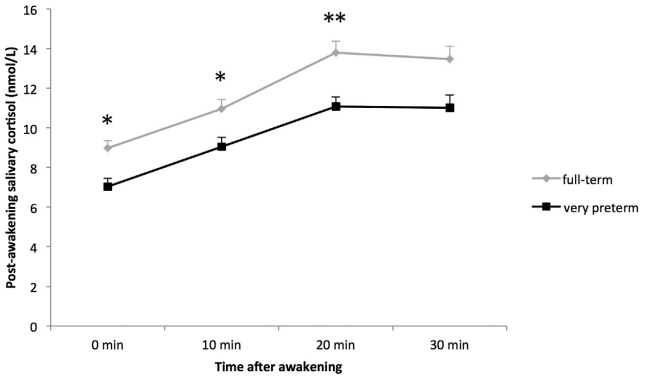



**Fig. 2.** Post-awakening salivary cortisol secretion of very preterm and full-term children.*p < .05, **p < .01 (two-tailed).

**Table 3**
Multiple regression results with sleep parameters predicting post-awakening cortisol measures.

| Sleep variables[a] | Post-awakening cortisol secretion | | |
|---|---|---|---|
| | First sample (S1) | $AUC_I$ | $AUC_G$ |
| Sleep onset time | 0.18† | 0.13 | 0.36*** |
| Awakening time[b] | −0.13 | 0.15† | −0.03 |
| Sleep duration (h) | −0.18† | −0.11 | −0.34*** |
| Sleep efficiency | −0.02 | 0.05 | 0.03 |
| Nocturnal awakenings | −0.01 | 0.00 | −0.01 |
| Stage 1 sleep (%) | 0.16† | −0.11 | 0.11 |
| Stage 2 sleep (%) | −0.04 | 0.07 | 0.01 |
| Slow wave sleep (%) | −0.05 | 0.00 | −0.07 |
| REM sleep (%) | 0.04 | 0.00 | 0.04 |
| REM latency (min) | −0.10 | −0.08 | −0.20* |

*Note*: Data are standardized regression coefficients. $AUC_G$: area-under-the-concentration-time-curve with respect to the ground, $AUC_I$: area-under-the-concentration-time-curve with respect to the increase, REM: rapid eye movement.

† p < 0.10.
* p < 0.05.
*** p < 0.001 (two-tailed).
[a] Adjusted for children's age, sex, season, prematurity status, and awakening time.
[b] Adjusted for children's age, sex, season, and prematurity status.

$p < 0.001$) and REM latency ($\beta = -0.20$, $t = -2.30$, $p = 0.023$). Sleep efficiency, nocturnal awakenings, stage 2 sleep, SWS, and REM sleep were unrelated with post-awakening $AUC_G$. In addition, none of the sleep variables were significantly associated with S1 and the post-awakening CAR ($AUC_I$). Moreover, there was no evidence for moderation of the relationship between objective sleep measures and indices of post-awakening cortisol secretion by prematurity status or sex (data not shown).

### 3.5. Mediation of the relationship between prematurity status and post-awakening cortisol secretion by sleep

Finally, we examined whether differences in sleep of the preceding night accounted for differences in post-awakening cortisol secretion between children born very preterm and full-term. Mediation was tested applying a bootstrapping approach using the INDIRECT procedure (Preacher and Hayes, 2008). Sleep onset time was the only sleep variable that was significantly associated with the independent variable (prematurity status: B = −0.40, $SE = 0.18$, $t = -2.25$, $p = 0.027$) and an outcome variable (with post-awakening cortisol secretion $AUC_G$: B = 0.36, $SE = 0.10$, $t = 3.57$, $p < 0.001$ controlling children's age, sex, awakening-time, and season of assessment; both independent and outcome variable were z-standardized prior to analyses to improve interpretability). The indirect path via sleep onset time on $AUC_G$ was significant (B = −0.14; 95% bootstrap bias-corrected confidence interval from −0.35 to −0.03). Moreover, the association of prematurity status with $AUC_G$ was partially attenuated when sleep onset time was additionally controlled which is consistent with partial mediation (from B = −0.52, $SE = 0.18$, $t = -2.95$, $p = 0.004$ to B = −0.36, $SE = 0.18$ $t = -2.01$, $p = 0.047$).

## 4. Discussion

This is the first study that focused on differences in HPA axis activity between very preterm and full-term children examining the role of sleep measured with in-home PSG. Our key findings are that very preterm birth was related to lower post-awakening cortisol levels and decreased cortisone in hair, suggesting decreased HPA axis activity. In addition, earlier sleep onset time and longer sleep duration were associated with lower post-awakening cortisol secretion. Earlier sleep onset time partially mediated the association between prematurity status and post-awakening cortisol secretion.

### 4.1. Differences in salivary and hair glucocorticoids between very preterm and full-term children

First, we expected decreased HPA axis activity among very preterm compared to full-term children, which was partially sup-

ported by the data. Compared to full-term children, very preterm children showed lower post-awakening S1 and $AUC_G$, which is consistent with prior studies reporting down-regulation of HPA axis activity in very preterm children (Kaseva et al., 2014; Perkinson-Gloor et al., 2015; Wadsby et al., 2014). Also consistent with down-regulation of the HPA axis in very preterm children, we found lower hair cortisone, but not hair cortisol, levels in very preterm compared to full-term children, which is similar to a study reporting lower hair cortisol in preterm children (Grunau et al., 2013). The finding that only hair cortisone, but not cortisol, was related to preterm birth in the present study is difficult to interpret. It has been proposed that cortisone concentrations in hair may arise through local cortisol-to-cortisone conversion by the enzyme 11-beta-hydroxysteroid dehydrogenase type 2 and thus may reflect systemically circulating cortisol concentrations. Moreover, hair cortisone might even yield more reliable estimates of cumulative HPA axis activity than hair cortisol, as often highly outlying hair cortisol concentrations are found in a minority of the samples, which decreases reliability (see Stalder et al., 2013; for a more detailed discussion).

A first mechanism which may contribute to down-regulation of HPA axis activity in very preterm children may be long-term habituation related to prolonged exposure to stress during the postnatal phase involving medical complications and distressing treatments related to premature birth (Kaseva et al., 2014; Wadsby et al., 2014). Consistent with these findings, one study reported lower cortisol levels in school-age children who had more neonatal pain and stress related to a higher number of skin-breaking procedures after birth compared to children with less skin-breaking procedures (Brummelte et al., 2015). A second explanation may be pre- and neonatal therapeutic exposure to glucocorticoids, especially dexamethasone, which may possibly lead to down-regulation of the HPA axis activity in very preterm children (Karemaker et al., 2008). Decreased cortisol secretion after postnatal treatment with dexamethasone could however not be confirmed by Grunau et al. (2007) who studied basal salivary cortisol in preterm children aged 6, 8, and 18 months. Similarly, we found no significant association between pre- and neonatal treatments (including prenatal glucocorticoids, ventilation, intubation, and CPAP) and later HPA axis activity in the present study. Further possible mechanisms contributing to alteration of HPA axis activity include immaturity of the adrenal gland in very preterm children leading to adrenal insufficiency (Fernandez and Watterberg, 2009) as well as pregnancy related aspects, such as maternal infections, inflammations, and prenatal stress, which may increase the risk of preterm birth and neurodevelopmental alterations (Buss et al., 2012; Goldenberg et al., 2008).

However, there are also studies with contrasting results. Two prior studies for instance found higher cortisol levels right at awakening in preterm compared to full-term children aged 8–12 years (Buske-Kirschbaum et al., 2007), particularly in girls (Quesada et al., 2014). There are three possibly relevant factors for these inconsistent findings.

A first possibly relevant factor is related to differences in birth weight/gestational age. Buske-Kirschbaum et al. (2007) and Quesada et al. (2014) also included moderately preterm children (gestational age between 32nd and 36th week) while the present study only included very preterm children. Though speculative, it is possible that there is a negative relationship between birth weight(/gestational age) and HPA axis activity above a certain level of birth weight(/gestational age) – as it was for instance found for boys with a birth weight between 2600 g–4200 g (Jones et al., 2006) – while this relationship becomes inverted below this level of birth weight(/gestational age), such that in children below a birth weight of around 2000 g(/32nd gestational week) there is a positive relationship between birth weight(/gestational age) and HPA axis activity indicating down-regulation of the HPA axis with increasing degree of prematurity. As there were no children born moderately preterm in the current study we could not test this assumption. In a similar vein, the inconsistency in previous research might be related to the number of SGA children in the sample. While for instance in our study only 4 out of 85 very preterm children were born SGA, this ratio was considerably higher in Quesada et al. (2014) with 9 out of 30 preterm children.

A second possibly relevant factor for these inconsistent findings is related to sex differences. In general, sex differences in HPA axis activity have often been reported. Consistent with our study, Grunau et al. (2013) for instance found higher hair cortisol in boys. Important for differences between preterm and full-term children, Quesada et al. (2014) found moderation of the association between prematurity status and HPA axis activity by sex – preterm girls had higher awakening cortisol levels than full-term girls but no such differences were found in boys. In our study there were somewhat more boys than girls (58% vs 42%) which might bias our overall findings towards effects in boys. As we found no moderation of the effects of prematurity status by sex, we however do not favor this explanation.

A third possibly relevant factor for these inconsistent findings is related to differences in stress exposure and medical treatments for preterm children. Different treatment regimens at different study sites may lead to differential effects on HPA axis activity. Taken together, divergent findings regarding HPA axis activity in children of prior studies may be due to differences in gestational age and birth weight, sex, and different treatment regimens in the pre- and early postnatal phase in different samples.

### 4.2. Differences in sleep between very preterm and full-term children

Second, we expected earlier sleep onset times and poorer sleep patterns in very preterm compared to full-term children. We could confirm that very preterm children had earlier sleep onset times compared to term-born children. This finding is consistent with results from Björkqvist et al. (2014), Hibbs et al. (2014), and Strang-Karlsson et al. (2010), who also found earlier sleep onset times and more morningness (i.e., the characteristic of being most active and alert during the morning) in adolescents and adults born very preterm or with very low birth weight. In contrast to the findings from the prior wave of our study when children were approximately two years younger (Perkinson-Gloor et al., 2015), we could not confirm more stage 2 sleep and less SWS in very preterm compared to full-term children in the present study wave. Between middle childhood and early adolescence sleep architecture greatly develops involving decreases in SWS and REM sleep and increases in stage 1 and stage 2 sleep (Ohayon et al., 2004). It is possible that these changes in sleep architecture during late childhood may have led to the convergence of the sleep architecture between very preterm and full-term children. However, we found that very preterm girls had more nocturnal awakenings than full-term girls while no such difference was found in boys. In the prior study wave, very preterm children also showed more nocturnal awakenings but no sex differences were found (Perkinson-Gloor et al., 2015; Lemola et al., 2015).

### 4.3. Associations of post awakening cortisol with objective sleep

Third, we hypothesized post-awakening cortisol to be negatively associated with sleep duration, sleep continuity (as represented by higher sleep efficiency and less nocturnal awakenings), and SWS and to be positively associated with light sleep and REM-sleep. Data did partially support this assumption in that increased post-awakening $AUC_G$ was associated with shorter sleep

duration. This is consistent with studies showing increased HPA axis activity to be associated with short sleep (Fernandez-Mendoza et al., 2014; Lemola et al., 2015; Räikkönen et al., 2010). In addition, we found that post-awakening $AUC_G$ was positively related to sleep onset time and negatively associated with REM latency. However, no relationship of post-awakening cortisol with sleep continuity, SWS, and REM-sleep was found. Again, it is possible that the prior findings (Hatzinger et al., 2013; Lemola et al., 2015) could not be replicated due to older age of the children in the present study.

### *4.4. Mediation of the relationship between prematurity status and post-awakening cortisol secretion by sleep*

We further explored the research question if differences in sleep of the preceding night accounted for differences in post-awakening cortisol secretion between very preterm and full-term children. Partial mediation of the effect of prematurity status on decreased post-awakening cortisol secretion by earlier sleep onset time was found. It is therefore possible that decreased HPA axis activity and early sleep onset time (i.e. morningness) – phenomena which both have often been reported in very preterm children (e.g. Hibbs et al., 2014; Kaseva et al., 2014) – share a common etiology. Having said that, one has to bear in mind that the difference in sleep onset time between very preterm and full-term children was only 13 min in the present study which reflects a modest to moderate effect size ($d = 0.44$). Moreover, based on our data it remains impossible to settle the question regarding the direction of causality.

### *4.5. Strengths and limitations*

Our study has some limitations. First, we cannot draw conclusions regarding causal relations due to the correlative study design. Second, salivary cortisol was only measured on a single day, which may reduce reliability and decrease the power to find positive results. As single day measurement does not introduce systematic error, this may be regarded as less problematic for the interpretation of positive findings than confounding by systematically covarying state factors introducing systematic error (see Stalder et al., 2016; for a detailed discussion). Third, we have no objective information on participants' compliance regarding the instructions of saliva collection, which may also reduce reliability of the morning cortisol secretion indices (Stalder et al., 2016). Future research may avoid this limitation by saliva sampling with electronic time stamp. Fourth, pubertal stage and menstrual cycle, which can both affect post-awakening cortisol secretion, were not assessed. Finally, there are several other factors that may have a long-term influence on children's HPA axis activity that could not be controlled such as maternal stress and socioeconomic status of the family during pregnancy and children's concurrent psychosocial stress.

Among the strengths of our study, sleep assessment was conducted at the children's home by PSG which allowed studying the relationship between HPA axis activity and the sleep pattern of the preceding night as well as controlling for objectively measured awakening times. Moreover, we also consider it a strength of the study that HPA axis activity was measured in both saliva, which informs on the acute HPA axis activity, and in hair by which cumulative HPA axis activity across the preceding months can be assessed.

## 5. Conclusions

In conclusion, our study suggests that children born very preterm have lower levels of cortisol at awakening and lower overall post-awakening cortisol secretion, lower cortisone in hair, and slightly earlier sleep onset than full-term children. The results are consistent with previous research indicating that very preterm birth is related to possible down-regulation of HPA axis activity during late childhood and early adolescence. Moreover, the results indicate less post-awakening cortisol secretion in children with longer sleep duration, earlier sleep onset, and longer REM latency. In particular, earlier sleep onset co-occurred with decreased HPA axis activity in very preterm children. Thus, our results support the notion that HPA axis activity and sleep are associated and that in accordance with previous studies on animals and humans a down-regulation of the HPA axis activity may be programmed early in life. Future research may examine the possible role of down-regulation of the HPA axis activity in very preterm children for their psychosocial adjustment, cognitive and academic functioning, and psychological wellbeing.

## Conflict of interest

The authors declare no conflict of interest.

## Contributors

Sakari Lemola designed the study. Natalie Maurer, Nadine Perkinson-Gloor, and Sakari Lemola executed and supervised the data collection, provided the statistical analyses, and wrote the first draft of the manuscript. Natalie Maurer, Nadine Perkinson-Gloor, Tobias Stalder, Priska Hagmann-von Arx, Serge Brand, Edith Holsboer-Trachsler, Sven Wellmann, Alexander Grob, Peter Weber, and Sakari Lemola contributed to the interpretation of the data, planning the manuscript, internal revision and rewriting of the first draft of the manuscript, and approved the final manuscript.

## Role of funding sources

This research was financially supported by the Swiss National Science Foundation (Projects: Sleep, cognitive, and socio-emotional development in preterm children during middle and late childhood, Grant number: 143962; Socio-emotional development and mental health of preterm children: The role of HPA-axis function, sleep, neuroplasticity, and physical exercise during the transition to adolescence, Grant number: 159362), and the Research Fund of the University of Basel (Project: Early origins of self-regulation and sleep, Grant number DPE2083). The sponsors had no role in study design, data collection, data analysis, data interpretation, or in the writing of the report.

