

Sleep, physical activity, and health in children – a developmental perspective

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ABSTRACT

Adequate rest and periods of activity are important for maintaining physiological homeostasis, for the adaptive functioning of the stress-response systems, and they promote psychological well-being. However, knowledge on the associations of sleep and physical activity with stress system functioning, and of physical activity with psychiatric problems is limited especially in children and youth.

This study was designed to address three research questions, (1) whether sleep is associated with cardiovascular function in 8-year-old children, (2) whether physical activity is associated with psychiatric problems in 8-year-old children, and (3) whether physical activity is associated with hypothalamic-pituitary-adrenocortical axis (HPAA) function in 8- and 12-year-old children.

The participants came from an urban community-based cohort originally comprising 1049 infants born in 1998 in Helsinki, Finland. Sleep and physical activity were objectively measured using accelerometers. Sleep was also assessed using parent-reported questionnaire-based data.

Of the 413 children invited to a follow-up, 321 participated at a mean age of 8.1 years. Of these, 231 to 274 were included in the analyses of sleep and ambulatory blood pressure, or cardiovascular reactivity to the Trier Social Stress Test for Children (TSST-C). The children's mothers and teachers filled in a questionnaire reporting common childhood psychiatric problems, and 199 children had valid data on physical activity and psychiatric problems from both observers. HPAA activity was measured via salivary cortisol concentrations, 252 of the children with valid data on physical activity had data on diurnal salivary cortisol, and 248 had data on salivary cortisol responses to the TSST-C.

Later, of the 920 adolescents invited to a further follow-up, 451 participated at a mean age of 12.3 years. Of these, 283 adolescents with valid physical activity data provided data on diurnal salivary cortisol, and 272 adolescents provided data on salivary cortisol responses to a low-dose overnight dexamethasone suppression test (DST), a method used to study the individual physiological variation in HPAA feedback inhibition.

In contrast with a wealth of evidence especially from adults, the results showed that sleep in healthy children was not associated with an unhealthy cardiovascular phenotype. Higher physical activity levels were associated with a lower probability for psychiatric problems in children as well as lower HPAA reactivity to psychosocial stress at 8 years of age. In addition, in early adolescence (12 years of age) physical activity was associated with lower morning cortisol levels in girls and higher HPAA suppression in response to the DST in boys.

These results provide evidence on the health-related associations of sleep and physical activity in a community-based cohort of children. These findings offer insight into the influence of physical activity on physical and mental well-being, by suggesting that physical activity could promote health by moderating HPAA function. As the results are correlational in nature, further research using a prospective controlled methodology is called for. This study emphasizes the importance of sustaining and supporting high physical activity levels throughout childhood and adolescence.

TIIVISTELMÄ

Riittävä lepo ja fyysinen aktiivisuus ovat keskeisiä fysiologisen tasapainon ja stressijärjestelmien toiminnan kannalta. Molemmat tekijät myös tukevat psyykkistä hyvinvointia. Erityisesti lapsia ja nuoria koskeva tieteellinen tieto unen ja fyysisen aktiivisuuden yhteyksistä stressijärjestelmien toimintaan, ja fyysisen aktiivisuuden yhteyksistä psykiatriseen oireiluun, on kuitenkin vielä vähäistä. Tämä väitöskirja vastaa kolmeen tutkimuskysymykseen: (1) onko unen laatu ja määrä yhteydessä kardiiovaskulaarijärjestelmän aktiivisuuteen 8-vuoden iässä, (2) onko fyysinen aktiivisuus yhteydessä psykiatristen oireiden esiintyvyyteen 8-vuoden iässä, ja (3) onko fyysinen aktiivisuus yhteydessä hypotalamus–aivolisäke–lisämunuaiskuori-akselin (HPA-akseli) toimintaan 8- ja 12-vuoden iässä.

Tutkimuksen osallistajat ovat osa kaupunkilaisväestöön pohjautuvaa seurantatutkimusta, johon osallistui alun perin 1049 vuonna 1998 Helsingissä syntynyttä lasta. Unta ja fyysistä aktiivisuutta mitattiin objektiivisesti kiihtyvyyssantureilla. Unta arvioitiin myös vanhempien täyttämän kyselylomakkeen avulla.

Kutsutuista 413 lapsesta 321 osallistui jatkotutkimukseen keskimäärin 8.1-vuoden iässä. Näistä lapsista 231–274 osallistui analyyseihin unen ja vuorokausiverenpaineen yhteyksistä tai unen yhteyksistä kardiiovaskulaariseen reaktiivisuuteen psykososiaalisessa stressitestissä (lapsille muokattu Trierin Sosiaalinen Stressikoe, TSST-C). Lasten äidit ja opettajat täyttivät yleisimpiä lasten psykiatrisia oireita koskevan kyselyn. Käyttökelpoista tutkimusaineistoa sekä fyysisestä aktiivisuudesta että psykiatrisista oireista molemmilta havainnoitsijoilta saatiin 199 lapselta. HPA-akselin toimintaa arvioitiin syljestä mitattujen kortisolitasojen avulla. Käyttökelpoista aineistoa sekä fyysisestä aktiivisuudesta että vuorokausikortisolista saatiin 252 lapselta ja käyttökelpoista aineistoa fyysisestä aktiivisuudesta ja kortisolitasoista TSST-C:n jälkeen saatiin 248 lapselta.

Myöhemmin 920 nuorta kutsuttiin uuteen jatkotutkimukseen keskimäärin 12.3-vuoden iässä, ja heistä 451 osallistui. Käyttökelpoista aineistoa sekä fyysisestä aktiivisuudesta että vuorokausikortisolista saatiin 283 nuorelta. Lisäksi 248 nuorelta saatiin käyttökelpoista aineistoa fyysisestä aktiivisuudesta ja kortisolitasoista yön yli

tehdyn matala-annoksen deksametasonisuppressiotestin (DST) jälkeen, jonka avulla tutkittiin yksilöllistä fysiologista vaihtelua HPA-akselin negatiivisen palautejärjestelmän toiminnassa.

Useista aikaisemmista tutkimustuloksista poiketen terveillä 8-vuotiailla lapsilla uni ei ollut yhteydessä sydän- ja verisuonitautien riskiä lisäävään kardiovaskulaariseen fenotyyppiin. 8-vuoden iässä fyysisesti aktiivisemmilla lapsilla oli matalampi riski kärsiä psykiatrisista oireista. Lisäksi aktiivisten lasten HPA-akselin reaktiivisuus psykososiaaliseen stressiin oli vähän liikkuvia lapsia matalampi. Varhaisessa murrosiässä (12-vuotiaana) tyttöjen korkeampi fyysinen aktiivisuus oli yhteydessä matalampiin kortisolitasoihin aamulla, kun taas aktiivisemmilla pojilla HPA-akselin suppressio DST:n jälkeen oli suurempaa.

Nämä tulokset lisäävät tieteellistä näyttöä unen ja fyysisen aktiivisuuden yhteyksistä hyvinvointiin lapsilla ja nuorilla. Tulokset saattavat myös tuoda lisää ymmärrystä fyysisen aktiivisuuden ja psyykkisen hyvinvoinnin yhteyksiä selittäviin malleihin näyttämällä, että liikunta saattaa tukea hyvinvointia säätelemällä HPA-akselin toimintaa. Koska tämän tutkimuksen löydökset ovat korrelatiivisia, tarvitaan jatkossa myös kokeellisia pitkittäistutkimuksia, jotta voitaisiin perehtyä löydösten syy-seuraus -suhteisiin. Tämän tutkielman löydökset korostavat erityisesti liikuntaan kannustamisen ja liikunnan määrän ylläpitämisen tärkeyttä lapsuudesta varhaiseen murrosikään.

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Helsinki, the 29th of September, 2014

Silja Martikainen

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original articles, which are referred to with their roman numerals **I-V** in the text.

