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

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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

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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

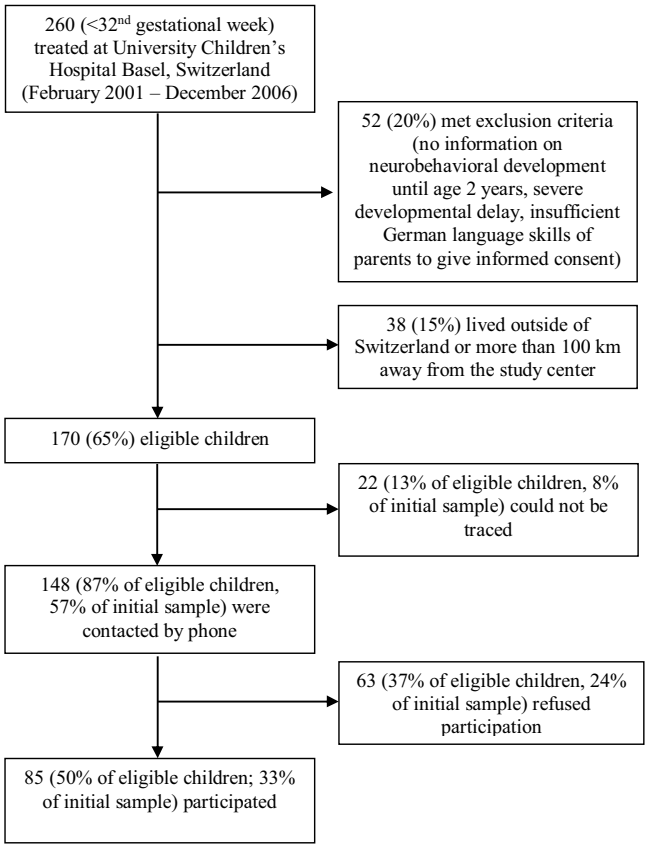

Fig. 1. Inclusion procedure of very preterm children.