## 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 the polysomnographic data and the Swiss National Science Foundation and the University of Basel for funding the research.

## References

Aarnoudse-Moens, C.S.H., Weisglas-Kuperus, N., van Goudoever, J.B., Oosterlaan, J., 2009. Meta-analysis of neurobehavioral outcomes in very preterm and/or very low birth weight children. Pediatrics 124, 717–728.

Anand, K.J.S., 2001. Consensus statement for the prevention and management of pain in the newborn. Arch. Pediatr. Adolesc. Med. 155, 173–180.

Björkqvist, J., Paavonen, J., Andersson, S., Pesonen, A.K., Lahti, J., Heinonen, K., Eriksson Räikkönen, J.K., Hovi, P., Kajantie, E., Strang-Karlsson, S., 2014. Advanced sleep-wake rhythm in adults born prematurely confirmation by actigraphy-based assessment in the Helsinki study of very low birth weight adults. Sleep Med. 15, 1101–1106.

Brooks, E., Canal, M.M., 2013. Development of circadian rhythms: role of postnatal light environment. Neurosci. Biobehav. Rev. 37, 551–560.

Brummelte, S., Chau, C.M., Cepeda, I.L., Degenhardt, A., Weinberg, J., Synnes, A.R., Grunau, R.E., 2015. Cortisol levels in former preterm children at school age are

predicted by neonatal procedural pain-related stress. Psychoneuroendocrinology 51, 151–163.
Buske-Kirschbaum, A., Krieger, S., Wilkes, C., Rauh, W., Weiss, S., Hellhammer, D.H., 2007. Hypothalamic-pituitary-adrenal axis function and the cellular immune response in former preterm children. J. Clin. Endocrinol. Metab. 92, 3429–3435.
Buss, C., Entringer, S., Swanson, J.M., Wadhwa, P.D., 2012. The role of stress in brain development: the gestational environment's long-term effects on the brain. Cerebrum 12, 1–16.
Child Trends, 2015 Preterm births. Retrieved from http://www.childtrends.org/?indicators=preterm-births.
Clements, A.D., 2013. Salivary cortisol measurement in developmental research: where do we go from here? Dev. Psychobiol. 55, 205–220.
Cohen, J., 1988. Statistical Power Analysis for the Behavioral Sciences, 2nd ed. Lawrence Erlbaum Associates, Hillsdale, New York.
Elder, G.J., Wetherell, M.A., Barclay, N.L., Ellis, J.G., 2014. The cortisol awakening response –applications and implications for sleep medicine. Sleep Med. Rev. 18, 215–224.
Faul, F., Erdfelder, E., Lang, A.G., Buchner, A., 2007. G* Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behav. Res. Methods 39, 175–191.
Feng, X., Wang, L., Yang, S., Qin, D., Wang, J., Li, C., Lv, L., Ma, Y., Hu, X., 2011. Maternal separation produces lasting changes in cortisol and behavior in rhesus monkeys. Proc. Natl. Acad. Sci. U. S. A. 108, 14312–14317.
Fernandez, E.F., Watterberg, K.L., 2009. Relative adrenal insufficiency in the preterm and term infant. J. Perinatol. 29, 44–49.
Fernandez-Mendoza, J., Vgontzas, A.N., Calhoun, S.L., Vgontzas, A., Tsaoussoglou, M., Gaines, J., Liao, D., Chrousos, G.P., Bixler, E.O., 2014. Insomnia symptoms, objective sleep duration and hypothalamic-pituitary-adrenal activity in children. Eur. J. Clin. Invest. 44, 493–500.
Gao, W., Stalder, T., Foley, P., Rauh, M., Deng, H., Kirschbaum, C., 2013. Quantitative analysis of steroid hormones in human hair using a column-switching LC-APCI–MS/MS assay. J. Chromatogr. B 928, 1–8.
Gao, W., Kirschbaum, C., Grass, J., Stalder, T., 2016. LC–MS based analysis of endogenous steroid hormones in human hair. J. Steroid Biochem. Mol. Biol. 162, 92–99.
Goldenberg, R.L., Culhane, J.F., Iams, J.D., Romero, R., 2008. Epidemiology and causes of preterm birth. Lancet 371, 75–84.
Grunau, R.E., Haley, D.W., Whitfield, M.F., Weinberg, J., Yu, W., Thiessen, P., 2007. Altered basal cortisol levels at 3, 6, 8 and 18 months in infants born at extremely low gestational age. J. Pediatr. 150, 151–156.
Grunau, R.E., Cepeda, I.L., Chau, C.M., Brummelte, S., Weinberg, J., Lavoie, P.M., Ladd, M., Hirschfeld, A.F., Russell, E., Koren, G., Van Uum, S., Brant, R., Turvey, S.E., 2013. Neonatal pain-related stress and NFKBIA genotype are associated with altered cortisol levels in preterm boys at school age. PLoS One 8, e73926.
Hatzinger, M., Brand, S., Perren, S., Von Wyl, A., Stadelmann, S., von Klitzing, K., Holsboer-Trachsler, E., 2013. In pre-school children, sleep objectively assessed via sleep-EEGs remains stable over 12 months and is related to psychological functioning, but not to cortisol secretion. J. Psychiatr. Res. 47, 1809–1814.
Hibbs, A.M., Storfer-Isser, A., Rosen, C., Ievers-Landis, C.E., Taveras, E.M., Redline, S., 2014. Advanced sleep phase in adolescents born preterm. Behav. Sleep Med. 12, 412–424.
Jones, A., Godfrey, K.M., Wood, P., Osmond, C., Goulden, P., Phillips, D.I.W., 2006. Fetal growth and the adrenocortical response to psychological stress. Clin. Endocrinol. Metab. 91, 1868–1871.
Kajantie, E., Räikkönen, K., 2010. Early life predictors of the physiological stress response later in life. Neurosci. Biobehav. Rev. 35, 23–32.
Karemaker, R., Kavelaars, A., ter Wolbeek, M., Tersteeg-Kamperman, M., Baerts, W., Veen, S., Samsom, J.S., Visser, G.H.A., van Bel, F., Heijnen, C.J., 2008. Neonatal dexamethasone treatment for chronic lung disease of prematurity alters the hypothalamus-pituitary-adrenal axis and immune system activity at school age. Pediatrics 121, e870–e878.
Kaseva, N., Wehkalampi, K., Pyhälä, R., Moltchanova, E., Feldt, K., Pesonen, A.K., Heinone, K., Hovi, P., Järvenpää, A.-L., Andersson, S., Eriksson, J.G., Räikkönen, K., Kajantie, E., 2014. Blunted hypothalamicäpituitaryäadrenal axis and insulin response to psychosocial stress in young adults born preterm at very low birth weight. Clin. Endocrinol. 80, 101–106.
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.
Lemola, S., 2015. Long-term outcomes of very preterm birth. Eur. Psychol. 20, 128–137.
Miller, R., Plessow, F., Kirschbaum, C., Stalder, T., 2013. Classification criteria for distinguishing cortisol responders from nonresponders to psychosocial stress: evaluation of salivary cortisol pulse detection in panel designs. Psychosomat. Med. 75, 832–840.
Monk, C., Feng, T., Lee, S., Krupska, I., Champagne, F.A., Tycko, B., 2016. Distress during pregnancy: epigenetic regulation of placenta glucocorticoid-related genes and fetal neurobehavior. Am. J. Psychiatr. 173, 705–713.
Ohayon, M.M., Carskadon, M.A., Guilleminault, C., Vitiello, M.V., 2004. Meta-analysis of quantitative sleep parameters from childhood to old age in healthy individuals: developing normative sleep values across the human lifespan. Sleep 27, 1255–1273.
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. J. Psychiatr. Res. 60, 141–147.
Pesonen, A.K., Martikainen, S., Kajantie, E., Heinonen, K., Wehkalampi, K., Lahti, J., Strandberg, T., Räikkönen, K., 2014. The associations between adolescent sleep, diurnal cortisol patterns and cortisol reactivity to dexamethasone suppression test. Psychoneuroendocrinology 49, 150–160.
Preacher, K.J., Hayes, A.F., 2008. Asymptotic and resampling strategies for assessing and comparing indirect effects in multiple mediator models. Behav. Res. Methods 40, 879–891.
Pruessner, J.C., Kirschbaum, C., Meinlschmid, G., Hellhammer, D.H., 2003. Two formulas for computation of the area under the curve represent measures of total hormone concentration versus time-dependent change. Psychoneuroendocrinology 28, 916–931.
Quesada, A.A., Tristão, R.M., Pratesi, R., Wolf, O.T., 2014. Hyper-responsiveness to acute stress, emotional problems and poorer memory in former preterm children. Stress 17, 389–399.
Räikkönen, K., Matthews, K.A., Pesonen, A.K., Pyhälä, R., Paavonen, E.J., Feldt, K., Jones, A., Philips, D.I.W., Seckl, J.R., Heinonen, K., Lahti, J., Komsi, N., Järvenpää, A.-L., Eriksson, J.G., Strandberg, T.E., Kajantie, E., 2010. Poor sleep and altered hypothalamic-pituitary-adrenocortical and sympatho-adrenal-medullary system activity in children. J. Clin. Endocrinol. Metab. 95, 2254–2261.
Rechtschaffen, A., Kales, A., 1968. A Manual of Standardized Terminology, Techniques and Scoring System for Sleep Stages of Human Subjects. Washington Public Health Service, US Government Printing Office Washington, DC.
Rosen, C.L., Larkin, E.K., Kirchner, H.L., Emancipator, J.L., Bivins, S.F., Surovec, S.A., Martin, R.J., Redline, S., 2003. Prevalence and risk factors for sleep-disordered breathing in 8- to 11- year-old children: association with race and prematurity. J. Pediatr. 142, 383–389.
Saigal, S., Doyle, L.W., 2008. An overview of mortality and sequelae of preterm birth from infancy to adulthood. Lancet 371, 261–269.
Stalder, T., Kirschbaum, C., 2012. Analysis of cortisol in hair – state of the art and future directions. Brain Behav. Immun. 26, 1019–1029.
Stalder, T., Steudte, S., Miller, R., Skoluda, N., Dettenborn, L., Kirschbaum, C., 2012. Intraindividual stability of hair cortisol concentrations. Psychoneuroendocrinology 37, 602–610.
Stalder, T., Kirschbaum, C., Alexander, N., Bornstein, S.R., Gao, W., Miller, R., Stark, S., Bosch, J.A., Fischer, J.E., 2013. Cortisol in hair and the metabolic syndrome. J. Clin. Endocrinol. Metab. 98, 2573–2580.
Stalder, T., Kirschbaum, C., Kudielka, B.M., Adam, E.K., Pruessner, J.C., Wüst, S., Dockray, S., Smyth, N., Evans, P., Hellhammer, D.H., Miller, R., Wetherell, M.A., Lupien, S.J., Clow, A., 2016. Assessment of the cortisol awakening response: expert consensus guidelines. Psychoneuroendocrinology 63, 414–432.
Strang-Karlsson, S., Kajantie, E., Pesonen, A.K., Räikkönen, K., Hovi, P., Lahti, J., Heinonen, K., Järvenpää, A.L., Eriksson, J.G., Andersson, S., Paavonen, E.J., 2010. Morningness propensity in young adults born prematurely: the Helsinki study of very low birth weight adults. Chronobiol. Int. 27, 1829–1842.
Wadsby, M., Nelson, N., Ingemansson, F., Samuelsson, S., Leijon, I., 2014. Behaviour problems and cortisol levels in very-low-birth-weight children. Nord. J. Psychiatry 68, 626–632.

# APPENDIX B: Study 2

Urfer-Maurer, N., Ludyga, S., Stalder, T., Brand, S., Holsboer-Trachsler, E., Gerber, M., Grob, A., Weber, P., & Lemola, S. (2018). Heart rate variability and salivary cortisol in very preterm children during school age. *Psychoneuroendocrinology, 87*, 27-34.

Psychoneuroendocrinology 87 (2018) 27–34

Contents lists available at ScienceDirect

Psychoneuroendocrinology

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

# Heart rate variability and salivary cortisol in very preterm children during school age

Natalie Urfer-Maurer[a], Sebastian Ludyga[b], Tobias Stalder[c], Serge Brand[b,d,e], Edith Holsboer-Trachsler[d], Markus Gerber[b], Alexander Grob[a], Peter Weber[f], Sakari Lemola[g,*]

[a] University of Basel, Department of Psychology, Basel, Switzerland
[b] University of Basel, Department of Sport, Exercise and Health, Sport Sciences Section, Basel, Switzerland
[c] University of Siegen, Clinical Psychology, Siegen, Germany
[d] University of Basel, Psychiatric Clinics, Center for Affective, Stress, and Sleep Disorders, Basel, Switzerland
[e] Kermanshah University of Medical Sciences (KUMS), Sleep Disorders Research Center, Kermanshah, Iran
[f] University Children's Hospital Basel, Division of Neuropediatrics and Developmental Medicine, Basel, Switzerland
[g] University of Warwick, Department of Psychology, University Road, CV4 7AL, United Kingdom

ARTICLE INFO

*Keywords:*
Preterm birth
Heart rate variability
HPA axis activity
Salivary cortisol
School-aged children
Polysomnography

ABSTRACT

The autonomic nervous system (ANS) plays a major role in the human stress response and reflects physical and psychological adaptability to a changing environment. Long-term exposure to early life stressors may alter the function of the ANS. The present study examines differences in the ANS between children born very preterm and full-term as well as the association between the ANS and the hypothalamic-pituitary-adrenal (HPA) axis, the other main branch of the human stress system.

Fifty-four healthy children born very preterm (< 32nd gestational week) and 67 full-term children aged 7–12 years provided data for the present study. Polysomnography (PSG) assessments were obtained during a night at the children's home in lying position at rest (wake) and during different sleep stages (stage 2 sleep, slow wave sleep, rapid-eye-movement sleep). Autonomic function was assessed by use of heart rate variability, specifically low frequency power (LF), high frequency power (HF), total spectral power (Tot Pow), and the LF/HF ratio. HPA axis activity was measured using salivary cortisol the next morning at awakening, 10, 20, and 30 min later.

Children born very preterm had lower LF/HF ratio during wake and stage 2 sleep compared to full-term children. Moreover, higher LF, Tot Pow, and LF/HF ratio during wake, stage 2 sleep, and REM sleep were related to more post-awakening cortisol secretion.

The present study provides evidence on long-term ANS alterations after very preterm birth. Moreover, findings suggest a relation between the ANS and the HPA axis and therefore support the notion of mutual feedback between the two human stress systems.

## 1. Introduction

The sympathetic nervous system (SNS) and the hypothalamic-pituitary-adrenal (HPA) axis are the two main branches involved in the human stress response. During acute stress, the autonomic nervous system (ANS), consisting of the SNS and the parasympathetic nervous system (PNS), induces immediate rapid bodily changes through modulation of noradrenergic and cholinergic neuronal communication and the quick release of adrenaline via the sympatho-adrenal medullary system (SAM; Charmandari et al., 2005; Stratakis and Chrousos, 1995). The SNS is involved in the so-called 'fight or flight' response – the immediate reaction to a stressor, while the complementary PNS regulates 'rest and digest' processes. In addition to stress response modulation, the ANS is involved in the regulation of various physiological functions, such as the heart rate. Autonomic function can be measured by electrocardiography (ECG) and the assessment of heart rate variability (HRV; Shaffer et al., 2014). HRV describes the change in beat-to-beat intervals over time and can be separated into different frequency domain bands, with low frequency power (LF: 0.04–0.15 Hz) reflecting a combination of sympathetic and parasympathetic nervous system activity, high frequency power (HF: 0.15–0.4 Hz) predominantly reflecting parasympathetic activity, total spectral power (Tot Pow: 0.0033–0.40 Hz) reflecting the global ANS activity, and the LF/HF ratio reflecting sympathovagal balance (Stein and Pu, 2012;

* Corresponding author.
*E-mail address:* s.lemola@warwick.ac.uk (S. Lemola).

http://dx.doi.org/10.1016/j.psyneuen.2017.10.004
Received 17 July 2017; Received in revised form 18 August 2017; Accepted 3 October 2017

Task Force, 1996). These frequency-domain HRV indices are assumed to be trait-like markers of autonomic function (Montano et al., 2009) and a change towards increased LF/HF ratio or decreased HF reflecting a dominance of sympathetic over parasympathetic activity has been shown to be associated with poor physical and mental health (Acharya et al., 2006; Friedman, 2007). However, also overly increased HRV may be non-optimal since it may reflect non-efficient physiological functioning and energy utilization (Shaffer et al., 2014). The role of the balance between sympathetic behavioral activation and parasympathetic inhibition for behavioral and emotional regulation is object of theoretical models including the polyvagal and the neurovisceral model (Porges, 1995, 2007; Thayer et al., 2009). In their core, both models propose that fine-tuning of the parasympathetic system is important for psychosocial adjustment to a changing environment.