- I** Martikainen, S., Pesonen, A. K., Feldt, K., Jones, A., Lahti, J., Pyhälä, R., Heinonen, K., Kajantie, E., Eriksson, J. & Räikkönen, K. (2011). Poor sleep and cardiovascular function in children. *Hypertension*, 58, 16–21.
- II** Martikainen, S., Pesonen, A. K., Feldt, K., Jones, A., Lahti, J., Pyhälä, R., Heinonen, K., Kajantie, E., Eriksson, J., Strandberg, T. & Räikkönen, K. (2013). Sleep problems and cardiovascular function in children. *Psychosomatic Medicine*, 75, 682–690.
- III** Martikainen, S., Pesonen, A. K., Lahti, J., Heinonen, K., Tammelin, T., Kajantie, E., Eriksson, J., Strandberg, T. & Räikkönen, K. (2012). Physical activity and psychiatric problems in children. *Journal of Pediatrics*, 161, 160–162.
- IV** Martikainen, S., Pesonen, A. K., Lahti, J., Heinonen, K., Feldt, K., Pyhälä, R., Tammelin, T., Kajantie, E., Eriksson, J. G., Strandberg, T. E. & Räikkönen, K. (2013). Higher levels of physical activity are associated with lower hypothalamic-pituitary-adrenocortical axis reactivity to psychosocial stress in children. *Journal of Clinical Endocrinology and Metabolism*, 98, 619–627.
- V** Martikainen, S., Pesonen, A. K., Lahti, J., Heinonen, K., Pyhälä, R., Tammelin, T., Kajantie, E., Strandberg, T. E., Reynolds R. M., & Räikkönen, K. (2014). Physical activity and hypothalamic-pituitary-adrenocortical axis function in adolescents. *Psychoneuroendocrinology*, 49, 96–105.

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ABBREVIATIONS

AUC	Area under the curve
BMI	Body mass index
BSA	Body surface area
CBCL	Child behavior checklist
CI	Confidence interval
CO	Cardiac output
CPM	Counts per minute
DBP	Diastolic blood pressure
DOS	DSM-IV oriented scales
DSM-IV	Diagnostic and statistical manual of mental disorders, 4 th edition
DST	Dexamethasone suppression test
EEG	Electroencephalogram
HF HRV	High frequency heart rate variability
HPAA	Hypothalamic-pituitary-adrenocortical axis
MAP	Mean arterial pressure
MD	Mean difference
MET	Metabolic equivalent
MVPA	Moderate to vigorous physical activity
NREM	Non-rapid eye movement
OR	Odds ratio
PDS	Pubertal Development Scale
PEP	Pre-ejection period
REM	Rapid eye movement
SAMS	Sympathetic adrenal medullary system
SBP	Systolic blood pressure
SD	Standard deviation
SDSC	Sleep disturbance scale for children
TPR	Total peripheral resistance
TRF	Teacher's report form
TSST	Trier social stress test
TSST-C	Trier social stress test for children
VPA	Vigorous physical activity

1 INTRODUCTION

Both regular sleep and physical activity patterns are key factors in sustaining healthy circadian rhythms and for the adaptive functioning of the stress systems. Poor sleep and low levels of physical activity, in children and adolescents, are associated with negative physical and mental health outcomes.

Up to 40% of all children are estimated to suffer from sleep problems and the problems persist in approximately half of those affected (Fricke-Oerkermann et al., 2007). In addition, sedentary lifestyle is common in children and adolescents (Hallal, Wells, Reichert, Anselmi, & Victora, 2006), and with age, children become less likely to meet the recommendations for daily physical activity (Currie et al., 2012; Nader, Bradley, Houts, McRitchie, & O'Brien, 2008).

The transition from childhood to adolescence marks a period of increased vulnerability to mental disorders (Dekker et al., 2007). Supporting sufficient sleep and higher physical activity levels in youth are among the life-style interventions that should be considered in order to prevent stress-related illnesses. However, there is a need for further scientific understanding of the associations of sleep, physical activity, and health from a developmental perspective.

1.1 Sleep and physical activity in stress and well-being

1.1.1 Circadian rhythms

Biological and psychological functioning, as well as social interactions, are determined by circadian rhythmicity (Czeisler & Gooley, 2007). Disruptions and desynchrony of these rhythms may lead to compromised physical (Golombek et al., 2013) and mental health (Germain & Kupfer, 2008). Varying sleep and activity periods are one of the most visible manifestations of the diurnal rhythms. They are also considered as important environmental factors entraining the body's biological clocks (Borbély & Achermann, 1999; Dijk & von Schantz, 2005).

Changes in the functioning of the hypothalamic-pituitary-adrenocortical-axis (HPAA), a major neuroendocrine stress system, as well as physiological changes in the

cardiovascular system functioning are crucial for maintaining the body's homeostasis (internal stability) throughout the day. Both follow similar diurnal fluctuations with increased activity during daytime and lowered activation at night (Hermida, Ayala, & Portaluppi, 2007; Weitzman et al., 1971), increasing alertness and promoting rest. In addition to the maintenance of balanced diurnal functions, the activity of these systems is needed for an adequate response to different stressors (McEwen, 1998).

1.1.2 Stress and allostatic load

Definitions of stress are varied in literature and have been developed over an extended time period (Chrousos & Gold, 1992). In a broad sense, stress can be viewed as any actual or perceived threat to the individual's physical or psychological balance. Contemporary theories have also emphasized the importance of unpredictability to the concept of stress (Koolhaas et al., 2011).

The demands of physical stress to the body's homeostasis are met with a process referred as allostasis "regaining stability through change" (Sterling & Eyer, 1988). Allostatic processes include a network of various humoral and neuronal mechanisms responding to the changes in the environment (Sterling & Eyer, 1988) affecting, for example, the cardiovascular system to increase blood pressure in response to the individual's different activities throughout the day (James, 2007).

In addition to the beneficial adaptation to stressors, however, a prolonged activation of the stress response systems is known to be detrimental for health (Lupien, McEwen, Gunnar, & Heim, 2009; McEwen, 1998). The concept of "allostatic load" introduced by McEwen and Stellar (1993) refers to the prolonged negative effects "the wear and tear" of the stress system activity on the body, which can lead to a higher susceptibility to various psychological and physiological health risks (McEwen, 2008).

1.1.3 The role of sleep and physical activity

As it is known that allostatic load sensitizes the body to negative health outcomes, knowledge on the factors possibly moderating the stress systems' activity and alleviating stress is important for promoting health.

Both sleep (Pace-Schott & Hobson, 2002) and physical activity (Hughes & Piggins, 2012) play a crucial role in maintaining the body's biological rhythms. In addition, both

are known to be associated with beneficial outcomes regarding cardiovascular function (Ayas et al., 2003; Eguchi et al., 2008; Gangwisch et al., 2006; Gottlieb et al., 2006; Javaheri, Storfer-Isser, Rosen, & Redline, 2008; Mezick, Hall, & Matthews, 2012) and HPA activity (Buckley & Schatzberg, 2005; Klaperski, 2013; Pesonen et al., 2012; Rääkkönen et al., 2010; Rimmelé et al., 2007; Rimmelé et al., 2009; Traustadóttir, Bosch, & Matt, 2005).

Better sleep and higher amounts of physical activity are also associated with fewer psychiatric problems (DeVincent, Gadow, Delosh, & Geller, 2007; Johnson et al., 2008; Parfitt, Pavey, & Rowlands, 2009; Pesonen et al., 2010; Strauss, Rodzilsky, Burack, & Colin, 2001) and better health in general (Kantomaa, Tammelin, Ebeling, & Taanila, 2008; Physical Activity Guidelines Advisory Committee, 2008; Riddoch et al., 2009; Strong et al., 2005).

Sleep and physical activity can be considered as important factors for sustaining homeostasis, alleviating stress, and promoting both physical and mental well-being. However, the associations between physical activity, sleep, and health, are still poorly understood especially during childhood and adolescence, and further scientific knowledge is warranted. The proceeding chapters will outline the functioning of the cardiovascular system and the HPA, and how their prolonged hyper- or hypoactivity may relate to individual's well-being. Further, the development and changes in sleep and physical activity and current knowledge of their health related associations are discussed, especially from the viewpoint of HPA activity and cardiovascular function.