The ANS matures during gestation and the first months after birth (David et al., 2007; Sahni et al., 2000) and stress during these sensitive phases may lead to long–term programming of the ANS (Fyfe et al., 2014). One major stress factor during this phase that occurs in around 10% of all children worldwide is preterm birth (Blencowe et al., 2013). In particular, children born very preterm are endowed with immature organs and are exposed to several illness-related adversities and invasive treatments (Lemola et al., 2015; Roberts and Dalziel, 2006). Later in their lives, very preterm children are more likely to suffer from physical disorders and psychological disturbances, such as depression, burnout, and anxiety disorders (Aarnoudse-Moens et al., 2009; Aylward, 2005; Lemola et al., 2015), which, in turn, may be associated with alterations in autonomic function (Kanthak et al., 2017; Licht et al., 2008; van Gestel and Steier, 2011). Compared to their peers born at term, infants born preterm show decreased HRV right after birth and at theoretical term (Landrot et al., 2007; Patural et al., 2008). These changes in HRV indicate a reduced regulatory capacity, so that infants born preterm may have more difficulty in adaptively responding to environmental stressors (Shaffer et al., 2014). Regarding the question how preterm birth affects ANS development at a later age up to 7 years, the evidence is more mixed. Specifically, studies reporting that preterm children either exhibited higher LF/HF ratio (Fyfe et al., 2015), lower LF (Yiallourou et al., 2013), or lower HF (Fyfe et al., 2015; Yiallourou et al., 2013), or failed to reveal differences in frequency domains at all (Fyfe et al., 2015; Landrot et al., 2007; Yiallourou et al., 2013). In addition, a recent study by Rakow et al. (2013) including nine-year old children showed rather global HRV reductions, characterized by lower very low frequency power (VLF), LF, HF, Tot Pow, and a trend towards a lower LF/HF ratio, in children born very preterm and small for gestational age (SGA) full-terms. The above–mentioned inconsistent findings regarding HRV differences between children born preterm and full-term might be due to differences in the age ranges studied as well as differences in the measurement setting, which might introduce variance to the findings. Specifically, studies with infants measured HRV during sleep (Fyfe et al., 2015; Yiallourou et al., 2013), while studies including older children conducted ECGs over a 24 h period (Landrot et al., 2007; Rakow et al., 2013).

The second arm of the human stress system, the HPA axis, reacts more slowly by regulating the secretion of glucocorticoids, including cortisol (Clements, 2013) and is supposed to play a major role in chronic stress (Miller et al., 2007). The HPA axis can be measured through salivary cortisol assessments. Cortisol secretion increases across the first 30–45 min after morning awakening, a phenomenon termed the cortisol awakening response (CAR; Clow et al., 2004; Stalder et al., 2016). There is evidence that an increased CAR is associated with stress and a reduced CAR with fatigue, burnout, and exhaustion, despite considerable heterogeneity in findings (Chida and Steptoe, 2009). As both the HRV and the HPA axis are proposed to be trait-like characteristics that play a major role for emotional adaptability and regulation (Porges, 1995, 2007; Thayer and Lane, 2000; Chida and Steptoe, 2009), it is an important question how these two systems are interrelated. An earlier study by Stalder et al. (2011) on the relationship between HRV and the CAR found that lower global HRV was related to an elevated CAR in young adults. Interestingly, these CAR-HRV associations were consistently found for HRV assessments taken in a laboratory setting and over the pre- and post-awakening periods as well as for measures of overall HRV, LF, and HF (Stalder et al., 2011). There are only few studies, which have examined the relation between ANS and HPA axis activity in children. One study by Michels et al. (2013), including children aged 5–10 years, reported higher LF and LF/HF ratio during 10 min in supine position in a quiet room in the afternoon to be associated with a larger CAR. However, another study by Rotenberg and McGrath (2016) found no such associations in children and adolescents aged 8–18 years conducting 24 h ECGs.

A first aim of the present study was thus to examine potential differences in HRV between school-age children born very preterm and those born full-term by measuring HRV during a wake episode in a lying position at rest before sleep onset and during sleep. There are two advantages of measuring HRV separately in the evening before sleep as well as during night sleep within different sleep stages. First, this involves a more standardized measurement situation across participants compared to 24 h ambulatory assessments, since HRV is assessed during the same circadian phase and sleep stages, which may reduce the acute impact of daily experience on HRV measurement. Second, this strategy allows us to determine whether differences between very preterm and full-term children are consistent across these different psychophysiological states. Following Rakow et al. (2013), we examined HRV parameters in children born very preterm and full-term. In addition to prior studies (Landrot et al., 2007; Rakow et al., 2013), we measured HRV parameters in a lying position at rest before sleep onset and during separate sleep stages (stage 2 sleep, slow wave sleep [SWS], and rapid eye movement [REM] sleep). A second aim was to test the association between the ANS (measured through HRV) and HPA axis activity (measured as the post-awakening cortisol secretion in the morning after HRV assessment). Thereby, we address the apparent gap in research regarding the association between HRV and HPA axis activity in school-aged children.

## 2. Methods

### 2.1. Study population and procedure

The data for the present study comes from the second wave (May 2013–September 2014) of the Basel Study of Preterm Children (BSPC). Recruitment procedures have been described elsewhere in detail (see Perkinson-Gloor et al. (2015), and Lemola et al. (2015), for reports on the first study wave and Urfer-Maurer et al. (2017) and Maurer et al. (2016) for reports on the second study wave, including results regarding HPA axis activity in children born very preterm). In total, 54 (44.6%) healthy very preterm children (< 32 weeks of gestation; age: $M$ = 9.62 years, $SD$ = 1.36; range: 7.33–12.33 years) and 67 (55.4%) age and sex matched full-term children (age: $M$ = 9.66 years, $SD$ = 1.51; range: 7.5–12.92 years; see Table 1) are included in the present report as they had one night of in-home electroencephalography (EEG) and readable electrocardiogram (ECG) data. Children born very preterm were recruited from an initial cohort of 260 prematurely born children treated at the University Children's Hospital Basel (Switzerland). Full-term children were recruited from official birth notification. For each participant, parents gave written informed consent and assent was obtained from the child. Ethical approval was obtained from the Ethics Committee of Basel (Basel, Switzerland, 122/11) and the study was performed in accordance with the ethical standards laid down in the Declaration of Helsinki.

### 2.2. Variables

#### 2.2.1. HRV assessment and analysis

Using Compumedics Somté PSG during a single night at the

**Table 1**
Descriptive statistics for study variables and Pearson's correlation of child's age and sex with heart rate variability parameters and salivary cortisol secretion ($N$ = 121).

| | M/N | (SD/%) | r Age | Sex |
|---|---|---|---|---|
| Age, years | 9.64 | (1.44) | | |
| Sex, male[a] | 72 | (59.5) | | |
| Prematurity status, born very preterm | 54 | (44.6) | | |
| Gestational age, weeks | 35.25 | (5.11) | | |
| HRV indices | | | | |
| Wake | | | | |
| LF Pow, $ms^2$ | 4238.12 | (5125.02) | −0.15 | 0.24** |
| HF Pow, $ms^2$ | 2284.38 | (2152.74) | −0.11 | 0.19* |
| Tot Pow, $ms^2$ | 25548.23 | (39309.55) | −0.17† | 0.26** |
| LF/HF ratio | 1.78 | (0.82) | −0.06 | 0.18† |
| EDR, Hz | 0.23 | (0.04) | −0.05 | 0.00 |
| Stage 2 sleep | | | | |
| LF Pow, $ms^2$ | 2585.51 | (2773.13) | −0.13 | −0.02 |
| HF Pow, $ms^2$ | 3866.23 | (3157.31) | −0.17† | −0.07 |
| Tot Pow, $ms^2$ | 12498.09 | (13247.04) | −0.07 | −0.11 |
| LF/HF ratio | 0.84 | (0.66) | −0.00 | −0.02 |
| EDR, Hz | 0.25 | (0.04) | −0.26** | 0.03 |
| SWS | | | | |
| LF Pow, $ms^2$ | 1586.26 | (1711.52) | −0.13 | 0.07 |
| HF Pow, $ms^2$ | 3005.10 | (2667.87) | −0.07 | 0.01 |
| Tot Pow, $ms^2$ | 7656.72 | (8416.52) | −0.15† | 0.11 |
| LF/HF ratio | 0.67 | (0.54) | 0.01 | 0.01 |
| EDR, Hz | 0.26 | (0.05) | −0.29** | 0.07 |
| REM sleep | | | | |
| LF Pow, ms2 | 2743.49 | (2618.58) | 0.02 | −0.03 |
| HF Pow, ms2 | 3586.34 | (2792.48) | −0.00 | 0.01 |
| Tot Pow, ms2 | 13605.89 | (15027.19) | 0.03 | −0.03 |
| LF/HF ratio | 1.03 | (0.75) | −0.02 | −0.06 |
| EDR, Hz | 0.25 | (0.04) | −0.22* | 0.21* |
| Salivary morning cortisol secretion[b] | | | | |
| $AUC_G$ | 0.51 | (0.07) | 0.01 | 0.03 |
| $AUC_I$ | 0.57 | (0.07) | −0.08 | −0.19* |
| First sample (S1) | 0.87 | (0.19) | 0.06 | 0.16† |
| Second sample | 0.98 | (0.17) | −0.01 | 0.05 |
| Third sample | 1.09 | (0.15) | −0.05 | −0.06 |
| Fourth sample | 1.05 | (0.20) | 0.07 | 0.01 |

*Note:* SWS: slow wave sleep, REM: rapid eye movement, $AUC_G$: area-under-the-concentration-time-curve with respect to the ground, $AUC_I$: area-under-the-concentration-time-curve with respect to the increase.
†p < 0.1, *p < 0.05, **p < 0.01 (two-tailed).
[a] Coding of sex: 1 = male; 2 = female.
[b] Log-transformed before building $AUC_G/AUC_I$.

children's home, electrocardiogram was recorded in lying position at rest without movement (wake) and during sleep. The amplified signal was low-pass filtered (30 Hz) and digitized at 256 Hz. Collected data was exported to Kubios HRV Analysis Software 2.1 (Matlab, Kuopio, Finland) for offline processing and analysis. Procedures were in line with the HRV analysis guidelines (Task Force, 1996) and the expert performing the analysis was blinded to the group allocation (prematurity status). Based on the adaptive QRS detection algorithm of Kubios (Tarvainen et al., 2014), R-wave time instants were automatically detected and verified by visual inspection. The resulting HRV time series were converted to equidistantly sampled series by using a 4 Hz cubic spline interpolation. To remove slow nonstationary trends from the signal, a linear detrend correction based on smoothness priors regularization (0.001 hz cut-off) was applied to the R-R series (Tarvainen et al., 2002). Frequency domain measures were estimated from short-term recordings collected during rest in bed before sleep onset (15 min), stage 2 sleep, and SWS as well as REM sleep. The classification of sleep stages was based on polysomnographic assessments (see 2.2.3). For each HRV recording period, five consecutive 5 min segments (25 min) containing no changes in sleep stages, artifacts or erratic heart beats were averaged. If more than one block of segments fulfilled these criteria, the first valid epoch after sleep onset was selected for further analysis. Averaged segments were subjected to Fast-Fourier transform by using Welch's periodogram (300 s with 50% overlap) and divided into very low frequency (VLF: 0–0.04 Hz), low frequency (LF: 0.04–0.15 Hz), and high frequency (HF: 0.15–0.4 Hz) bands. In addition, LF/HF power ratio and the total spectral power were calculated. The LF band is modulated by a combination of sympathetic and parasympathetic nervous system inputs, whereas the HF is considered to reflect parasympathetic activity (Acharya et al., 2006; Stein and Pu, 2012).

#### 2.2.2. Post-awakening cortisol secretion assessment

Parents collected four saliva samples from their children at 0, 10, 20, and 30 min after the child's awakening on a normal school-day. Children were not allowed to eat, drink, and brush their teeth until saliva sampling was completed. Saliva samples were collected using the "Salivette" device (Sarstedt, Nümbrecht/Germany). Analyses of free salivary cortisol concentrations were conducted with 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). Statistical analyses were conducted according to the published guidelines on post-awakening cortisol assessment (Stalder et al., 2016). The level of cortisol on awakening (S1), the area-under-the-curve with respect to increase ($AUC_I$) and with respect to ground ($AUC_G$; Pruessner et al., 2003) were estimated to quantify different aspects of post-awakening cortisol secretion. Salivary cortisol variables were log-transformed before building $AUC_G$ and $AUC_I$. The endpoint of the pre-awakening cortisol increase was defined as S1 and the cortisol awakening response (CAR) was interpreted as $AUC_I$. In addition, the overall post-awakening cortisol secretion was defined as $AUC_G$ (Stalder et al., 2016).

To evaluate the time point of saliva sampling, parents reported children's light-on-time (children woke up naturally or were woken up by alarm clock or by their parents; mode of awakening was not separately assessed) and awakening time was additionally measured by PSG. However, the time-point of saliva sampling was not additionally measured by electronic time stamp. Analyses including salivary cortisol were controlled for the difference between parent-reported light-on-time/cortisol sampling time and awakening time according to PSG ('parent reported light-on-time/cortisol sampling time' – 'in-home PSG awakening time' > 5 min; Stalder et al., 2016). Season and awakening time as measured by PSG were additionally controlled for. Please see supplemental Table S1 for further information regarding control variables according to the CAR consensus guidelines (Stalder et al., 2016).

#### 2.2.3. Sleep assessment

Children's sleep was assessed using the Compumedics Somté PSG during a single night at the children's home. Polysomnogram signals C3/A2 and C4/A1 EEG, right and left electrooculogram and bipolar submental electromyogram were obtained. Two experienced raters analyzed the EEG recordings according to the standard procedures (Rechtschaffen and Kales, 1968).

### 2.3. Statistical analysis

To test our first hypothesis, we performed analyses of covariance (ANCOVA) with prematurity status as independent and frequency-domain HRV measures (LF, HF, Tot Pow, LF/HF ratio) as dependent variables. Moreover, we performed repeated-measures ANCOVAs with HRV indices during the different sleep stages (wake, stage 2 sleep, SWS, REM sleep) as within subject factor and prematurity status as fixed factor. Analyses regarding differences in HRV were controlled for children's age, sex, BMI, and first language, since these variables were correlated to HRV parameters. Effect sizes were calculated following Cohen (1969, 1988) with d = 0.20 and $\eta^2_p$ = 0.01 indicating small, d = 0.50 and $\eta^2_p$ = 0.06 indicating medium, and d = 0.80 and $\eta^2_p$ = 0.14 indicating large effect sizes. To test our second hypothesis,

multiple regression analyses with HRV parameters as independent variable and salivary cortisol as dependent variable were calculated, entering one HRV parameter and the covariates at a time. Bootstrap procedures were applied for robust estimation of standard errors (Chernick, 2008). Statistical analyses were performed with IBM® SPSS® Statistics 22 (IBM Corporation, Armonk NY, USA) for Apple Mac®.

## 3. Results

### 3.1. Preliminary analyses

Table 1 shows descriptive statistics and Pearson correlations of child age and sex with HRV indices and post-awakening cortisol secretion. Child age was negatively related to ECG-derived respiration (EDR) during sleep stage 2, SWS, and REM sleep. Girls showed higher LF, HF, and Tot Pow during wake and more EDR during REM sleep than boys. Regarding post-awakening cortisol secretion, girls had a smaller $AUC_I$ than boys.

Regarding intra-individual changes in HRV during the transition from wake to stage 2 sleep, SWS, and REM sleep there was a significant quadratic effect regarding LF ($F(1120) = 51.13$, $p < 0.001$, $\eta^2_p = 0.30$), Tot Pow ($F(1120) = 40.86$, $p < 0.001$, $\eta^2_p = 0.25$), and LF/HF ratio ($F(1120) = 255.73$, $p < 0.001$, $\eta^2_p = 0.68$). The shape of this quadratic relationship was such that LF, Tot, and LF/HF ratio decreased from wake to stage 2 sleep and SWS, which was followed by a somewhat less pronounced increase in the transition to REM sleep (see Fig. 1). Regarding HF, there was a significant cubic effect ($F(1120) = 30.64$, $p < 0.001$, $\eta^2_p = 0.20$), since HF increased with the transition from wake to stage 2 sleep, however, decreased during SWS and increased again during REM-sleep.

### 3.2. Differences in HRV between children born very preterm and full-term

Table 2 shows differences in HRV parameters between children born very preterm and full-term. Very preterm children had a lower LF/HF ratio during wake and during stage 2 sleep compared to full-term children. There were no differences in any of the HRV parameters during SWS and REM sleep between children born very preterm and full-term.

Regarding sleep stage × prematurity status interactions on HRV parameters, there was a significant interaction on LF/HF ratio by the transition from wake to stage 2 sleep and SWS. Moreover, there was a significant interaction on LF, HF, and Tot Pow by the transition from stage 2 sleep to SWS and REM sleep. Results are displayed in Fig. 1.

### 3.3. Association between HRV and post-awakening cortisol secretion

Table 3 shows associations between HRV parameters and post-awakening cortisol secretion. Higher LF during wake, stage 2 sleep, and REM sleep and higher LF/HF ratio during wake and higher Tot Pow during REM sleep were associated with more $AUC_G$. Higher LF and Tot Pow during stage 2 sleep were related to more $AUC_I$. Moreover, higher LF/HF ratio during wake was associated with more S1. No other significant relation between HRV parameters and post-awakening cortisol secretion was found.

## 4. Discussion

This is the first study that examined HRV differences in school-aged very preterm and full-term born children during different sleep stages and considering the association between HRV parameters and HPA axis activity. The main findings were that children born very preterm had lower LF/HF ratio compared to full-term children during wake and stage 2 sleep. Moreover, across the whole sample, there was some indication that higher LF, Tot Pow, and LF/HF ratio at wake and during sleep were associated with increased overall morning cortisol secretion.

### 4.1. Differences in HRV between children born very preterm and full-term

Children born very preterm had a lower LF/HF ratio during wake and during stage 2 sleep compared to children born full-term, which is in line with Rakow et al. (2013) who found a tendency towards a lower LF/HF ratio in 9 year old children born very preterm and SGA full-term. However, and in contrast to Rakow et al. (2013), no differences were found in the other frequency domain parameters (LF, HF, and Tot Pow) between children born very preterm and full-term. As a difference between the two studies, Rakow et al. (2013) conducted 24 h ECG, while we measured HRV parameters in lying position at rest without movement (wake) and during different sleep stages. Interestingly, Rakow et al. (2013) concluded that the HRV differences were due to processes associated with low birth weight rather than with gestational age, since they found no differences between children born very preterm and full-term SGA. Based on our sample, it is not possible to address this assumption, since no separate sample of SGA children was included in our study.

Differences in maturation of the two ANS branches could account for differences in LF/HF ratio between children born very preterm and full-term. During prenatal life sympathetic activity is predominant, while parasympathetic activity begins to increase rapidly between 25 and 32 weeks of gestation (David et al., 2007; Schneider et al., 2009). However, children born very preterm spend this crucial period outside of their mother's womb in the neonatal intensive care unit, where environmental conditions for the development of the ANS are markedly different. Children born very preterm are exposed to many distressing events after birth (Lemola et al., 2015; Roberts and Dalziel, 2006), which might provoke increased sympathetic activation. In this vein, previous studies focusing on preterm children at the beginning of their lives, reported less parasympathetic and more sympathetic activity (Landrot et al., 2007; Patural et al., 2008). During later development, there is evidence of a steady increase in parasympathetic activity compared to sympathetic activity until age 6–7 years, which is reflected in a declining LF/HF ratio. This decline was more pronounced in preterm than in full-term children (Landrot et al., 2007). A possible explanation for a reduced sympathetic activity in later life is a persistently down-regulation of the sympathetic arm of the ANS in a similar vein as it has been discussed for the other human stress system – the HPA axis (Feng et al., 2011; Kaseva et al., 2014; Maurer et al., 2016) – in response to the excessive activation in early life eventually leading to parasympathetic activity predominance. The assumption of long-term sympathetic down-regulation by early-life stress is further in line with evidence from twin studies showing that environmental factors play a major role for cardiovascular autonomic function (e.g. Osztovits et al., 2011). It is possible, that epigenetic mechanisms are involved in long-term programming of the cardiovascular autonomic function (Esler et al., 2008).

Regarding intra-individual changes in HRV during the transition from wake to SWS, sympathetic activity decreased progressively, while parasympathetic activity increased from wake to stage 2 sleep. From SWS to REM sleep sympathetic activity increased again. This is in line with previous research showing a decreased sympathetic activity with the transition from wake to non-REM sleep and an increased sympathetic activity with the transition from non-REM to REM sleep (Trinder et al., 2001; Versace et al., 2003). This pattern reflects the notion of increasing relaxation with the progression to deeper sleep stages.

With the transition from wake to stage 2 sleep and SWS children born very preterm showed a flatter decrease in LF/HF ratio than children born full-term. Relatedly, children born very preterm showed a flatter decrease in LF and Tot Pow from stage 2 sleep to SWS and a flatter increase from SWS to REM-sleep. Regarding HF, full-term children showed a stronger decline from stage 2 sleep to SWS and a stronger increase from SWS to REM-sleep than very preterm born children. Our results are in line with studies showing an overall lower wake-time sympathetic activity in children born preterm (e.g. Rakow

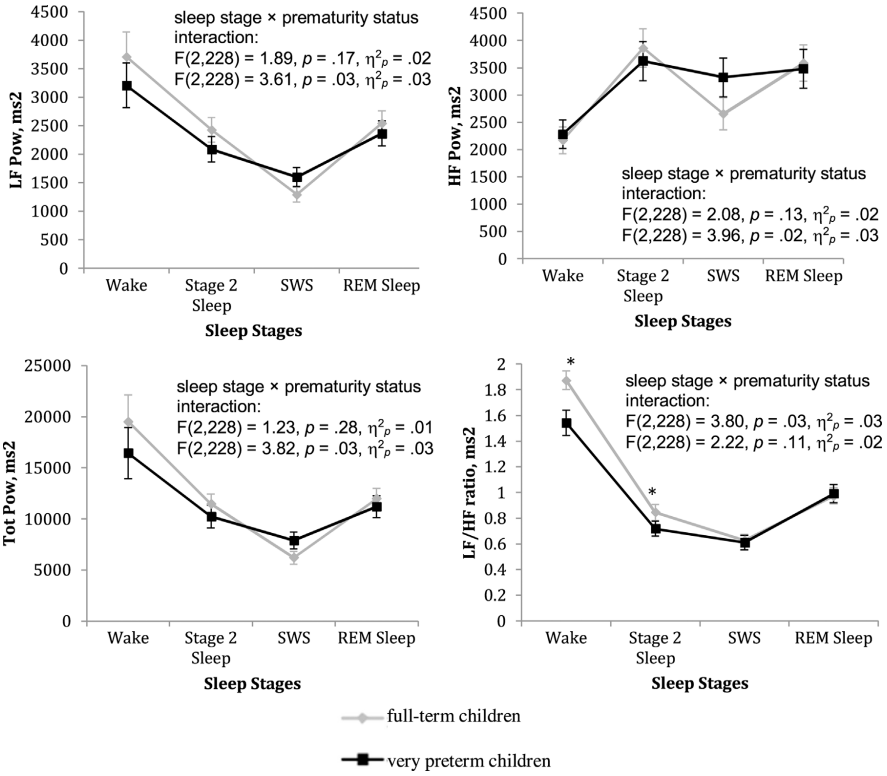



**Fig. 1.** Sleep stage × prematurity status interaction on HRV parameters.
upper line: sleep stage × prematurity status regarding the transition from wake to stage 2 sleep and SWS, lower line: sleep stage × prematurity status regarding the transition from stage 2 sleep to SWS and REM sleep.
*significant differences in HRV parameters between children born very preterm and full-term.
all variables adjusted for first language, children's age, sex, and BMI.

et al., 2013). However, in SWS full-term children reached approximately the same level of LF, Tot Pow, and LF/HF ratio as very preterm children.

### 4.2. Association between HRV and post-awakening cortisol secretion

The present study is one of the few studies examining the association between the ANS and the HPA axis. We saw some indication that higher HRV characterized by a shift towards sympathetic dominance (higher LF, Tot Pow, and LF/HF ratio) during wake, stage 2 sleep, and REM sleep is associated with more overall post-awakening salivary cortisol secretion. No association was found between HF and post-awakening cortisol secretion. Our results are in line with Michels et al. (2013), who found higher LF in supine position in the afternoon to be associated with a larger $AUC_I$. Moreover and in line with Stalder et al. (2011), we found no association between LF/HF ratio and $AUC_I$. However, our findings are in contrast to Stalder et al. (2011) regarding the association between LF and HF and $AUC_I$. While they reported that lower LF and HF were related to an increased $AUC_I$, we found higher LF to be related to an increased $AUC_I$. Moreover, they found no significant association between HRV parameters and S1. Differences in age between the studied samples could account for the discrepancies between our results and those from Stalder et al. (2011) who studied young adults (mean age: 23 years), while our study included children aged between 7 and 12 years.

Our results indicate an association between the ANS and the HPA axis – reflected by a co-occurrence of high LF, Tot Pow, and LF/HF ratio during wake, stage 2 sleep, and REM sleep and high post-awakening HPA axis activity. This coincides with evidence that both the ANS activity and the HPA axis are involved in emotion regulation (Porges, 1995, 2007; Thayer and Lane, 2000) and both have trait-like properties representing relatively stable biological markers for stress and related psychological outcomes. It is for instance known that general life stress and poor physical and mental health are associated with both increased HPA axis activity reflected in a higher $AUC_I$ and $AUC_G$ (Chida and Steptoe, 2009) as well as with a higher LF, Tot Pow, and LF/HF ratio (Acharya et al., 2006; Friedman, 2007). Moreover, the relationship between ANS activity and the HPA axis may also reflect that they both receive input from the amygdala and hypothalamus (Tafet and Bernardini, 2003), which may align their activity.

### 4.3. Limitations

The current study is not without limitations. First, it is not possible to draw conclusions regarding causal relations due to the correlative study design. Second, only one night of HRV measurement and one

**Table 2**
Heart rate variability parameters in very preterm and full-term children.

| | Very preterm (n = 54) | | | Full-term (n = 67) | | | *d* | $p^a$ |
|---|---|---|---|---|---|---|---|---|
| | M | (SD) | BC 95%-CI[a] | M | (SD) | BC 95%-CI[a] | | |
| Wake | | | | | | | | |
| LF Pow, $ms^2$ | 3514.57 | 3755.39 | [2638.21, 4522.33] | 4821.28 | 5971.38 | [3524.30, 6293.15] | 0.27 | 0.172 |
| HF Pow, $ms^2$ | 2401.25 | 2258.27 | [1859.69, 3008.39] | 2190.19 | 2076.17 | [1718.73, 2693.39] | 0.14 | 0.463 |
| Tot Pow, $ms^2$ | 18968.22 | 25435.34 | [12884.98, 25856.73] | 30851.53 | 47180.80 | [20579.03, 42452.38] | 0.32 | 0.093 |
| LF/HF ratio | 1.62 | 0.95 | [1.39, 1.86] | 1.91 | 0.68 | [1.76, 2.07] | 0.41 | 0.047 |
| EDR, Hz | 0.24 | 0.04 | [0.23, 0.25] | 0.23 | 0.04 | [0.22, 0.24] | 0.37 | 0.072 |
| Stage 2 sleep | | | | | | | | |
| LF Pow, $ms^2$ | 2140.55 | 1788.46 | [1691.20, 2621.86] | 2944.14 | 3334.84 | [2227.57, 3785.92] | 0.37 | 0.124 |
| HF Pow, $ms^2$ | 3869.30 | 3504.67 | [3047.55, 4853.99] | 3863.76 | 2874.26 | [3229.76, 4530.58] | 0.03 | 0.731 |
| Tot Pow, $ms^2$ | 10785.25 | 9935.15 | [8429.67, 13503.81] | 13878.59 | 15344.77 | [10669.86, 17598.68] | 0.28 | 0.245 |
| LF/HF ratio | 0.72 | 0.42 | [0.61, 0.83] | 0.94 | 0.79 | [0.76, 1.14] | 0.43 | 0.035 |
| EDR, Hz | 0.26 | 0.04 | [0.25, 0.27] | 0.25 | 0.03 | [0.24, 0.25] | 0.33 | 0.108 |
| SWS | | | | | | | | |
| LF Pow, $ms^2$ | 1828.74 | 2027.15 | [1391.65, 2352.29] | 1390.84 | 1392.55 | [1094.75, 1723.08] | 0.27 | 0.150 |
| HF Pow, $ms^2$ | 3430.19 | 2906.15 | [2702.94, 4237.49] | 2662.49 | 2427.30 | [2135.10, 3235.01] | 0.33 | 0.066 |
| Tot Pow, $ms^2$ | 9144.79 | 10573.40 | [6888.57, 11889.72] | 6457.37 | 5978.97 | [5209.92, 7904.29] | 0.33 | 0.096 |
| LF/HF ratio | 0.67 | 0.59 | [0.53, 0.82] | 0.67 | 0.50 | [0.56, 0.78] | 0.02 | 0.991 |
| EDR, Hz | 0.27 | 0.06 | [0.26, 0.29] | 0.25 | 0.04 | [0.25, 0.26] | 0.34 | 0.129 |
| REM sleep | | | | | | | | |
| LF Pow, ms2 | 2485.14 | 1985.09 | [2014.31, 3038.83] | 2951.72 | 3033.84 | [2322.68, 3719.68] | 0.25 | 0.307 |
| HF Pow, ms2 | 3559.81 | 2840.99 | [2869.88, 4345.49] | 3607.72 | 2774.10 | [2946.60, 4308.72] | 0.07 | 0.798 |
| Tot Pow, ms2 | 12437.62 | 11803.27 | [9750.92, 15777.18] | 14547.48 | 17224.48 | [11064.39, 18778.80] | 0.21 | 0.402 |
| LF/HF ratio | 1.00 | 0.55 | [0.86, 1.16] | 1.05 | 0.88 | [0.88, 1.26] | 0.08 | 0.728 |
| EDR, Hz | 0.25 | 0.04 | [0.24, 0.26] | 0.24 | 0.03 | [0.24, 0.25] | 0.25 | 0.242 |