1.2 The cardiovascular system

1.2.1 Functioning

The cardiovascular system is responsible for the circulation of blood, providing oxygen and nutrients throughout the body. Blood circulation is maintained by the cardiac output (CO) (the volume of blood pumped by the heart) and constriction of the arteries (peripheral resistance). The rate of blood flow in the arteries is measured by blood pressure, which represents the maximum (systolic) and minimum (diastolic) of the pulse wave created by the rhythmic pumping of the heart (James, 2007).

The main regulator of the cardiovascular system is the autonomic nervous system, separated into sympathetic and parasympathetic branches. Parasympathetic (cholinergic) activity is dominant during rest periods, whereas sympathetic (adrenergic) activity dominates in alert states and in response to stress. The sympathetic adrenal medullary system (SAMS) activity leads to the release of catecholamines epinephrine and norepinephrine, affecting the increase in heart rate and blood pressure (McEwen, 2003).

Changes in the cardiovascular function accommodate the body to its changing needs during rest and activity periods as well as in response to stress. As discussed earlier, cardiovascular function follows a diurnal cycle. Blood pressure decreases nocturnally during sleep (nocturnal dipping), rises sharply after awakening and typically reaches its highest levels during the first hours after awakening (Hermida et al., 2007).

1.2.2 Measuring cardiovascular system activity

Systolic and diastolic blood pressure (SBP and DBP) can be measured by the use of auscultatory and oscillometric techniques. Auscultatory method is based on detecting the Korotkoff's sounds (created by occluding the brachial artery by an inflatable cuff) using a stethoscope. The oscillometric method uses a pressure sensor to detect the mean arterial pressure (MAP) and SBP (by occluding blood flow from the arm or finger). In this method DBP is estimated by the use of device specific algorithms (Lurbe, Sorof, & Daniels, 2004). In addition to these methods blood pressure can also be assessed via tonometry, where the arterial pressure is measured by compressing the radial artery of the wrist, this method can provide semi-continuous measures of blood pressure for approximately once in every 12 to 15 heart beat intervals, the Vasotrac blood pressure measurement device uses this technique (Cua, Thomas, Zurakowski, & Laussen, 2005; Feldt et al., 2011).

As blood pressure levels change over the course of the day and during different activities, the 24-hour ambulatory blood pressure (ABP) measurement has been considered to better characterize the individual's BP level when compared to a single blood pressure measurement. In the 24-hour ABP method, blood pressure is typically measured at 15 to 30 minute intervals during the daytime and 20 to 60 minutes at night over a 24-hour period (Urbina et al., 2008). Using this method day and night specific

mean values for blood pressure can be assessed. Additionally the percentage of measurements exceeding sex and height (or age) specific 95th percentile limits, referred as the ABP load (%), can be calculated. 24-hour ABP is also useful in eliminating the so-called ‘white-coat’ effect, referring to the increased blood pressure values associated with clinic measurements (Wühl, Hadtstein, Mehls, Schaefer, & Escape Trial Group, 2004).

In addition to measuring blood pressure, CO can be measured using impedance cardiography, an electrical measure of blood flow in the thorax. Using blood pressure and CO data, the total peripheral resistance (TPR) can be calculated as $(MAP / CO) \times 80$ (Feldt et al., 2011).

Additionally, by assessing the changes in the heart’s electrical activity over each heart beat interval with electrocardiogram, the autonomic nervous system activity, including pre-ejection period (PEP) and high frequency heart rate variability (HF HRV), can be detected. PEP represents the time interval between the beginning of the electrical stimulation of the heart to the ejection of blood from the heart’s left ventricle, and it is considered as an index of cardiac sympathetic activation (Berntson et al., 1994). HF HRV is an index of parasympathetic activity (reflecting the variation in the vagal control of the heart), and it represents the high frequency component of the variability in heart beat intervals that can be identified from the heart rate data using Fast Fourier Transformation technique (Berntson et al., 1997).

1.2.3 Development and health implications

Normative levels of blood pressure increase throughout childhood into adolescence, and they are sex and age specific (Wühl, Witte, Soergel, Mehls, Schaefer, & German Working Group on Pediatric Hypertension, 2002). Men have higher blood pressure levels than women, and boys are at risk to develop high blood pressure levels when reaching adulthood more commonly than girls (Dasgupta et al., 2006).

Identifying hypertension in pediatric populations is based on age or height specific reference values calculated separately for girls and boys (Wühl et al., 2002). When the 24-hour ABP protocol is used, mean BP below the 95th percentile of sex and age or height specific reference values, and blood pressure load below 25% are considered as normal (Lurbe et al., 2004). For example in 8-year-olds the 95th percentile upper limits

for normal daytime ambulatory SBP and DBP are 124.3 mmHg and 81.8 mmHg for girls and 125.3 mmHg and 81.8 mmHg for boys, whereas in 16-year-olds the upper limits are 130.9 mmHg and 82.1 mmHg for girls and 143.9 mmHg and 83.5 mmHg for boys (Urbina et al., 2008).

High blood pressure levels pose multiple health risks. Longitudinal data show that elevated blood pressure levels in childhood are associated with hypertension (W. Bao, Threefoot, Srinivasan, & Berenson, 1995), manifestations of carotid atherosclerosis (Raitakari et al., 2003) and coronary heart disease (Erlingsdottir, Indridason, Thorvaldsson, & Edvardsson, 2010) in adulthood.

In addition to resting levels, also cardiovascular reactivity to both physical and psychological stressors has various health implications. It has been shown that cardiovascular reactivity to stress predicts risks of subsequent stroke (Everson et al., 2001), coronary calcification (Matthews, Zhu, Tucker, & Whooley, 2006), increased left ventricular mass (Treiber et al., 2003), and hypertension (Matthews et al., 2004), beyond that of resting blood pressure.

High blood pressure and hypertension in pediatric populations are more commonly recognized nowadays than in the past (Lurbe et al., 2009). Furthermore blood pressure tracks over time from childhood to adulthood (Chen & Wang, 2008) making early identification and prevention important.

1.3 The HPAA

1.3.1 Functioning

HPAA activation (e.g., in response to stress) is initiated by the secretion of corticotropin releasing hormone from the paraventricular nucleus of hypothalamus, leading to the release of adrenocorticotrophic hormone from the pituitary gland, and finally to the secretion of glucocorticoids (cortisol in humans) from the adrenal cortex. Cortisol itself then exerts negative feedback inhibition within the HPAA by binding to the glucocorticoid and mineralocorticoid receptors in different levels of the axis, including the hypothalamus and the pituitary, and in different brain regions, leading to the shut-down of the system (Lupien et al., 2009).

HPAA activity follows a diurnal cycle. Cortisol secretion is pulsatile, and the lowest cortisol concentrations have been found in the period of 4 hours before and 2 hours after bed time, after which cortisol secretion increases and reaches its peak during approximately one hour after awakening to decline again towards the nocturnal nadir (Weitzman et al., 1971).

The secretion of cortisol initiated by HPAA activation is important for adequate stress responses, repressing inflammation, and enhancing the effects of catecholamines, as well as leading to an increase in appetite, changes in metabolism to release energy, and improved consolidation of emotionally important stimuli (McEwen, 2003). When compared to the fast and relatively short lived responses of the autonomic nervous system to stress, the HPAA response is slower and takes a longer time in returning to its initial state.

1.3.2 Measuring HPAA activity

HPAA activity can be noninvasively measured by assessing the cortisol concentrations from saliva samples, which represent the biologically active proportion of cortisol (“free cortisol”) unbound to circulating proteins (such as corticosteroid-binding globulin) as in blood (Kudielka, Gierens, Hellhammer, Wust, & Schlotz, 2012). Salivary cortisol samples are typically collected at varying time intervals over the course of the day to indicate the diurnal cortisol pattern and cortisol awakening response (Kudielka et al., 2012).

In addition to assessing the diurnal pattern of HPAA activation, the HPAA reactivity to stressors can be measured by the use of different stress tests. Social-evaluative stress tests, such the Trier Social Stress Test (TSST) (Kirschbaum, Pirke, & Hellhammer, 1993), are considered to be the best ways to experimentally induce stress for the assessment of individual differences in HPAA reactivity (Dickerson & Kemeny, 2004).

Furthermore, the individual physiological variation in the HPAA feedback inhibition can be assessed by measuring cortisol levels after a low-dose overnight dexamethasone suppression test (DST). Similarly as cortisol, dexamethasone also binds to the glucocorticoid receptors, inducing HPAA feedback inhibition (Best, Nelson, & Walker, 1997; Kajantie et al., 2003; Reynolds et al., 2001).

1.3.3 Development and health implications

The diurnal pattern of HPA functioning is already evident in 3-month-old infants (Price, Close, & Fielding, 1983). However, the era of early childhood, starting towards the end of the first year, is often considered as a “stress hyporesponsive period”, when cortisol responses to stress are relatively low (Lupien et al., 2009).

HPAA activity increases along with age and pubertal maturation (Gunnar, Wewerka, Frenn, Long, & Griggs, 2009). More adult-like response patterns of the HPA become evident around mid-adolescence, showing an increased sex-specificity (Ordaz & Luna, 2012). In adults, women are reported to have lower cortisol responses to stress than men (Kajantie & Phillips, 2006; Kudielka & Kirschbaum, 2005), which is likely to be mediated by hormonal changes (A. M. Bao, Hestiantoro, Van Someren, Swaab, & Zhou, 2005). The lower cortisol levels found in women are hypothesized to be adaptive in order to protect the fetus from excessive exposure to maternal glucocorticoids during pregnancy (Kajantie & Phillips, 2006).

In adolescents, however, findings on the direction of the sex-differences are contradictory, showing both higher and lower levels of activity in girls as compared to boys (Adam et al., 2010; Bouma, Riese, Ormel, Verhulst, & Oldehinkel, 2009; Gunnar, et al., 2009; Reynolds et al., 2013). The sex-specific differences in HPA function might also have health implications. The sex-specific changes in the occurrence of psychopathology, such as depression, which is more prevalent in adolescent girls than boys (Dekker et al., 2007), could partly relate to the emerging differences in HPA functioning during adolescence (Lupien et al., 2009; Ordaz & Luna, 2012).

Normal functioning of the HPA is important for health, and both hypo- and hyperactivity of the HPA have been linked with adversity. For example, major depressive disorder has been consistently associated with elevated cortisol levels (Brown, Varghese, & McEwen, 2004; Pariante & Miller, 2001), nonsuppression of cortisol levels after the DST has been found in patients with affective disorders, supporting a hypothesis that the feedback inhibition of HPA is compromised (Brown et al., 2004; Newell-Price, Trainer, Besser, & Grossman, 1998; Pariante & Miller, 2001). In contrast to the findings on depressed patients, post-traumatic stress disorder (resulting from severe traumatic experiences) has been associated with attenuated cortisol levels and increased suppression of cortisol in response to the DST (Yehuda,

2002). According to Yehuda (2002), this pattern might result from cortisol hyporeactivity during the traumatic experience leading to a process of negative physiological and psychological alterations impairing recovery and coping in the future.

Stress is known to have negative effects on the developing brain (Lupien et al., 2009). Different hypotheses have been formed to explain these effects; the neurotoxicity hypothesis states that increased glucocorticoid levels leads to suboptimal resistance of the neurons to subsequent health hazards, whereas the vulnerability hypothesis expects that alterations in brain structures precede the development of e.g. depression or post-traumatic stress disorder increasing the individual's susceptibility to them (Lupien et al., 2009).

1.4 Sleep

1.4.1 Definition

Sleep is a state of unresponsiveness to the surroundings characterized with behavioral attributes such as inertness, closed eyes, and physical inactivity (Carskadon & Dement, 2011). The sleep-wake cycle is regulated by homeostatic processes (accumulation of neurochemicals) as well as a circadian process entrained by environmental factors (e.g., light exposure, physical activity, and eating behaviors) (Borbély & Achermann, 1999; Dijk & von Schantz, 2005).

The electroencephalograph (EEG) patterns during sleep have special characteristics showing cycles of changing sleep stages occurring overnight (sleep architecture). A typical sleep cycle starts with a progression through 4 stages of non-rapid eye movement (NREM) sleep and ends in rapid eye movement (REM) sleep. The duration of a typical sleep cycle in adults is approximately 90 minutes (Carskadon & Dement, 2011). The depth of sleep increases in every NREM stage, and stages 3 and 4 are considered as slow wave sleep with synchronized low frequency and high amplitude EEG waveforms (Pace-Schott & Hobson, 2002). REM sleep is characterized with a nonsynchronous EEG close to the awake pattern, a decrease in muscular tone, and periods of rapid eye movements (Hobson, 2009), as well as a high incidence of dream recall if awakened (Dement & Kleitman, 1957).

The functions of sleep are still a matter of debate. Sleep undoubtedly serves for various purposes, such as memory consolidation (Marshall, L. & Born, 2007; Stickgold, 2006), and promoting synaptic and cellular homeostasis (Tononi & Cirelli, 2014). An interesting new theory has proposed that sleep functions as a time period when brain metabolites can be cleared from the central nervous system, thus protecting the nervous system from the effects of toxins (Xie et al., 2013).

1.4.2 Measuring sleep

Most common measures of sleep include polysomnography, actigraphy, and questionnaire based assessment. Polysomnography includes simultaneous measures of EEG, muscle tone, and eye movement (Carskadon & Dement, 2011). As it is the only measure by which specific sleep stages can be reliably identified, it is often considered as “the gold standard” in sleep assessment.

However, due to their cost-efficiency and ease of use for the participants, actigraphic measures of sleep duration and quality are often carried out. Actigraphs, or accelerometers, are small motion detectors, typically worn on the wrist or hip, assessing acceleration by activity counts during a selected epoch of time (e.g., counts per minute, cpm). Based on a predetermined sleep algorithm, the raw accelerometer data on the wearer’s movements is used to differentiate sleep from wake states (The Actiwatch User Manual, 2008). In addition to the estimation of sleep duration, accelerometers can provide data on sleep quality, such as sleep efficiency (“actual time spent asleep / time in bed”), sleep fragmentation (“number of minutes moving / assumed sleep period” + “the number of immobile phases lasting one minute / the total number of immobile phases”), and sleep latency (“The latency before sleep onset following bed time”) (The Actiwatch User Manual, 2008).

Actigraphy is considered valid in determining sleep especially in healthy subjects, but also regarding certain sleep problems (e.g., circadian rhythm sleep disorders) (Morgenthaler et al., 2007). An average correlation of total sleep time measured by actigraphy and polysomnography has been found to be 0.71 (Morgenthaler et al., 2007). An epoch-by-epoch comparison in 3- to 18-year-olds between polysomnography and two different accelerometers revealed sensitivity from 0.89 to 0.97, specificity from

0.54 to 0.77, and accuracy from 0.87 to 0.90 in detecting sleep from wake states (Meltzer, Walsh, Traylor, & Westin, 2012).

In addition to polysomnography and actigraphy, questionnaire based measures are also often preferred due to their high cost-efficiency. Participants typically answer questions on sleep duration or keep a sleep diary on their bed times and awakening times. However, diaries and questionnaire based sleep assessment in children have been estimated inadequate as sole measures of sleep, especially when parental reports are used (Werner, Molinari, Guyer, & Jenni, 2008). Particularly, the estimates of sleep duration based on diaries are longer than accelerometer based estimates (Werner et al., 2008), which should be considered when comparing studies using actigraphy and self-reports. As a strength, questionnaires can be used to assess the occurrence of specific sleep problems and complaints (such as nightmares or daytime sleepiness) (Bruni et al., 1996), which cannot be detected by polysomnography or accelerometer based measures.