*Note:* SWS: slow wave sleep, REM: rapid eye movement, BC 95%-CI: bias-corrected 95% bootstrap confidence intervals.
all variables adjusted for first language, children's age, sex, and BMI.
[a] Bootstrapped values based on 5000 samples.

morning of saliva sampling were conducted, which may reduce reliability. Third, while we sought to follow the guidelines of the CAR consensus report (e.g. consideration of objective awakening times and trait-related confounders), there were also some limitations in this regard. The study design did not include any objective verification of saliva sampling times and thus influences of participant non-compliance cannot be fully excluded. Furthermore, we did not have data on the full set of covariates specified in the consensus report available (Stalder et al., 2016). Moreover, for the wake-state measurement HRV parameters were assessed in lying position in the evening before sleep onset. These parameters may therefore not be directly comparable to other wake-state ECG recordings, such as 24 h or stress ECGs. Finally, there was no simultaneous HRV and HPA axis activity assessment. Future studies may assess HRV and HPA axis concurrently at different

**Table 3**
Multiple regression results with heart rate variability parameters predicting post-awakening cortisol measures.

| | Post-awakening cortisol secretion | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | First sample (S1) | | | | | $AUC_I$ | | | | | $AUC_G$ | | | | |
| | β | B | SE[a] | BC 95%-CI[a] | p[a] | β | B | SE[a] | BC 95%-CI[a] | p[a] | β | B | SE[a] | BC 95%-CI[a] | p[a] |
| Wake | | | | | | | | | | | | | | | |
| LF Pow, $ms^2$ | 0.10 | 0.00 | 0.00 | [0.00, 0.00] | 0.336 | 0.09 | 0.00 | 0.00 | [0.00, 0.00] | 0.341 | 0.22 | 0.00 | 0.00 | [0.00, 0.00] | 0.036 |
| HF Pow, $ms^2$ | −0.06 | 0.00 | 0.00 | [0.00, 0.00] | 0.572 | 0.16 | 0.00 | 0.00 | [0.00, 0.00] | 0.081 | 0.07 | 0.00 | 0.00 | [0.00, 0.00] | 0.500 |
| Tot Pow, $ms^2$ | 0.10 | 0.00 | 0.00 | [0.00, 0.00] | 0.397 | 0.10 | 0.00 | 0.00 | [0.00, 0.00] | 0.261 | 0.23 | 0.00 | 0.00 | [0.00, 0.00] | 0.050 |
| LF/HF ratio | 0.23 | 0.05 | 0.02 | [0.01, 0.12] | 0.028 | −0.10 | −0.01 | 0.01 | [−0.03, 0.01] | 0.344 | 0.23 | 0.02 | 0.01 | [0.00, 0.04] | 0.027 |
| Stage 2 sleep | | | | | | | | | | | | | | | |
| LF Pow, $ms^2$ | 0.02 | 0.00 | 0.00 | [0.00, 0.00] | 0.805 | 0.16 | 0.00 | 0.00 | [0.00, 0.00] | 0.030 | 0.18 | 0.00 | 0.00 | [0.00, 0.00] | 0.047 |
| HF Pow, $ms^2$ | −0.14 | 0.00 | 0.00 | [0.00, 0.00] | 0.193 | 0.11 | 0.00 | 0.00 | [0.00, 0.00] | 0.277 | −0.10 | 0.00 | 0.00 | [0.00, 0.00] | 0.345 |
| Tot Pow, $ms^2$ | −0.07 | 0.00 | 0.00 | [0.00, 0.00] | 0.336 | 0.19 | 0.00 | 0.00 | [0.00, 0.00] | 0.027 | 0.08 | 0.00 | 0.00 | [0.00, 0.00] | 0.254 |
| LF/HF ratio | 0.12 | 0.03 | 0.03 | [−0.01, 0.10] | 0.198 | 0.00 | 0.00 | 0.01 | [−0.03, 0.02] | 0.997 | 0.17 | 0.02 | 0.01 | [0.00, 0.03] | 0.055 |
| SWS | | | | | | | | | | | | | | | |
| LF Pow, $ms^2$ | 0.12 | 0.00 | 0.00 | [0.00, 0.00] | 0.344 | 0.04 | 0.00 | 0.00 | [0.00, 0.00] | 0.617 | 0.19 | 0.00 | 0.00 | [0.00, 0.00] | 0.116 |
| HF Pow, $ms^2$ | −0.07 | 0.00 | 0.00 | [0.00, 0.00] | 0.511 | 0.04 | 0.00 | 0.00 | [0.00, 0.00] | 0.613 | −0.07 | 0.00 | 0.00 | [0.00, 0.00] | 0.511 |
| Tot Pow, $ms^2$ | 0.03 | 0.00 | 0.00 | [0.00, 0.00] | 0.770 | 0.04 | 0.00 | 0.00 | [0.00, 0.00] | 0.692 | 0.07 | 0.00 | 0.00 | [0.00, 0.00] | 0.575 |
| LF/HF ratio | 0.01 | 0.00 | 0.04 | [−0.07, 0.09] | 0.898 | −0.02 | 0.00 | 0.01 | [−0.03, 0.03] | 0.874 | 0.01 | 0.00 | 0.02 | [−0.03, 0.04] | 0.955 |
| REM sleep | | | | | | | | | | | | | | | |
| LF Pow, ms2 | 0.14 | 0.00 | 0.00 | [0.00, 0.00] | 0.072 | 0.04 | 0.00 | 0.00 | [0.00, 0.00] | 0.675 | 0.22 | 0.00 | 0.00 | [0.00, 0.00] | 0.008 |
| HF Pow, ms2 | −0.08 | 0.00 | 0.00 | [0.00, 0.00] | 0.428 | 0.08 | 0.00 | 0.00 | [0.00, 0.00] | 0.394 | −0.05 | 0.00 | 0.00 | [0.00, 0.00] | 0.630 |
| Tot Pow, ms2 | 0.10 | 0.00 | 0.00 | [0.00, 0.00] | 0.152 | 0.02 | 0.00 | 0.00 | [0.00, 0.00] | 0.832 | 0.14 | 0.00 | 0.00 | [0.00, 0.00] | 0.047 |
| LF/HF ratio | 0.09 | 0.02 | 0.02 | [−0.02, 0.09] | 0.238 | −0.01 | 0.00 | 0.01 | [−0.02, 0.02] | 0.894 | 0.11 | 0.01 | 0.01 | [−0.01, 0.04] | 0.230 |

*Note:* SWS: slow wave sleep, REM: rapid eye movement, $AUC_G$ = area-under-the-concentration-time-curve with respect to the ground, $AUC_I$ = area-under-the-concentration-time-curve with respect to the increase.
all variables adjusted for children's age, sex, prematurity status, season, awakening time, BMI, and awakening time difference.
[a] Bootstrapped values based on 5000 samples.

stages of the diurnal cycle and during different situations (e.g. during stress vs. during relaxation) to unravel their diurnal co-variation. Finally, longitudinal assessment of the ANS and the HPA axis activity and their interplay from infancy to childhood in children born preterm and full-term would allow to examine differential trajectories of the two stress systems in children with different levels of early risk exposure.

## 5. Conclusions

In conclusion, the present study provides evidence of ANS alterations after very preterm birth during later childhood. Our study suggests that children born preterm show an altered balance between sympathetic and parasympathetic activity, with a relative increase in parasympathetic compared to sympathetic activity, during wake and stage 2 sleep, but not during SWS and REM sleep. Moreover, there is an association between HRV parameters during wake and sleep with salivary morning cortisol secretion implying mutual feedback between the SAM and the HPA axis – higher LF, Tot Pow, and LF/HF ratio are related to higher post-awakening cortisol secretion.

## Conflict of interest

The authors declare no conflict of interest.

## Contributors

Sakari Lemola designed the study. Natalie Urfer-Maurer and Sakari Lemola executed and supervised the data collection, provided the statistical analyses, and wrote the first draft of the manuscript. Natalie Urfer-Maurer, Sebastian Ludyga, Tobias Stalder, Serge Brand, Edith Holsboer-Trachsler, Markus Gerber, Alexander Grob, Peter Weber, and Sakari Lemola contributed to the interpretation of the data, planning the manuscript, internal revision and rewriting of the first draft of the manuscript, and approved the final manuscript.

## 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 (Projects: Sleep, cognitive, and socio-emotional development in preterm children during middle and late childhood, Grant number: 143962; Socio-emotional development and mental health of preterm children: The role of HPA-axis function, sleep, neuroplasticity, and physical exercise during the transition to adolescence, Grant number: 159362) and the University of Basel, Basel, Switzerland (Project: Early origins of self-regulation and sleep, Grant number DPE2083) for funding the research.

## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.psyneuen.2017.10.004.

## References

Aarnoudse-Moens, C.S.H., Weisglas-Kuperus, N., van Goudoever, J.B., Oosterlaan, J., 2009. Meta-analysis of neurobehavioral outcomes in very preterm and/or very low birth weight children. Pediatrics 124, 717–728.
Acharya, U.R., Joseph, K.P., Kannathal, N., Lim, C.M., Suri, J.S., 2006. Heart rate variability: a review. Med. Biol. Eng. Comput. 44, 1031–1051.
Aylward, G.P., 2005. Neurodevelopmental outcomes of infants born prematurely. J. Dev. Behav. Pediatr. 26, 427–440.
Blencowe, H., Cousens, S., Chou, D., Oestergaard, M., Say, L., Moller, A.B., Kinney, M., Lawn, J., 2013. Born too soon: the global epidemiology of 15 million preterm births. Reprod. Health 10, S2.
Charmandari, E., Tsigos, C., Chrousos, G., 2005. Endocrinology of the stress response. Annu. Rev. Physiol. 67, 259–284.
Chernick, M.R., 2008. Bootstrap Methods: A Guide for Practitioners and Researchers. Wiley, Hoboken, NJ.
Chida, Y., Steptoe, A., 2009. Cortisol awakening response and psychosocial factors: a systematic review and meta-analysis. Biol. Psychol. 80, 265–278.
Clements, A.D., 2013. Salivary cortisol measurement in developmental research: where do we go from here? Dev. Psychobiol. 55, 205–220.
Clow, A., Thorn, L., Evans, P., Hucklebridge, F., 2004. The awakening cortisol response: methodological issues and significance. Stress 7, 29–37.
Cohen, J., 1969. Statistical Power Analysis for the Behavioral Sciences. Lawrence Erlbaum Associates, Hillsdale, New York.
Cohen, J., 1988. Statistical Power Analysis for the Behavioral Sciences, 2nd ed. Lawrence Erlbaum Associates, Hillsdale, New York.
David, M., Hirsch, M., Karin, J., Toledo, E., Akselrod, S., 2007. An estimate of fetal autonomic state by time-frequency analysis of fetal heart rate variability. J. Appl. Physiol. 102, 1057–1064.
Esler, M., Eikelis, N., Schlaich, M., Lambert, G., Alvarenga, M., Kaye, D., El-Osta, A., Guo, L., Barton, D., Pier, C., Brenchley, C., Dawood, T., Jennings, G., Lambert, E., 2008. Human sympathetic nerve biology. Ann. N. Y. Acad. Sci. 1148, 338–348.
Feng, X., Wang, L., Yang, S., Qin, D., Wang, J., Li, C., Lv, L., Ma, Y., Hu, X., 2011. Maternal separation produces lasting changes in cortisol and behavior in rhesus monkeys. Proc. Natl. Acad. Sci. U. S. A. 108, 14312–14317.
Friedman, B.H., 2007. An autonomic flexibility–neurovisceral integration model of anxiety and cardiac vagal tone. Biol. Psychol. 74, 185–199.
Fyfe, K.L., Yiallourou, S.R., Wong, F.Y., Horne, R.S., 2014. The development of cardiovascular and cerebral vascular control in preterm infants. Sleep Med. Rev. 18, 299–310.
Fyfe, K.L., Yiallourou, S.R., Wong, F.Y., Odoi, A., Walker, A.M., Horne, R.S., 2015. The effect of gestational age at birth on post-term maturation of heart rate variability. Sleep 38, 1635–1644.
Kanthak, M.K., Stalder, T., Hill, L.K., Thayer, J.F., Penz, M., Kirschbaum, C., 2017. Autonomic dysregulation in burnout and depression: evidence for the central role of exhaustion. Scand. J. Work Environ. Health. http://dx.doi.org/10.5271/sjweh.3647. (pii: 3647).
Kaseva, N., Wehkalampi, K., Pyhälä, R., Moltchanova, E., Feldt, K., Pesonen, A.K., Heinone, K., Hovi, P., Järvenpää, A.-L., Andersson, S., Eriksson, J.G., Räikkönen, K., Kajantie, E., 2014. Blunted hypothalamic-pituitary-adrenal axis and insulin response to psychosocial stress in young adults born preterm at very low birth weight. Clin. Endocrinol. 80, 101–106.
Landrot, I.D.R., Roche, F., Pichot, V., Teyssier, G., Gaspoz, J.M., Barthelemy, J.C., Patural, H., 2007. Autonomic nervous system activity in premature and full-term infants from theoretical term to 7 years. Auton. Neurosci. 136, 105–109.
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.
Licht, C.M., de Geus, E.J., Zitman, F.G., Hoogendijk, W.J., van Dyck, R., Penninx, B.W., 2008. Association between major depressive disorder and heart rate variability in the Netherlands Study of Depression and Anxiety (NESDA). Arch. Gen. Psychiatry 65, 1358–1367.
Maurer, N., Perkinson-Gloor, N., Stalder, T., Hagmann-von Arx, P., Brand, S., Holsboer-Trachsler, E., Wellmann, S., Grob, A., Weber, P., Lemola, S., 2016. Salivary and hair glucocorticoids and sleep in very preterm children during school age. Psychoneuroendocrinology 72, 166–174.
Michels, N., Sioen, I., Clays, E., De Buyzere, M., Ahrens, W., Huybrechts, I., Vanaelst, B., De Henauw, S., 2013. Children's heart rate variability as stress indicator: association with reported stress and cortisol. Biol. Psychol. 94, 433–440.
Miller, G.E., Chen, E., Zhou, E.S., 2007. If it goes up, must it come down? Chronic stress and the hypothalamic-pituitary-adrenocortical axis in humans. Psychol. Bull. 133, 25–45.
Montano, N., Porta, A., Cogliati, C., Costantino, G., Tobaldini, E., Casali, K.R., Iellamo, F., 2009. Heart rate variability explored in the frequency domain: a tool to investigate the link between heart and behavior. Neurosci. Biobehav. Rev. 33, 71–80.
Osztovits, J., Horváth, T., Littvay, L., Steinbach, R., Jermendy, A., Tárnoki, A., Tárnoki, D., Métneki, J., Kollai, M., Jermendy, G., 2011. Effects of genetic vs. environmental factors on cardiovascular autonomic function: a twin study. Diabet. Med. 28, 1241–1248.
Patural, H., Pichot, V., Jaziri, F., Teyssier, G., Gaspoz, J.M., Roche, F., Barthelemy, J.C., 2008. Autonomic cardiac control of very preterm newborns: a prolonged dysfunction. Early Hum. Dev. 84, 681–687.
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. J. Psychiatr. Res. 60, 141–147.
Porges, S.W., 1995. Cardiac vagal tone: a physiological index of stress. Neurosci. Biobehav. Rev. 19, 225–233.
Porges, S.W., 2007. The polyvagal perspective. Biol. Psychol. 74, 116–143.
Pruessner, J.C., Kirschbaum, C., Meinlschmid, G., Hellhammer, D.H., 2003. Two formulas for computation of the area under the curve represent measures of total hormone concentration versus time-dependent change. Psychoneuroendocrinology 28, 916–931.
Rakow, A., Katz-Salamon, M., Ericson, M., Edner, A., Vanpée, M., 2013. Decreased heart rate variability in children born with low birth weight. Pediatr. Res. 74, 339–343.
Rechtschaffen, A., Kales, A., 1968. A Manual of Standardized Terminology, Techniques and Scoring System for Sleep Stages of Human Subjects. Washington Public Health Service, US Government Printing Office, Washington DC.
Roberts, D., Dalziel, S., 2006. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth (Review). Cochrane Database Syst. Rev. 3,