1.4.3 Sleep from childhood to adolescence

Sleep quantity and quality as well as sleep architecture change over the lifespan. Most significant changes occur during childhood and adolescence.

The development of sleep patterns in childhood begins with the consolidation of the sleep-wake cycle during the first months of infancy (Sadeh, Mindell, Luedtke, & Wiegand, 2009). It has been estimated from parental reports that newborns sleep 14.3 hours in average, of which 8.5 hours is night-time sleep, although the individual variability is high (Sadeh et al., 2009). The slow wave stages of NREM sleep become present as the brain develops during the first months of life, and after reaching its peak in young childhood the proportion of slow wave sleep starts declining (Carskadon & Dement, 2011). Childhood sleep duration decreases steadily with age, which is especially due to later bedtimes, rather than changes in get up times (Blair et al., 2012).

An analysis based on seven different European studies, using questionnaire or diary based data, provided an equation estimating that 9-year-olds sleep 10.1 hours on school days and 11.0 hours on non-school days, whereas for 18-year-olds the times were 8.3 and 9.8 hours, respectively (Olds, Blunden, Petkov, & Forchino, 2010). Regional variability in sleep duration was found high with European children sleeping (on school days) 60 to 120 minutes more than Asian children, and 20 to 60 minutes more than

children from the U.S. (Olds et al., 2010). Genetic factors and cultural differences (e.g., studying late at night) as well as factors related to data collection, such as differences in reporting daytime napping or underreporting the total sleep time, have been suggested to explain these differences (Matricciani, Blunden, Rigney, Williams, & Olds, 2013; Olds et al., 2010).

As discussed earlier, actigraphic estimates of sleep duration are lower than questionnaire-based reports. We have recently shown in Finnish children (Pesonen et al., 2014), at 8 years of age, the mean of both week and weekend sleep duration was 8.5 and 8.2 hours for girls and boys. Later, at 12 years of age, a mean of 7.8 hours was found for both boys and girls on weekdays, whereas the duration of weekend sleep was 8.5 hours for girls and 8.3 hours for boys (Pesonen et al., 2014).

One of the most remarkable changes in sleep occurs during the transition to adolescence. These changes include delayed sleep phase (Carskadon, Vieira, & Acebo, 1993) and changes in sleep architecture (decrease in EEG power), which might reflect cortical restructuring (synaptic pruning) during this phase of development (Tarokh, Van Reen, LeBourgeois, Seifer, & Carskadon, 2011). It has been reported that changes in sleep precede the bodily pubertal changes, indicating that cortical development could affect sleep even before the secondary pubertal signs can be detected (Sadeh, Dahl, Shahar, & Rosenblat-Stein, 2009).

1.4.4 Poor sleep and sleep problems

According to the International Classification of Sleep Disorders (American Academy of Sleep Medicine, 2001) sleep disorders are categorized into four groups, (1) *dysomnias*, relating to problems in initiating and maintaining sleep, or excessive sleepiness (e.g., insomnia and obstructive sleep apnea) (2) *parasomnias*, relating to behavioral or physiological problems during sleep (e.g., nightmares and sleepwalking) (3) *sleep disorders associated with mental, neurologic, or other medical disorders*, reflecting secondary sleep problems (related to e.g., mood or anxiety disorders) and (4) *proposed sleep disorders*, of which scientific evidence is limited (e.g., sleep hyperhidrosis).

In healthy children, the occurrence of sleep problems varies depending on the disorder and measure used. For instance, 36.9% of parents reported their 6- to 13-year-old children as having problems of excessive sleepiness at least three times per week,

whereas, only 4.1% reported frequent problems related to sleep breathing disorders (Spruyt, O'Brien, Cluydts, Verleye, & Ferri, 2005). A study by Fricke-Oerkermann et al. (2007) reported that up to 40% of 9-year-old children suffered from problems in initiating sleep and the problems persisted in approximately half of the children when followed one year later.

When studying the health related associations of sleep duration, it is common to use sleep as a continuous measure and/or focus on the dichotomized indices, for example representing the children with the lowest sleep quantity or quality (e.g., below the 10th percentile of the study participants) (Pesonen et al., 2009; Rääkkönen et al., 2010). Estimating appropriate sleep duration is, however, problematic due to the high individual variation in sleep, as discussed earlier, and thus there is no clear evidence for cutoff points for sufficient sleep duration in different age-groups (Matricciani et al., 2013). A high deviance from age, sex and region specific sleep duration, a large difference between weekend and weekday sleep, as well as reports of daytime somnolence could be considered as possible markers of insufficient sleep duration.

1.5 Sleep and cardiovascular function in children

In children and youth, poor sleep has been associated with various negative health outcomes, including psychiatric problems (Pesonen et al., 2010; Sadeh, Gruber, & Raviv, 2002), attentional problems (Paavonen et al., 2009), cognitive problems (Paavonen et al., 2010; Sadeh et al., 2002), obesity (Bayer, Rosario, Wabitsch, & von Kries, 2009), as well as increased cortisol levels at awakening and in response to stress (Rääkkönen et al., 2010).

One commonly reported health association with sleep relates to the increased cardiovascular risks. There is evidence from studies in adults that poor sleep is associated with hypertension (Gangwisch et al., 2006; Gottlieb et al., 2006) and cardiovascular disease (Ayas et al., 2003; Eguchi et al., 2008). However, further research into these associations in children is warranted. The studies that have addressed the associations between poor sleep and cardiovascular function in children are inconclusive, differ in their target populations and measures of sleep, and have produced contradictory results, as reviewed below.

1.5.1 Sleep quantity and quality, and cardiovascular function

In multiethnic samples from the U.S., actigraphic measures of poor sleep efficiency have been associated with elevated daytime measures of SBP, DBP, and hypertension in 13- to 16-year-olds (Javaheri et al., 2008). Furthermore, short sleep duration has been associated with elevated 24-hour SBP, DBP, and prehypertension in 14- to 19-year-olds (Mezick et al., 2012).

Other studies have relied upon parent- or teacher-reports to assess sleep duration indirectly. In these studies, longer sleep has been associated variously with increased blood pressure (Sampei, Dakeishi, Wood, & Murata, 2006), decreased blood pressure (Sung et al., 2008), and no change in blood pressure (Bayer, Neuhauser, & von Kries, 2009) in groups that differed by age and ethnicity, with sample sizes ranging from 117 (Sampei et al., 2006) to 12 680 (Sung et al., 2008). In many of these studies, measures of resting cardiovascular function have been limited to occasional blood pressure measurements. Furthermore, cardiovascular reactivity to stressors has not been addressed, which may be important in addition to resting blood pressure (Everson et al., 2001; Matthews et al., 2004; Matthews et al., 2006; Treiber et al., 2003).

1.5.2 Sleep problems and cardiovascular function

Regarding sleep problems and cardiovascular function, previous studies in children, with ages ranging from 3 to 17 years, have focused on sleep apnea and parent-reported snoring. Children diagnosed with sleep disordered breathing had higher than normal ambulatory SBP and DBP during wakefulness and sleep (Amin et al., 2008; Kohyama, Ohinata, & Hasegawa, 2003; Leung et al., 2006; Li et al., 2008), an increase in basal sympathetic activity during wakefulness, and impaired autonomic reaction in response to breathing tests and to a head-up tilt test (Montesano et al., 2010), as well as increased sympathetic vascular reactivity during sight manoeuvres and in response to a cold-pressor test (L. M. O'Brien & Gozal, 2005).

High polysomnographic apnea-hypopnea index (> 3) in children who snored according to their parents was associated with higher ambulatory night-time SBP and DBP, and daytime DBP. Normal apnea-hypopnea index in children who snored was associated with higher DBP levels while asleep, but it was not associated with the other ABP measures (Li, Au, Ho, Fok, & Wing, 2009). Another study found no associations

between parent-reported snoring and SBP and DBP measured on one occasion in the morning (Kaditis et al., 2005). Although high cardiovascular reactivity to psychosocial stress is a strong predictor of later cardiovascular disease (Everson et al., 2001; Matthews et al., 2004; Matthews et al., 2006), as discussed earlier, its relationships with sleep problems in children has not been studied.

1.6 Physical activity

1.6.1 Definition

According to the Physical Activity and Health report by the U.S. Department of Health and Human Services (1996, p. 20) physical activity is defined as “bodily movement produced by the contraction of skeletal muscle that increases energy expenditure above the basal level”. Different categorizations of physical activity focus on its intensity as well as on its type and purpose, as described below.

The intensity of physical activity describes the amount of energy needed to carry out a specific task. Metabolic equivalents (METs) are commonly used to describe physical activity intensity. An intensity of one MET describes the oxygen consumption while at rest ($3.5 \text{ ml O}_2 \times \text{kg}^{-1} \times \text{min}^{-1}$) (U.S. Department of Health and Human Services, 1996).

Intensities lower than 1.5 METs refer to sedentary time, intensities between 1.5 and 3 or 4 METs refer to light physical activity, and higher intensities refer to moderate (3 or 4 to 6 METs) or vigorous (above 6 METs) physical activities. All activities with at least moderate intensity can also be referred to as moderate to vigorous physical activity (MVPA). Both 3 and 4 METs have been used as cutoff points for moderate intensity activities, although 3 METs might be considered as a too low cutoff in discriminating moderate physical activity from lower intensity activities (Mattocks et al., 2007)

Physical activity can be divided into different types based on the aims of the activity. Physical exercise includes activities that are aimed at increasing physical fitness, which includes various abilities such as muscular strength and endurance, body composition, and cardiorespiratory fitness (the ability to provide oxygen to the body). All these abilities are vital for surviving daily challenges and carrying out different everyday

tasks with necessary energy and without extreme strain (U.S. Department of Health and Human Services, 1996).

1.6.2 Measuring physical activity

Physical activity measures are typically based on questionnaire data, motion counters (accelerometers and pedometers), heart rate measurements, and direct observation (Rowlands, Ingledew, & Eston, 2000). In a meta-analysis by Rowlands et al. (2000) direct observation and motion counters were found to be the most valid measures of physical activity.

As described earlier regarding sleep, accelerometers (or actigraphs) are small motion counters. They are typically worn on the wrist or hip over at least over a four day period when used to assess physical activity (Troost, Pate, Freedson, Sallis, & Taylor, 2000). They can provide data on very short bursts of activity and are not dependent on how well the participants remember their daily activities. Accelerometers are superior to pedometers as they can also be used to measure the intensity of a specific activity.

Both self-reports and parental reports of physical activity may fail to describe the characteristic level of typical physical activity. This is noteworthy especially in younger children, among whom the usual activity pattern consists of different levels of very short bursts of intense physical activity scattered among varying intervals of low and moderate intensity during the day (Bailey et al., 1995). In addition parents may not always be aware of all of their child's activities. However, questionnaires can provide data on some aspects of physical activity that cannot be measured by objective devices (Syväoja et al., 2013), such as the specific types of physical activity (e.g. participating in organized sports, swimming, riding a bicycle, etc.) during the measurement period.

1.6.3 Continuity and change of physical activity

The amount and emphasis of physical activity changes as children grow older (Strong et al., 2005). In 8-year-olds and younger, the emphasis of physical activity is on the motor skill development, whereas in older children the emphasis shifts towards practicing specific physical skills, increasing physical fitness, and participating in organized sports (Strong et al., 2005).

Approximately 30 to 40% of 2- to 18-year-old youth are considered to be sufficiently physically active depending on the measurement protocol used (Ekelund, Tomkinson, & Armstrong, 2011). The rank-order stability of physical activity over time from childhood to adolescence is moderate (Kristensen et al., 2008), but the overall level of physical activity decreases accompanied by an increase in sedentary time (Basterfield et al., 2011; Ortega et al., 2013).

The latest World Health Organization's Health Behaviour in School-Aged Children Report stated, using questionnaire-based data, that among 11-year-old Finnish children 25% of girls and 38% of boys took part in at least one hour of MVPA daily, whereas among 15-year-olds the percentages were 10% for girls and 17% for boys (Currie et al., 2012). In Finnish children the decrease in physical activity from childhood to adolescence was pronounced. When 39 countries were compared to each other, Finnish children ranked 4th in the amount of MVPA at the age of 11 years, whereas at the age of 15 they had fallen to the 22nd place (Currie et al., 2012).

1.7 Physical activity and health

1.7.1 Physical activity and psychological well-being

Physical activity is acknowledged as beneficial for both mental and physical well-being (Physical Activity Guidelines Committee, 2008). In school-aged children and youth, physical activity has been found to be associated with at least modest beneficial health outcomes regarding cholesterol, depression, bone density, blood pressure, obesity, and metabolic syndrome, whereas as a downside, physically active children do seem to have a higher likelihood for medically treated physical injuries (Janssen & Leblanc, 2010).

There is a growing evidence from recent studies that children who engage in higher levels of physical activity enjoy better psychological well-being, including higher self-esteem, and are less likely to suffer from psychiatric problems (Griffiths, Dowda, Dezateux, & Pate, 2010; Hamer, Stamatakis, & Mishra, 2009; Kantomaa et al., 2008; Parfitt & Eston, 2005; Parfitt et al., 2009; Sagatun, Sogaard, Bjertness, Selmer, & Heyerdahl, 2007). However, when studying physical activity and psychiatric problems in children various studies have focused on self-reports (Kantomaa et al., 2008; Sagatun

et al., 2007) or parent-reports (Griffiths et al., 2010; Hamer et al., 2009) on physical activity. In addition, studies have focused on internalizing problems (such as anxiety and depression) and to a lesser extent to externalizing problems (such as aggression and conflict with others) (Strong et al., 2005).

Results on the associations between children's psychiatric problems and physical activity, measured with objective devices over a period of several consecutive days, are few and restricted to symptoms of depression and anxiety with contradictory findings. In two studies on 10-year-olds (Parfitt & Eston, 2005) and 9- to 10-year-olds (Parfitt et al., 2009), a higher level of physical activity was associated with fewer symptoms of depression and anxiety. By contrast, a study of 10- to 16-year-olds did not find any association between the amount of vigorous physical activity and symptoms of anxiety (Strauss et al., 2001). Also, a study of 12-year-old girls found no associations between physical activity and depressive symptoms (Johnson et al., 2008).

Apart from methodological differences relating to the definition and measurement of daytime physical activity, the different age-ranges between the samples may contribute to the contradictory findings, as aging affects physical activity and the expression of psychiatric problems (Nyberg, Nordenfelt, Ekelund, & Marcus, 2009; Oldehinkel, Verhulst, & Ormel, 2011).

Consequently, the previous studies have been limited by relatively small sample sizes (Parfitt & Eston, 2005; Parfitt et al., 2009; Strauss et al., 2001), assessment of only a few aspects of psychiatric problems (Johnson et al., 2008; Parfitt & Eston, 2005; Parfitt et al., 2009; Strauss et al., 2001), inclusion of both pubertal children and children near puberty (Johnson et al., 2008; Parfitt & Eston, 2005; Parfitt et al., 2009; Strauss et al., 2001), and using self- or parent-reported measurement of physical activity (Griffiths et al., 2010; Hamer et al., 2009; Kantomaa et al., 2008; Sagatun et al., 2007). Further research using objective measurement of physical activity and assessing a wide range of psychiatric problems is warranted.

1.7.2 Physical activity and the HPA

Stress system activity is one of the potential mechanisms that could link physical activity with favorable health effects. The associations between physical activity and the HPA are multifaceted. It has been suggested that physical activity could serve as both

a stressor and a modifier of stress; the adaptation of the HPA, caused by physical activity might generalize to other stressors as well, including psychosocial ones (Hackney, 2006).