CD004454.
Rotenberg, S., McGrath, J.J., 2016. Inter-relation between autonomic and HPA axis activity in children and adolescents. Biol. Psychol. 117, 16–25.
Sahni, R., Schulze, K.F., Kashyap, S., Ohira-Kist, K., Fifer, W.P., Myers, M.M., 2000. Maturational changes in heart rate and heart rate variability in low birth weight infants. Dev. Psychobiol. 37, 73–81.
Schneider, U., Schleussner, E., Fiedler, A., Jaekel, S., Liehr, M., Haueisen, J., Hoyer, D., 2009. Fetal heart rate variability reveals differential dynamics in the intrauterine development of the sympathetic and parasympathetic branches of the autonomic nervous system. Physiol. Meas. 30, 215–226.
Shaffer, F., McCraty, R., Zerr, C.L., 2014. A healthy heart is not a metronome: an integrative review of the heart's anatomy and heart rate variability. Front. Physiol. 5, 1040.
Stalder, T., Evans, P., Hucklebridge, F., Clow, A., 2011. Associations between the cortisol awakening response and heart rate variability. Psychoneuroendocrinology 36, 454–462.
Stalder, T., Kirschbaum, C., Kudielka, B.M., Adam, E.K., Pruessner, J.C., Wüst, S., Dockray, S., Smyth, N., Evans, P., Hellhammer, D.H., Miller, R., Wetherell, M.A., Lupien, S.J., Clow, A., 2016. Assessment of the cortisol awakening response: expert consensus guidelines. Psychoneuroendocrinology 63, 414–432.
Stein, P.K., Pu, Y., 2012. Heart rate variability, sleep and sleep disorders. Sleep Med. Rev. 16, 47–66.
Stratakis, C.A., Chrousos, G.P., 1995. Neuroendocrinology and pathophysiology of the stress system. Ann. N. Y. Acad. Sci. 771, 1–18.
Tafet, G.E., Bernardini, R., 2003. Psychoneuroendocrinological links between chronic stress and depression. Prog. Neuropsychopharmacol. Biol. Psychiatry 27, 893–903.
Tarvainen, M.P., Ranta-aho, P.O., Karjalainen, P.A., 2002. An advanced detrending method with application to HRV analysis. IEEE Trans. Biomed. Eng. 49, 172–175.
Tarvainen, M.P., Niskanen, J.P., Lipponen, J.A., Ranta-Aho, P.O., Karjalainen, P.A., 2014. Kubios HRV–heart rate variability analysis software. Comput. Methods Programs Biomed. 113, 210–220.
Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996. Heart rate variability: standards of measurement, physiological interpretation and clinical use. Circulation 93, 1043–1065.
Thayer, J.F., Lane, R.D., 2000. A model of neurovisceral integration in emotion regulation and dysregulation. J. Affect. Disord. 61, 201–216.
Thayer, J.F., Hansen, A.L., Saus-Rose, E., Johnsen, B.H., 2009. Heart rate variability, prefrontal neural function, and cognitive performance: the neurovisceral integration perspective on self-regulation adaptation, and health. Ann. Behav. Med. 37, 141–153.
Trinder, J., Kleiman, J., Carrington, M., Smith, S., Breen, S., Tan, N., Kim, Y., 2001. Autonomic activity during human sleep as a function of time and sleep stage. J. Sleep Res. 10, 253–264.
Urfer-Maurer, N., Weidmann, R., Brand, S., Holsboer-Trachsler, E., Grob, A., Weber, P., Lemola, S., 2017. The association of mothers' and fathers' insomnia symptoms with school-aged children's sleep assessed by parent report and in-home sleep-electroencephalography. Sleep Med. 38, 64–70.
van Gestel, A.J., Steier, J., 2011. Autonomic dysfunction in patients with chronic obstructive pulmonary disease (COPD). J. Thorac. Dis. 2, 215–222.
Versace, F., Mozzato, M., Tona, G.D.M., Cavallero, C., Stegagno, L., 2003. Heart rate variability during sleep as a function of the sleep cycle. Biol. Psychol. 63, 149–162.
Yiallourou, S.R., Witcombe, N.B., Sands, S.A., Walker, A.M., Horne, R.S., 2013. The development of autonomic cardiovascular control is altered by preterm birth. Early Hum. Dev. 89, 145–152.

# APPENDIX C: Study 3

Urfer-Maurer, N., Weidmann, R., Brand, S., Holsboer-Trachsler, E., Grob, A., Weber, P., & Lemola, S. (2017). The association of mothers' and fathers' insomnia symptoms with school-aged children's sleep assessed by parent report and in-home sleep-electroencephalography. *Sleep Medicine, 38*, 64-70.

Sleep Medicine 38 (2017) 64–70

Contents lists available at ScienceDirect

Sleep Medicine

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

Original Article

# The association of mothers' and fathers' insomnia symptoms with school-aged children's sleep assessed by parent report and in-home sleep-electroencephalography

Natalie Urfer-Maurer [a], Rebekka Weidmann [a], Serge Brand [b, c, d], Edith Holsboer-Trachsler [b], Alexander Grob [a], Peter Weber [e], Sakari Lemola [f, *]

[a] Department of Psychology, University of Basel, Switzerland
[b] Psychiatric Clinics (UPK), Center for Affective, Stress, and Sleep Disorders (ZASS), University of Basel, Basel, Switzerland
[c] Department of Sport, Exercise and Health, Division of Sport and Psychosocial Health, University of Basel, Basel, Switzerland
[d] Sleep Disorders Research Center, Kermanshah University of Medical Sciences (KUMS), Kermanshah, Iran
[e] University Children's Hospital Basel, Division of Neuropediatrics and Developmental Medicine, University of Basel, Switzerland
[f] Department of Psychology, University of Warwick, Coventry, UK

ARTICLE INFO

*Article history:*
Received 1 March 2017
Received in revised form
12 June 2017
Accepted 4 July 2017
Available online 26 July 2017

*Keywords:*
Maternal and paternal insomnia
School-aged children
In-home sleep electroencephalography
Parent reports
Children's Sleep Habits Questionnaire
Actor–partner interdependence model

ABSTRACT

*Objective:* Sleep plays an essential role for children's well-being. Because children's sleep is associated with parental sleep patterns, it must be considered in the family context. As a first aim of the present study, we test whether parental insomnia symptoms are related to children's in-home sleep-electroencephalography (EEG). Second, we examine the association between parental insomnia symptoms and maternal and paternal perception of children's sleep using actor–partner interdependence models.
*Methods:* A total of 191 healthy children enrolled in public school and aged 7–12 years took part in the study. Ninety-six were formerly very preterm born children. Children underwent in-home sleep-EEG, and parents reported children's sleep-related behavior by using the German version of the Children's Sleep Habits Questionnaire. Further, parents completed the Insomnia Severity Index to report their own insomnia symptoms.
*Results:* Maternal but not paternal insomnia symptoms were related to less children's EEG-derived total sleep time, more stage 2 sleep, less slow wave sleep, later sleep onset time, and later awakening time. Mothers' and fathers' own insomnia symptoms were related to their reports of children's bedtime resistance, sleep duration, sleep anxiety, night wakings, and/or daytime sleepiness. Moreover, maternal insomnia symptoms were associated with paternal reports of children's bedtime resistance, sleep anxiety, and sleep-disordered breathing. The associations between parental insomnia symptoms and parents' perception of children's sleep could not be explained by children's objectively measured sleep.
*Conclusions:* Mothers' insomnia symptoms and children's objective sleep patterns are associated. Moreover, the parents' own insomnia symptoms might bias their perception of children's sleep-related behavior problems.



## 1. Introduction

Sleep plays an essential role for children's daytime functioning including their well-being, emotion regulation, cognitive functioning, and academic performance [1–4]. According to self- and parent-reports sleep problems are frequent: 30–40% of school-aged children seem to suffer from sleep disturbances such as difficulties initiating and maintaining sleep, as well as excessive daytime sleepiness [5,6].

There is compelling evidence that children's sleep is associated with parental sleep patterns [7–10], particularly with maternal sleep [8,9,11–14]. The association was especially salient when parents' and children's sleep were measured with the same method, e.g., when both parental and children's sleep were reported by the parents [14] or measured with actigraphy [9] or sleep-electroencephalography (EEG) [8]. However, to date no study

* Corresponding author. Department of Psychology, University of Warwick, University Road, Coventry, CV4 7AL, UK. Fax: +44 24 765 24225.
*E-mail address:* s.lemola@warwick.ac.uk (S. Lemola).

http://dx.doi.org/10.1016/j.sleep.2017.07.010
1389-9457/

examined the association between parental insomnia symptoms and children's sleep measured by polysomnography (PSG), the gold-standard of sleep assessment. Similarly, evidence on the association between one parent's insomnia symptoms and the co-parent's perception of child sleep is missing.

Several possible mechanisms that could account for the relationship between parents' and children's sleep have been suggested. First, children may learn sleep habits from their parents, which could lead to high correspondence between parents' and children's sleep quality [15]. Second, both parents and children could for instance be affected by poor family functioning [16–19] as well as by environmental stress related to poor socio-economic status leading to poor sleep patterns [20]. Third, children may share genetic variation with their parents that predisposes for poor sleep [21]. Fourth, in younger children, sleep difficulties can also affect parental sleep [22,23].

A methodological issue that could account for the association between parental insomnia and parent reports of children's sleep difficulties in particular, is that parental insomnia may affect their perception of children's sleep without any real underlying sleep problem of the child [24]. This can be important because parents are often the first to perceive their children's sleep problems and to seek help. Aside from causing unnecessary costs, treatment for sleep disorders without a real underlying indication might be harmful and eventually even trigger children's sleep disturbances [25,26]. This might happen in a similar fashion as described by Harvey's cognitive model of insomnia [27] which posits that selective attention and monitoring of sleep difficulties play a crucial role in triggering and perpetuating sleep disturbances.

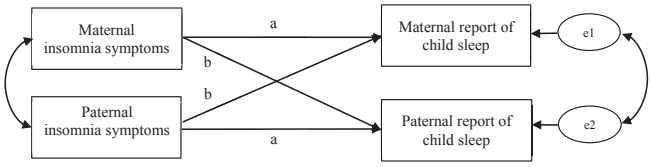
Moreover, parent reports are often used to assess children's sleep-related behavior and sleep problems in research, since parent reports are practical and inexpensive [28], although being error-prone and possibly biased due to the parents' own sleep difficulties [24,29]. Rönnlund et al. (2016) [24] for instance studied parents of children aged 2–6 years and measured children's sleep by actigraphy to identify to what degree parent reports were explained by children's actual sleep. Parents (who themselves suffered from poor sleep) more often reported sleep problems in their children, including disorders of initiating and maintaining sleep, disorders of sleep–wake transitions, and excessive daytime somnolence [24]. These associations could not be explained by objective (i.e., actigraphy) measures of children's sleep [24]. A possible explanation for this pattern of results is that parents who sleep poorly themselves show a negativity bias, such that they show increased attention towards and more often remember negative stimuli related to their child's sleep [24,30,31].

As a first aim of the present study, we tested whether maternal and paternal insomnia symptoms were related to children's sleep measured objectively with in-home sleep-EEG. Compared to laboratory-based PSG, in-home sleep-EEG assessment has the advantage that sleep is assessed in the ecological context where it normally occurs. We hypothesized that children show worse sleep patterns including shorter sleep duration and decreased sleep continuity when their mothers and fathers had increased insomnia symptoms. As a second aim of the present study we examined the association of parents' insomnia symptoms and their perception of their children's sleep. In order to account for the degree to which this relationship is explained by the children's actual sleep, we controlled children's objectively measured sleep (i.e., the EEG sleep-indices) in an additional step. We hypothesized that parents with more insomnia symptoms also perceive more sleep-related behavior problems in their children. Because the present study aims to extend our understanding of parental perception of children's sleep, the interdependence of maternal and paternal reports of children's sleep was examined using the Actor–partner interdependence model (APIM) [32]. Maternal and paternal perception of their children's sleep could be influenced by their own as well as by their partners' sleep problems. The APIM approach allowed to shed light onto the mutual interdependence of maternal and paternal perception of their children's sleep by disentangling so-called actor and partner effects; in the present context, actor effects denote associations between one parent's insomnia symptoms and his/her perception of the child's sleep-related behavior problems (Fig. 1, paths labeled 'a'), whereas partner effects reflect the associations between one parent's insomnia symptoms and the other parent's perception of the child's sleep-related behavior problems (Fig. 1, paths labeled 'b').

## 2. Material and methods

### 2.1. Study population and procedure

The data for the present study derived from the second wave (May 2013–September 2014) of the Basel Study of Preterm Children (BSPC). Recruitment procedures have been described elsewhere in detail (see, e.g., Lemola et al. [33] and Perkinson-Gloor et al. [34] for reports on the first study wave and Maurer et al. [35] for a report on the second study wave). In total, the second wave of the study included 191 healthy school-aged children (age: mean = 9.58 years, standard deviation (SD) = 1.47; range: 7.17–12.92 years; 109 (57.1%) were boys; see Table 1). Children underwent one night of in-home sleep-EEG, and parents completed the German version of the Children's Sleep Habits Questionnaire (CSHQ-DE; [36]) to rate children's sleep-related behavior and the Insomnia Severity Index (ISI; [37,38]) to rate their own insomnia symptoms. The total sample included 96 (50.3%) children born very preterm (<32 weeks of gestation) and 95 (49.7%) age- and sex-matched children born at term. Since children born very preterm and full-term differ in various sleep indices [34,35] the statistical analyses were controlled for preterm birth status. All children attended compulsory primary or secondary school in Switzerland. The study was approved by the Ethics Committee of Basel, assent was obtained from the children and written informed consent was obtained from the parents for each participant.




a, actor effect: effect of one parent's insomnia symptoms on his/her own report of the child's sleep.
b, partner effect: effect of one parent's insomnia symptoms on the other parent's report of the child's sleep.

**Fig. 1.** Actor–partner interdependence model with maternal and paternal insomnia symptoms predicting maternal and paternal perception of children's sleep-related behavior problems.

**Table 1**
Descriptive statistics for background variables and sleep-electroencephalography indices.

| | M/N | (SD/%) |
|---|---|---|
| Background variables | | |
| Age, years[a] | 9.58 | (1.47) |
| Sex, male | 109 | (57.10) |
| Prematurity status, born very preterm | 96 | (50.30) |
| Gestational age, weeks | 34.50 | (5.21) |
| Sleep-EEG indices[b] | | |
| Total sleep time (h) | 8.93 | (0.69) |
| Sleep efficiency (%) | 93.40 | (2.85) |
| Sleep onset latency (min) | 18.50 | (8.59) |
| WASO (min) | 18.77 | (14.18) |
| Stage 1 sleep (%) | 3.51 | (2.30) |
| Stage 2 sleep (%) | 47.53 | (4.98) |
| Slow wave sleep (%) | 21.46 | (4.81) |
| REM sleep (%) | 24.96 | (3.86) |
| REM latency (min) | 111.29 | (42.20) |
| Sleep onset time | 21:19:42 | (0:39:32) |
| Awakening time | 6:34:14 | (0:23:06) |

EEG, electroencephalography; REM, rapid eye movement; WASO, wake after sleep onset.
[a] Refers to 191 children, the total sample size.
[b] Refers to 146 children who underwent in-home sleep-EEG.

Post hoc power analysis using G*Power was conducted to evaluate the statistical power given the sample size of the study [39]. Post hoc calculations regarding correlations revealed a power of 0.80 to detect small to medium effect sizes (i.e., $r = 0.20$) at a 0.05 alpha level (two-sided; based on the total sample size). Therefore, the present study was deemed sufficiently powered to detect effect sizes of $r = 0.20$ [40].

### 2.2. Sleep assessment

Sleep was assessed using the Somté PSG (Compumedics, Singen, Germany), a portable sleep-monitoring device during a single night on a regular school day at the children's home. Sleep-EEG signals C3/A2 and C4/A1, right and left electrooculogram and bipolar submental electromyogram were obtained. The sleep-EEG reports were analyzed by two experienced raters according to standard procedures [41]. The following sleep indices were evaluated:

- Total sleep time (TST; time in bed minus time spent awake in hours).
- Sleep continuity: sleep efficiency (SE; TST/time in bed × 100), sleep onset latency (SOL; min), and wake after sleep onset (WASO; the amount of time awake from the initial sleep onset to the last awakening; min).
- Sleep architecture (%): stage 1 sleep, stage 2 sleep, slow-wave sleep (SWS), rapid-eye-movement (REM) sleep, and REM latency (min).

Furthermore, sleep onset time and awakening time are reported. Sleep-EEG data were available for 146 children.

To evaluate whether there was a first-night effect due to sleep-EEG assessment, children also reported whether they had a quiet night of sleep for the sleep-EEG night as well as for the following six nights. While for the sleep-EEG night 89.0% reported that they had a quiet night, this figure was on average 94.2% for the following six nights.

### 2.3. Parent reports of children's sleep-related behavior

Parents completed the CSHQ-DE [36], a retrospective questionnaire to examine sleep-related behavior in children regarding a 'typical' recent week. In most cases parents completed the questionnaire during the afternoon or early evening before sleep-EEG assessment was conducted. Items were answered on a three-point scale with the response options "usually" (5–7/week), "sometimes" (2–4/week), or "rarely" (0–1/week). Eight scales including one to eight items and reflecting the following sleep domains were calculated: bedtime resistance, sleep onset delay, sleep duration problems, sleep anxiety, night wakings, parasomnias, sleep-disordered breathing, and daytime sleepiness. In addition an overall sleep disturbance score was calculated. Higher scores indicate greater sleep-related behavior problems. Table 2 shows Cronbach's alpha for maternal and paternal reports of the CSHQ-DE scales, intraclass correlations (ICC) for maternal and paternal reports as an index of interrater agreement, and *t*-values for mean comparisons between maternal and paternal reports. Cronbach's alpha ranged from $\alpha = 0.41$ to $\alpha = 0.72$. Interrater agreements were fair to excellent for all scales and ranged from ICC = 0.54 to ICC = 0.88. On average, maternal reports of children's sleep duration problems, parasomnias, daytime sleepiness, and overall disturbance score were higher than paternal reports. For 185 children maternal reports and for 154 children paternal reports of sleep-related behavior were available.

### 2.4. Assessment of parental insomnia symptoms

Parents reported their current (i.e., last two weeks) insomnia symptoms on the German version of the ISI [37,38], a questionnaire consisting of seven items, rated on a five-point Likert scale. A higher ISI score indicates greater insomnia severity. Table 2 also shows Cronbach's alpha, ICC, and *t*-value for the ISI scale. For 184 children the mothers' reports and for 153 children the fathers' reports of their own insomnia symptoms were available. For 142 children both maternal reports of insomnia symptoms and children's sleep-EEG indices were available. For 123 children both paternal reports of insomnia symptoms and children's sleep-EEG indices were available.

### 2.5. Statistical analysis

Multiple regression analyses were conducted with parental insomnia symptoms as independent variables and children's sleep-EEG as dependent variable, to examine whether maternal and paternal insomnia symptoms are related to children's sleep measured objectively with in-home sleep-EEG (hypothesis 1). All analyses were controlled for children's age, sex, and prematurity status if not stated otherwise. Multiple regression analyses were performed with IBM® SPSS® Statistics 22 (IBM Corporation, Armonk NY, USA) for Apple Mac® and standardized betas, adjusted *t*-values, and adjusted *p*-values (two-tailed) are reported. To test hypothesis 2 (whether parents with more insomnia symptoms reported more sleep-related behavior problems in their children than parents with fewer insomnia symptoms) we computed APIMs with the lavaan package in R for each CSHQ-DE scale. APIMs were controlled for children's age, sex, and prematurity status. Further, we calculated APIMs that were additionally controlled for sleep-EEG patterns (TST and SE) to examine the degree to which effects of parental insomnia can be explained by children's actual sleep. For APIM analyses, unstandardized regression coefficients and adjusted *p*-values are reported. By z-standardization of the scales before the analyses, interpretation of the unstandardized regression coefficients is facilitated. The APIM analyses were conducted with the full sample of 191 parental couples. Full-information maximum likelihood estimation was used to deal with missing values, which is considered a more

**Table 2**
Descriptive statistics for parent reports of children's sleep-related behavior and the parents' own insomnia symptoms.

| | Maternal report | | Cronbach's α | Paternal report | | Cronbach's α | Intra-class correlations | *t*-value |
|---|---|---|---|---|---|---|---|---|
| | Mean | (SD) | | Mean | (SD) | | ICC | |
| Children's sleep patterns (CSHQ-DE)[a] | | | | | | | | |
| Bedtime resistance | 6.81 | (1.46) | 0.61 | 6.79 | (1.33) | 0.55 | 0.85 | −1.27 |
| Sleep onset delay | 1.36 | (0.62) | n/a | 1.41 | (0.68) | n/a | 0.75 | −0.29 |
| Sleep duration problems | 3.66 | (1.08) | 0.59 | 3.43 | (0.87) | 0.66 | 0.54 | 2.90** |
| Sleep anxiety | 4.90 | (1.44) | 0.64 | 4.75 | (1.30) | 0.62 | 0.80 | 0.67 |
| Night wakings | 3.53 | (0.92) | 0.57 | 3.56 | (0.84) | 0.41 | 0.77 | −0.69 |
| Sleep-disordered breathing | 3.35 | (0.87) | 0.72 | 3.28 | (0.75) | 0.69 | 0.88 | 1.51 |
| Parasomnias | 8.43 | (1.55) | 0.55 | 7.98 | (1.22) | 0.44 | 0.72 | 3.54*** |
| Daytime sleepiness | 12.54 | (2.39) | 0.59 | 12.19 | (2.37) | 0.57 | 0.73 | 2.18* |
| Sleep disturbance score | 42.17 | (5.02) | 0.71 | 41.09 | (4.77) | 0.70 | 0.82 | 3.27** |
| Parental insomnia problems (ISI)[b] | 14.07 | (4.23) | 0.74 | 13.92 | (3.66) | 0.67 | 0.08 | 0.62 |

CSHQ-DE, the German version of the Children's Sleep Habits Questionnaire; ICC, intra-class correlations; ISI, Insomnia Severity Index; SD, standard deviation.
*$p < 0.05$, **$p < 0.01$ (two-tailed), ***p < 0.001.
[a] Refers to 185 children with maternal reports and 154 children with paternal reports.
[b] Refers to 184 mothers and 153 fathers.

reliable procedure compared to other more conventional methods [42].

## 3. Results

### 3.1. Descriptive statistics and preliminary analyses

Table 1 shows descriptive statistics of background variables and children's sleep-EEG indices, while Table 2 shows descriptive statistics for parent-reported children's sleep-related behavior (CSHQ-DE scales), and parental insomnia symptoms (ISI scale).

Child age was negatively related to EEG-derived TST ($r = -0.48$, $p < 0.001$) and positively related to sleep onset time ($r = 0.40$, $p < 0.001$). Regarding maternal-reported sleep-related behavior, child age was negatively related to bedtime resistance ($r = -0.17$, $p = 0.019$), sleep anxiety ($r = -0.21$, $p = 0.005$), night wakings ($r = -0.17$, $p = 0.024$), and sleep disturbance score ($r = -0.16$, $p = 0.030$). Regarding paternal-reported sleep-related behavior, child age was negatively related to sleep anxiety ($r = -0.18$, $p = 0.025$) and positively related to sleep duration problems ($r = 0.19$, $p = 0.021$). Girls showed shorter EEG-derived REM latency ($t(144) = 2.35$, $p = 0.020$), earlier awakening time ($t(144) = 3.06$, $p = 0.003$), and more maternal and paternal reported sleep onset delay than boys ($t(183) = -2.14$, $p = 0.034$; $t(150) = -2.49$, $p = 0.014$). Very preterm children showed earlier sleep onset times compared to term-born children, while there were no further significant group differences regarding sleep-EEG indices (for a detailed report see Maurer et al. [35]). Mothers of very preterm born children reported fewer sleep duration problems ($t(183) = 2.72$, $p = 0.007$) and more sleep anxiety ($t(183) = -2.95$, $p = 0.011$) than mothers of full-term children. The remaining maternal-reported CSHQ-scales and paternal-reported sleep-related behaviors did not differ between children born very preterm and full-term.

### 3.2. Associations of parental insomnia symptoms with children's in-home sleep-EEG

Table 3 shows the association between parental insomnia symptoms and children's sleep-EEG indices. Increased maternal insomnia symptoms were associated with less children's sleep-EEG TST ($\beta = -0.17$, $t = -2.20$, $p = 0.029$), which is in line with our first hypothesis. There was no significant association between maternal insomnia and children's sleep-EEG continuity (SE, SOL, WASO). Moreover, increased maternal insomnia symptoms were associated with more stage 2 sleep ($\beta = 0.21$, $t = 2.50$, $p = 0.014$), less SWS ($\beta = -0.17$, $t = -2.05$, $p = 0.043$), later sleep onset time ($\beta = 0.25$, $t = 3.34$, $p = 0.001$), and later awakening time ($\beta = 0.20$, $t = 2.44$, $p = 0.016$) in children. No significant association between paternal insomnia symptoms and children's sleep-EEG was found.

**Table 3**
Association between parental insomnia symptoms and children's sleep-electroencephalography indices.

| | Maternal insomnia problems[a] | | Paternal insomnia problems[b] | |
|---|---|---|---|---|
| | β | *t* | β | *t* |
| Total sleep time (h) | −0.17* | −2.20 | 0.07 | 0.84 |
| Sleep efficiency | −0.12 | −1.39 | 0.18 | 1.96 |
| Sleep onset latency | 0.06 | 0.70 | −0.17 | −1.85 |
| WASO (min) | 0.08 | 0.90 | −0.10 | −1.07 |
| Stage 1 sleep (%) | −0.03 | −0.32 | 0.03 | 0.34 |
| Stage 2 sleep (%) | 0.21* | 2.50 | 0.03 | 0.29 |
| Slow-wave sleep (%) | −0.17* | −2.05 | −0.05 | −0.51 |
| REM sleep (%) | −0.03 | −0.36 | 0.02 | 0.20 |
| REM latency (min) | 0.01 | 0.17 | 0.09 | 1.01 |
| Sleep onset time | 0.25** | 3.34 | 0.03 | 0.39 |
| Awakening time | 0.20* | 2.44 | 0.12 | 1.29 |

Data adjusted for children's age, sex, and prematurity status. EEG, electroencephalography; REM, rapid eye movement; WASO, wake after sleep onset.
*$p < 0.05$, **$p < 0.01$ (two-tailed).
[a] Refers to 142 children with both sleep-EEG and maternal reports of insomnia symptoms.
[b] Refers to 123 children with both sleep-EEG and paternal reports of insomnia symptoms.

### 3.3. Associations of parental insomnia symptoms with parental perception of children's sleep-related behavior (APIM-analyses)

Table 4 shows the association between parental insomnia symptoms and children's sleep-related behavior as reported by the parents. Significant actor and partner effects emerged. For mothers, their own insomnia levels predicted their perception of children's bedtime resistance ($b = 0.28$, $p < 0.001$), sleep anxiety ($b = 0.23$, $p = 0.001$), night wakings ($b = 0.18$, $p = 0.015$), and overall sleep disturbance score ($b = 0.23$, $p = 0.001$) (actor effects). Moreover, maternal insomnia symptoms were positively linked to paternal perception of children's bedtime resistance ($b = 0.33$, $p < 0.001$), sleep anxiety ($b = 0.21$, $p = 0.009$), sleep-disordered breathing ($b = 0.19$, $p = 0.004$), and overall sleep disturbance score ($b = 0.19$, $p = 0.006$) (partner effects). All these associations remained significant when controlling children's sleep-EEG indices and were thus not explained by objective sleep measures.

**Table 4**
Results of actor–partner interdependence models for maternal and paternal insomnia predicting maternal and paternal reports of sleep-related behavior of their children.

| | Maternal report of child sleep | | Paternal report of child sleep | |
|---|---|---|---|---|
| | Actor effects (Maternal insomnia as predictor) | Partner effects (Paternal insomnia as predictor) | Actor effects (Paternal insomnia as predictor) | Partner effects (Maternal insomnia as predictor) |
| Bedtime resistance | 0.28***/0.28*** | 0.06/0.05 | 0.09/0.07 | 0.33***/0.32*** |
| Sleep onset delay | 0.07/0.02 | −0.13/−0.06 | −0.13/−0.08 | 0.13/0.09 |
| Sleep duration problems | 0.12/0.10 | 0.05/0.03 | 0.29***/0.29*** | 0.03/0.01 |
| Sleep anxiety | 0.23**/0.24** | 0.02/0.01 | 0.00/−0.03 | 0.21**/0.21** |
| Night wakings | 0.18*/0.17* | 0.03/0.02 | 0.08/0.09 | 0.15/0.14 |
| Sleep-disordered breathing | 0.13/0.12 | −0.14/−0.17 | 0.03/0.06 | 0.19**/0.19* |
| Parasomnias | 0.07/0.06 | 0.03/0.03 | 0.12/0.10 | 0.07/0.08 |
| Daytime sleepiness | 0.09/0.08 | 0.15/0.17* | 0.18*/0.19* | 0.05/0.06 |
| Sleep disturbance score | 0.23**/0.23** | 0.05/0.08 | 0.17*/0.19* | 0.19**/0.22** |

Effects are unstandardized estimates. Due to the z-standardization of scales prior to analyses they may be interpreted similar to standardized β regression coefficients. Estimates before the solidus (/) are controlled for child's age, sex, and prematurity status. Estimates after the solidus (/) are additionally controlled for sleep-electroencephalography patterns (total sleep time and sleep efficiency). Partner effects regarding maternal reports are the effects of paternal insomnia on the mothers' perception of children's sleep-related behavior. Partner effects regarding paternal reports are the effects of maternal insomnia reports on fathers' perception of children's sleep-related behavior.
*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

For fathers, insomnia symptoms were positively associated with their perception of children's sleep duration problems ($b = 0.29$, $p < 0.001$), daytime sleepiness ($b = 0.18$, $p = 0.021$), and the overall sleep disturbance score ($b = 0.17$, $p = 0.021$) (actor effects). These associations also remained significant when controlling children's sleep-EEG indices. However, paternal insomnia symptoms were unrelated to maternal perception of children's sleep-related behavior (partner effects) in the first step of the analyses (i.e., not controlling children's sleep-EEG indices). A significant association between paternal insomnia symptoms and mothers' perception of children's daytime sleepiness emerged only in the model that additionally controlled the children's sleep-EEG indices ($b = 0.17$, $p = 0.046$).

## 4. Discussion

This is the first study that reports associations between parental insomnia symptoms and children's sleep assessed with in-home sleep-EEG. Further, it analyzes for the first time actor and partner effects regarding the association between mothers' and fathers' insomnia symptoms and their perception of children's sleep. The key findings were that maternal but not paternal insomnia was related to children's EEG-derived sleep. Moreover, maternal insomnia symptoms were associated with both maternal and paternal reports of children's bedtime resistance and sleep anxiety. Paternal insomnia was related to the father's own reports of children's sleep duration problems and daytime sleepiness. These associations were not explained by the children's sleep-EEG indices.