Studies in adults have found that physically trained men exhibit lower cortisol responses to acute physical exercise, when compared to moderately trained or sedentary men (Luger et al., 1987). Trained men also showed significantly lower cortisol responses to a psychosocial stress test (TSST) when compared to their untrained counterparts (Rimmele et al., 2007). In another study, older (51- to 81-year-old) physically fit women showed lower cortisol responses to a different psychosocial stress test (Matt Stress Reactivity Protocol) when compared to unfit women of same age (Traustadottir et al., 2005). The same study also found that younger (19- to 36-year-old) fit and unfit women did not show differences in cortisol responses to stress when compared to each other (Traustadottir et al., 2005). However, a more recent study found that also among 18- to 23-year-old women, self-reported physical activity levels were associated with lower cortisol responses to a TSST for groups protocol (Klaperski, 2013).

In addition to assessing HPA responses to stress, very few studies have examined the associations of daily physical activity levels and diurnal HPA activity. In 46 young adult men and women, higher VPA was associated with higher hair cortisol concentrations (Gerber et al., 2013), presumably reflecting the long term accumulation of higher levels of cortisol after bouts of intense physical activity. In another study of 491 adult men and women, higher overall levels of self-reported physical activity were associated with elevated morning cortisol, steeper diurnal cortisol decline, and greater cortisol suppression after the DST (Vreeburg et al., 2009), suggesting a more dynamic HPA.

As HPA function (Kajantie & Phillips, 2006) and the quantity and quality of physical activity (Strauss et al., 2001) change by age and pubertal maturation, the generalization of the previous results to youth is precluded and studies examining these associations in both children and adolescents are needed. Only one study has examined these associations in youth. In a cohort study of 8- to 13-year-olds, parent-reported levels of physical activity were not associated with salivary cortisol responses to a psychosocial stress test (Trier Social Stress Test for Children, TSST-C) (Dockray,

Susman, & Dorn, 2009). However, as this study has a wide age-range, including both prepubertal and pubertal children (Dockray et al., 2009), the generalization of the results is precluded. Also the use of parental reports in assessing physical activity can be considered as a limitation.

Consequently, further research investigating the associations between physical activity and HPA axis function in groups of children and youth with a narrower age-range (both prepubertal and pubertal), and using objective measurement of physical activity is warranted. Furthermore, it is necessary to study the associations of physical activity and HPA axis activity separately in adolescent girls and boys as HPA axis activity is closely interlinked with sex steroid production, and sex-specific differences in HPA axis activity emerge during adolescence (Adam et al., 2010; Bouma et al., 2009; Gunnar et al., 2009; Reynolds et al., 2013). Further, boys often lag behind girls in pubertal maturation (e.g., Pesonen et al., 2014), which might be another source of sex-related variation in HPA axis activity and function in adolescence.

2 AIMS OF THE STUDY

1. To study the associations between sleep and cardiovascular function in 8-year-old children (Studies I and II)
2. To study the associations between physical activity and psychiatric problems in 8-year-old children (Study III)
3. To study the associations between physical activity and HPA function in 8-year-old and 12-year-old children (Studies IV and V)

3 METHODS

3.1 Participants

The participants came from an urban community-based cohort comprising 1049 infants born between March and November 1998 in Helsinki, Finland (Strandberg, Vanhanen, & McKeigue, 2001). The study design and selection of participants for Studies I to V is presented in Figure 1.

The Ethical Committee of the City of Helsinki Health Department and the Ethical Committee of the Helsinki University Hospital for Children and Adolescents at Helsinki and the Uusimaa Hospital District approved the project. Parents/caregivers and children gave informed, written consent.

3.1.1 Selection of participants at 8 years of age

In 2006, a subsample of the cohort was invited to a follow-up. Of the 413 children invited, 321 (77.7%) participated in the follow-up at the mean age of 8.1 years (standard deviation (SD) = 0.3, range 7.4 to 8.9 years) (Pesonen et al., 2009; Räikkönen et al., 2010). Because the primary objective of the initial study was to examine the effects of maternal licorice consumption during pregnancy on their offspring's developmental outcomes, participants at 8 years of age were recruited to over-represent children whose mothers consumed higher amounts of licorice. Apart from the less frequent maternal smoking during pregnancy ($P = 0.022$), the participants did not differ from the invited nonparticipants.

In Study I, complete data on sleep, blood pressure, and cardiovascular function were available for 231 (72.0%) and 265 (82.6) children, without sleep breathing disorders, respectively. In Study II, data on sleep problems, blood pressure, and cardiovascular function were available for 241 (75.1%) and 274 (85.4%) children respectively. In Study III, data on physical activity and mother- and teacher-reported psychiatric problems were available for 199 (62.0%) children. In Study IV, data on physical activity and HPA function were available for 252 (78.5%) and 248 (77.3%) children regarding diurnal salivary cortisol and salivary cortisol levels in response to psychosocial stress.

3.1.2 Selection of participants at 12 years of age

Between 2009 and 2011, all initial cohort members who had given permission to be contacted and whose addresses were traceable were invited to a further follow-up. An invitation letter was sent to 920 adolescents and their parents (87.7% of the original cohort), of which 692 (75.2%) could be contacted by phone. Of them 451 (65.2% of the contacted) participated in a follow-up at a mean age of 12.3 years (SD = 0.5, range 11.0–13.2 years). Non-participation was related to younger maternal age at the participant's birth ($P = 0.022$), less frequent consumption of any alcohol ($P = 0.011$) and lower consumption of glycyrrhizin in licorice during pregnancy ($P = 0.044$).

In Study V, complete data on physical activity and diurnal salivary cortisol were available for 283 adolescents (62.7%), and on physical activity and salivary cortisol after the DST for 272 adolescents (60.5%).