### *4.1. Associations of parental insomnia symptoms with children's in-home sleep-EEG*

In accordance with our first hypothesis, maternal insomnia was related to children's sleep duration measured by EEG. In addition, maternal insomnia was associated with children's sleep-EEG architecture including more stage 2 sleep and less SWS and sleep timing including later sleep onset and awakening time. However, maternal insomnia was unrelated to children's sleep continuity measured by sleep-EEG. Paternal insomnia and children's sleep-EEG indices were unrelated. These findings are in line with prior studies reporting associations between maternal and children's sleep patterns as measured both by sleep-EEG [8] or by actigraphy [9] but not between paternal and children's sleep patterns [9]. A possible explanation for a stronger association between maternal insomnia symptoms and children's objective sleep patterns might be that mothers in Switzerland tend to spend more time with their children than fathers [43,44]. Maternal and children's sleep may therefore also influence each other more strongly.

### *4.2. Associations of parental insomnia symptoms with parental perception of children's sleep-related behavior*

Consistent with our second hypothesis and the results from Rönnlund et al. [24] we found that parents with more insomnia symptoms also reported more sleep-related behavior problems for their children. Mothers with higher levels of insomnia symptoms perceived more bedtime resistance, sleep anxiety, and night wakings in their children (maternal actor effects for CSHQ-DE scales). Maternal insomnia problems were also associated with paternal perception of bedtime resistance, sleep anxiety, and sleep disordered breathing (partner effects). In turn, fathers with higher levels of insomnia symptoms perceived more sleep duration problems and daytime sleepiness (actor effects). However, paternal insomnia symptoms were not associated with maternal perception of children's sleep duration problems and daytime sleepiness (partner effects). The only partner effect, which was between paternal insomnia symptoms and maternal perception of child's daytime sleepiness, emerged after controlling children's sleep-EEG.

Possible explanations for the association of maternal insomnia with children's bedtime resistance and sleep anxiety include interactions between children's and parental sleep-related behavior. Children's sleep difficulties and subsequent behavior could prevent parents from having a good night's sleep or vice versa [10,11]. Further, it is possible that some of the families' homes provided generally unfavorable sleep environments, e.g., due to environmental noise [20]. Moreover, shared genetic risk could account for vulnerabilities to sleep difficulties in parents and children [21]. A possible explanation for a greater number of partner effects related to maternal insomnia symptoms might again be that mothers spend more time with their children than fathers and that there might be more mutual influences [43,44]. On the other hand, it is also possible that mothers report their perception of children's sleep difficulties to their partners more often than vice versa. These reports, however, can already be influenced by maternal sleep problems.

Notably, none of the above-mentioned associations between parental insomnia symptoms and children's sleep-related behavior problems, as reported by the parents, could be explained by

objective measures of children's sleep. Therefore, one alternative explanation of the association between parental sleep difficulties and their reports of children's sleep is over-reporting of children's sleep problems – parents with insomnia symptoms may exhibit an attention bias towards negative sleep-related stimuli including their children's sleep problems [30,31]. This interpretation is generally in line with a prior study reporting an association between poor parental sleep and parent ratings of their two- to six-year-old children's sleep controlling children's objective sleep measured by actigraphs [24]. In opposition to this interpretation, however, it can be argued that one night of in-home sleep-EEG may not accurately represent children's common sleep behavior. Nevertheless, a prior study using in-home sleep-EEG in children showed relatively high stability across 18 months, particularly regarding EEG-derived sleep duration and sleep architecture [45]. In sum, it is possible that parental insomnia leads to over-reporting regarding their children's sleep problems. Moreover, it is possible that parental selective attention and monitoring of children's sleep difficulties may in some cases even trigger children's sleep disturbances in a similar fashion to that described by Harvey's cognitive model of insomnia [27]. From a clinical perspective it therefore appears important to carefully diagnose children's sleep difficulties taking the family context into account.

### 4.3. Strengths and limitations

The major strength of our study is that children's sleep was measured by in-home sleep-EEG, which increases the ecological validity of sleep assessment compared to laboratory based PSG. In addition, information from both parents was available and actor and partner effects regarding the association between parental insomnia and parental perception of children's sleep could be examined.

However, the current study is not without limitations. First, in-home sleep-EEG was only conducted during one single night, which may decrease reliability compared to assessment across multiple nights. Relatedly, there was no EEG-adaptation night and therefore it is not possible to rule out first-night effects. By contrast, parents referred to a longer period of time when rating their children's sleep (i.e., one week) and their own insomnia symptoms (i.e., two weeks). Second, the study sample included very preterm children and age- and sex-matched controls, therefore, the findings may not necessarily apply to the general population. Third, parental insomnia symptoms were assessed with self-report questionnaires, which do not necessarily reflect clinically relevant insomnia.

## 5. Conclusions

The present study implies that it is important to consider children's sleep in the family context. In particular, maternal insomnia appears to be associated with children's objectively measured sleep duration, sleep architecture (stage 2 sleep and SWS), and sleep onset and awakening time. These associations may reflect a mutual interdependence between maternal and children's sleep. Parental insomnia symptoms were also associated with parental perception of children's sleep-related behavior problems, in particular regarding bedtime resistance, sleep duration problems, sleep anxiety, night wakings, and daytime sleepiness. On the one hand, these associations may also be seen in the light of the mutual interdependence of parental and children's sleep. On the other hand, these associations may at least partly reflect parental overrating of children's sleep-related behavior problems due to a negativity bias in parents, who suffer from insomnia symptoms themselves, as the associations were not explained by objective measures of children's sleep. It is possible that selective attention and increased monitoring of children's sleep alongside unindicated treatment attempts may even pose a risk for children's duration and quality of sleep.

## 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 (Project: Sleep, Cognitive, and Socio-emotional Development in Preterm Children during Middle and Late Childhood, grant number 143962; Socio-emotional development and mental health of preterm children: The role of HPA-axis function, sleep, neuroplasticity, and physical exercise during the transition to adolescence, Grant number: 159362) and the University of Basel (Project: Early origins of self-regulation and sleep, Grant number DPE2083) for funding the research.

## Conflict of interest

The authors have no conflicts of interest to declare.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: http://dx.doi.org/10.1016/j.sleep.2017.07.010.

## References

[1] Astill RG, Van der Heijden KB, Van IJzendoorn MH, et al. Sleep, cognition, and behavioral problems in school-age children: a century of research meta-analyzed. Psychol Bull 2012;138:1109–38.
[2] Dewald JF, Meijer AM, Oort FJ, et al. The influence of sleep quality, sleep duration and sleepiness on school performance in children and adolescents: a meta-analytic review. Sleep Med Rev 2010;14:179–89.
[3] Gregory AM, Sadeh A. Sleep, emotional and behavioral difficulties in children and adolescents. Sleep Med Rev 2012;16:129–36.
[4] Brand S, Hatzinger M, Stadler C, et al. Does objectively assessed sleep at five years predict sleep and psychological functioning at 14 years? – Hmm, yes and no! J Psychiatr Res 2015;60:148–55.
[5] Fricke-Oerkermann L, Plück J, Schredl M, et al. Prevalence and course of sleep problems in childhood. Sleep 2007;30:1371–7.
[6] Spruyt K, O'Brien LM, Cluydts R, et al. Odds, prevalence and predictors of sleep problems in school-age normal children. J Sleep Res 2005;14:163–76.
[7] El-Sheikh M, Sadeh A. Sleep and development: advancing theory and research. Monogr Soc Res Child Dev 2015;80:1–215.
[8] Kalak N, Gerber M, Kirov R, et al. The relation of objective sleep patterns, depressive symptoms, and sleep disturbances in adolescent children and their parents: a sleep-EEG study with 47 families. J Psychiatr Res 2012;46:1374–82.
[9] Kouros CD, El-Sheikh M. Within family relations in objective sleep duration, quality, and schedule. Child Dev 2016:1–18. http://dx.doi.org/10.1111/cdev.12667/full.
[10] Brand S, Gerber M, Hatzinger M, et al. Evidence for similarities between adolescents and parents in sleep patterns. Sleep Med 2009;10:1124–31.
[11] Bajoghli H, Alipouri A, Holsboer-Trachsler E, et al. Sleep patterns and psychological functioning in families in northeastern Iran; evidence for similarities between adolescent children and their parents. J Adolesc 2013;36:1103–13.
[12] Meltzer LJ, Mindell JA. Relationship between child sleep disturbances and maternal sleep, mood, and parenting stress: a pilot study. J Fam Psychol 2007;21:67–73.
[13] Zhang J, Li AM, Fok TF, et al. Roles of parental sleep/wake patterns, socioeconomic status, and daytime activities in the sleep/wake patterns of children. J Pediatr 2010;156:606–12.
[14] Mindell JA, Sadeh A, Kwon R, et al. Relationship between child and maternal sleep: a developmental and cross-cultural comparison. J Pediatr Psychol 2015;40:689–96.
[15] Reid GJ, Huntley ED, Lewin DS. Insomnias of childhood and adolescence. Child Adolesc Psychiatr Clin N Am 2009;18:979–1000.
[16] Gregory AM, Moffitt TE, Ambler A, et al. Maternal insomnia and children's family socialization environment. Sleep 2012;35:579–82.
[17] El-Sheikh M, Buckhalt JA, Mize J, et al. Marital conflict and disruptions to children's sleep. Child Dev 2006;77:31–43.
[18] Tynjälä J, Kannas L, Levälahti E, et al. Perceived sleep quality and its precursors in adolescents. Health Promot Int 1999;14:155–66.

[19] Bernert RA, Merrill KA, Braithwaite SR, et al. Family life stress and insomnia symptoms in a prospective evaluation of young adults. J Fam Psychol 2007;21:58–66.
[20] Bell BG, Belsky J. Parents, parenting, and children's sleep problems: exploring reciprocal effects. Br J Dev Psychol 2008;26:579–93.
[21] Barclay NL, Gregory AM. Quantitative genetic research on sleep: a review of normal sleep, sleep disturbances and associated emotional, behavioural, and health-related difficulties. Sleep Med Rev 2013;17:29–40.
[22] Gay CL, Lee KA, Lee SY. Sleep patterns and fatigue in new mothers and fathers. Biol Res Nurs 2004;5:311–8.
[23] Lee KA, Zaffke ME, McEnany G. Parity and sleep patterns during and after pregnancy. Obstet Gynecol 2000;95:14–8.
[24] Rönnlund H, Elovainio M, Virtanen I, et al. Poor parental sleep and the reported sleep quality of their children. Pediatrics 2016. http://dx.doi.org/10.1542/peds.2015-3425.
[25] Matricciani LA, Olds TS, Blunden S, et al. Never enough sleep: a brief history of sleep recommendations for children. Pediatrics 2012;129:548–56.
[26] Iglowstein I, Jenni OG, Molinari L, et al. Sleep duration from infancy to adolescence: reference values and generational trends. Pediatrics 2003;111:302–7.
[27] Harvey AG. A cognitive model of insomnia. Behav Res Ther 2002;40:869–93.
[28] Sadeh A. Sleep assessment methods. Monogr Soc Res Child Dev 2015;80:33–48. III.
[29] Sadeh A, Mindell J, Rivera L. "My child has a sleep problem": a cross-cultural comparison of parental definitions. Sleep Med 2011;12:478–82.
[30] Gobin CM, Banks JB, Fins AI, et al. Poor sleep quality is associated with a negative cognitive bias and decreased sustained attention. J Sleep Res 2015;24:535–42.
[31] Jansson-Fröjmark M, Bermås M, Kjellén A. Attentional bias in insomnia: the dot-probe task with pictorial stimuli depicting daytime fatigue/malaise. Cogn Ther Res 2013;37:534–46.
[32] Kenny DA, Kashy DA, Cook WL. Dyadic data analysis. New York. 2006.
[33] Lemola S, Perkinson-Gloor N, Hagmann-von Arx P, et al. Morning cortisol secretion in school-age children is related to the sleep pattern of the preceding night. Psychoneuroendocrinology 2015;52:297–301.
[34] Perkinson-Gloor N, Hagmann-von Arx P, Brand S, et al. The role of sleep and the hypothalamic-pituitary-adrenal axis for behavioral and emotional problems in very preterm children during middle childhood. J Psychiatr Res 2015;60:141–7.
[35] Maurer N, Perkinson-Gloor N, Stalder T, et al. Salivary and hair glucocorticoids and sleep in very preterm children during school age. Psychoneuroendocrinology 2016;72:166–74.
[36] Schwerdtle B, Hautzinger M. Validation and psychometric properties of the German version of the Children's sleep habits questionnaire (CSHQ-DE). Somnologie (Berl) 2010;14:260–6.
[37] Bastien CH, Vallières A, Morin CM. Validation of the Insomnia Severity Index as an outcome measure for insomnia research. Sleep Med 2001;2:297–307.
[38] Morin C. Insomnia. New York: Guilford Press; 1993.
[39] Faul F, Erdfelder E, Lang AG, et al. G* Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behav Res Meth 2007;39:175–91.
[40] Cohen J. Statistical power analysis for the behavioral sciences. 2nd ed. Hillsdale, New York: Lawrence Erlbaum Associates; 1988.
[41] Rechtschaffen A, Kales A. A manual for standardized terminology, techniques and scoring system for sleep stages of human subjects. Los Angeles: BIS/BRI; 1968. p. 1–12.
[42] Allison PD. Missing data techniques for structural equation modeling. J Abnorm Psychol 2003;112:545–57.
[43] SFSO. Veränderungen beim Zeitaufwand für Haus- und Familienarbeit: 1997–2007. Bundesamt für Statistik Schweiz (Swiss Federal Statistical Office); 2009. p. 27.
[44] Craig L. Does father care mean fathers share? A comparison of how mothers and fathers in intact families spend time with children. Gend Soc 2006;20:259–81.
[45] Perkinson-Gloor N, Hagmann-von Arx P, Brand S, et al. Intraindividual long-term stability of sleep electroencephalography in school-aged children. Sleep Med 2015;16:1348–51.

## APPENDIX D: Selbständigkeitserklärung

Hiermit erkläre ich, dass ich die Dissertation „Biological processes related to positive development after preterm birth: The interplay between sleep, hypothalamic-pituitary-adrenal axis activity, and autonomic functioning, and the role of parental insomnia symptoms“ 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.

Basel, im April 2018

Natalie Urfer-Maurer

# APPENDIX E: Curriculum Vitae

| | |
|---|---|
| Name: | Natalie Urfer-Maurer |
| Nationality: | Swiss (Basel, BS) |
| Date of Birth: | June 9, 1990 |

**Higher Education**

| | |
|---|---|
| 2015 – 2018 | Research assistant and doctoral student at the Department of Psychology, Division of Developmental and Personality Psychology, University of Basel, Switzerland |
| 2013 – 2015 | Master of Science in Psychology, Major in Clinical Psychology and Neuroscience, University of Basel, Switzerland |
| 2010 – 2013 | Bachelor of Science in Psychology, University of Basel, Switzerland |

**School Education**

| | |
|---|---|
| 2006 – 2009 | High School, Oberwil, Switzerland |
| 2002 – 2006 | Secondary School, Therwil, Switzerland |
| 1997 – 2002 | Primary School, Therwil, Switzerland |

**Internships**

| | |
|---|---|
| 2015 | Intern at Universitäre Psychiatrische Kliniken Basel, Zentrum Spezielle Psychotherapie, AbteilungVerhaltenstherapie-stationär, Basel, Switzerland |
| 2013 | Intern at the Department of Psychology, project “Sleep, cognitive, and socio-emotional development in preterm children during middle and late childhood”, Basel, Switzerland |