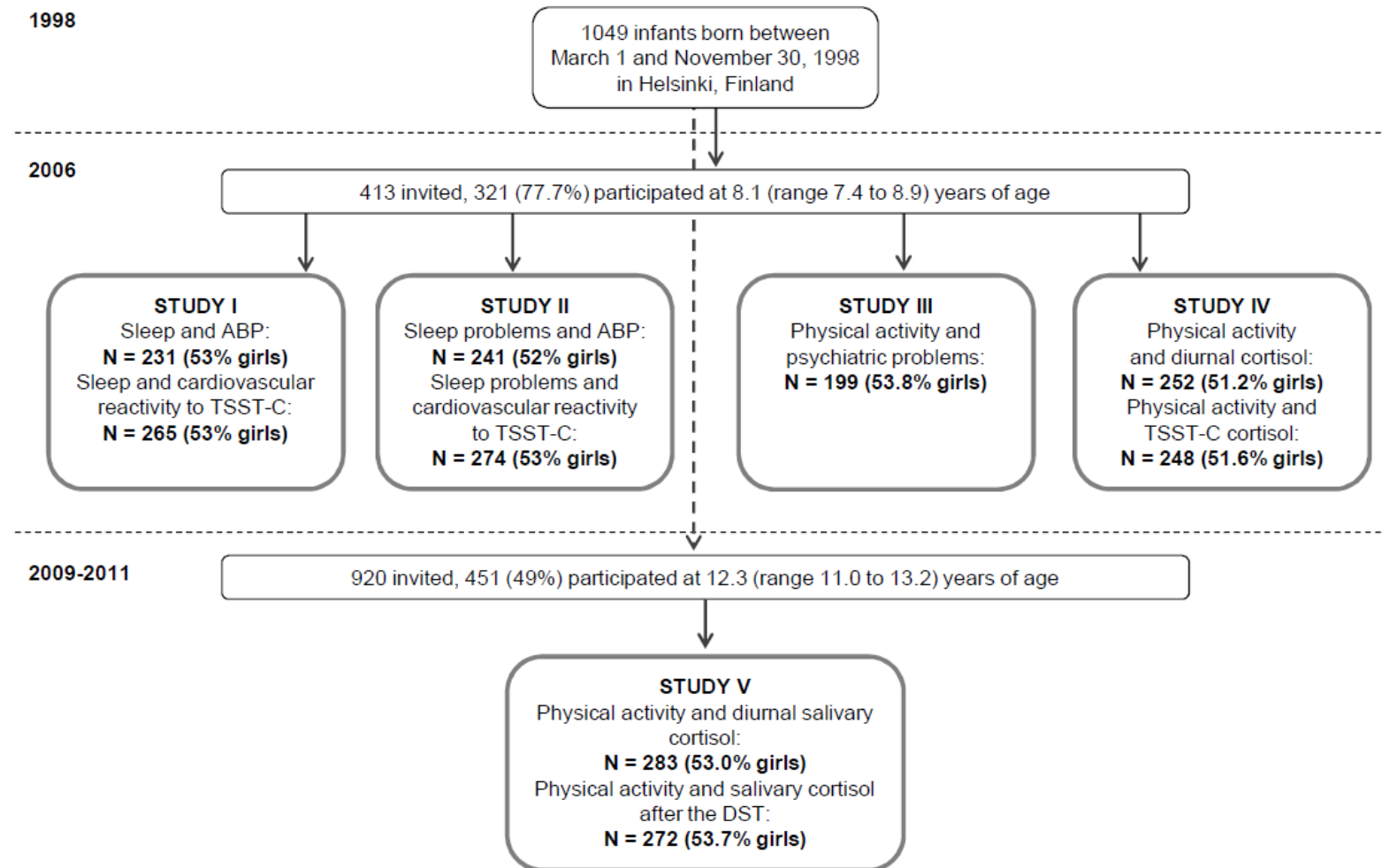


Figure 1. Study design and selection of the participants in 2006 (at 8 years of age) and 2009-2011 (at 12 years of age).

3.2 Sleep at 8 years of age

3.2.1 Objective measures of sleep

Sleep was objectively measured using accelerometers (Actiwatch AW4 and AW7, Cambridge Neurotechnology Ltd., UK) worn on the non-dominant wrist. The children and their caregivers were instructed to keep a sleep diary on bed times (lights off) and get up times and to press a button/event marker on the device at those times. The data were visually inspected for any discrepancies between the sleep diary, event markers, and physical activity data. Discrepancies (of more than 5 min) in one to two of the analyzed nights were found for 21% of the participants and in discrepancies in three or more nights for 8% of the participants.

Following details led to the exclusion of the specific night from the data: the device was not used, no information on bedtimes was given, the child was already sleeping at reported bedtime according to the data, information on wake up time was not given and was not interpretable from the physical activity data, or there were changes to normal routines due to, for example, illness or travel, as reported by the parents (Pesonen et al., 2009). Only children with more than two nights of valid data were included in the analyses. Following these criteria, the sleep data were analyzed for an average duration of 6.1 nights (SD = 1.2, range 3–13) per participant.

Data were scored using Actiwatch Activity & Sleep Analysis software (v.5.42) with medium sensitivity and 1-minute epochs. We used the validated Actiwatch algorithm (Meltzer et al., 2012), which defines “sleep start” as the first ten minutes of continuous immobility. Sleep duration refers to the actual sleeping time. Sleep efficiency was defined as the percentage of time in bed that was spent asleep. The number of minutes spent moving as a percentage of time spent in bed and the percentage of immobility phases lasting less than one minute were summed to yield the fragmentation index (an indicator of restlessness). Sleep latency was defined as the delay between reported bedtime and sleep onset.

3.2.2 Parent-reported sleep problems

The parents filled in a 26-item Sleep Disturbance Scale for Children (SDSC) (Bruni et al., 1996). Each item describes sleep-related behavior during the past 6 months and is rated on a 5-point scale. The SDSC yields six subscales representing the most common areas of sleep problems in childhood and adolescence (examples of the scales are given in Table 1).

Following Spruyt et al. (2005), a sleep disorder was classified to be present if any of the items on the sleep disorder subscale were occurring at least three nights per week during the past 6 months, with the exception of the items belonging to the disorders of arousal and disorders of excessive daytime somnolence. These had to be present at least one or two nights per week. Based on this classification, having any sleep disorder (1 = yes, 0 = no) was defined as having at least one sleep problem on any of the 6 sleep disturbance subscales. Children with a specific sleep disorder were contrasted against the comparison-group of 159 children who were free of any sleep problems based on this classification.

Table 1. Description of the sleep problems, measured by the SDSC (Bruni et al., 1996).

Subscale	Examples of items
Dyssomnias	
Disorder of initiating and maintaining sleep	The child goes to bed reluctantly After waking up in the night, the child has difficulty to fall asleep again
Sleep breathing disorders	The child has difficulty in breathing during the night The child snores
Disorders of excessive somnolence	The child awakes in the morning feeling tired The child falls asleep suddenly in inappropriate situations
Parasomnias	
Sleep-wake transition disorders	The child shows repetitive actions such as rocking or head banging while falling asleep The child startles or jerks parts of the body while falling a sleep
Disorders of arousal/nightmares	You have observed the child sleepwalking The child has nightmares which he/she does not remember the next day
Other	
Sleep hyperhidrosis	The child sweats excessively while falling asleep The child sweats excessively during the night

3.3 Physical activity at 8 and 12 years of age

Physical activity was objectively measured by the same omnidirectional accelerometers used in the sleep assessment (Actiwatch AW4 and AW7, Cambridge Neurotechnology Ltd., UK), using 1-minute epochs. All periods with no detected movement during ten consecutive epochs (10 min) were recorded as missing values. Physical activity was calculated daily over 12 hours from 9:00 h onwards. Only days with data available for at least 10 hours were included in the analyses.

The overall physical activity described as cpm is an indicator of the total volume of physical activity. This variable was calculated by dividing total counts by monitoring time (min) per day and averaged over the measurement period.

The amount of minutes spent daily in different physical activity intensity categories was calculated for the participants and averaged over the measurement period. For Study III, a prediction equation by Heil et al. was used (Heil, 2006) to define MVPA (above 4 METs, 2297 cpm) from lower intensity activity. For Studies IV and V, a more recently published prediction equation by Ekblom et al. (2012) was used to define sedentary time (below 1.5 METs, 320 cpm), light physical activity (between 1.5 and 3 METs, 1048 cpm), MVPA (above 3 METs, 1048 cpm), and vigorous physical activity (VPA) (above 6 METs, 1624 cpm), with markedly lower cutoff points.

The analyses using the 3 METs cutoff point (light physical activity and MVPA) were considered as supplementary (used in Study V only), because 4 METs cutoff was not provided by Ekblom et al. (2012) and the 3 METs threshold may be considered too low in discriminating moderate physical activity from lower intensity activities (Mattocks et al., 2007).

For the statistical analyses, to calculate the percentage of time spent in a specific physical activity intensity, the number of minutes accumulated in that intensity were divided by the monitoring time and averaged over the measurement period.

3.4 Psychosocial stress protocol at 8 years of age

At the age of 8 years the children's reactivity to psychosocial stress was measured using the TSST-C protocol (Buske-Kirschbaum et al., 1997; Feldt et al., 2011; Jones et al., 2006) during which salivary cortisol, blood pressure, electrocardiography and thoracic impedance were recorded.

The children were scheduled to arrive in the clinic at 10:00 h, 12:00 h, or at 14:00 h and were asked to abstain from eating for 2 hours before arrival. After the child and parent/caregiver had signed an informed consent, a saliva sample, termed "arrival" hereafter, was obtained and weight and height of the child were measured.

For the cardiovascular measurements, a baseline recording of 5 minutes was conducted prior to the stress test in a standing position watching a comforting movie with the parent/caregiver present. Also the baseline saliva sample was obtained (mean = 36.5; SD = 6.2 min after the arrival sample).

After the baseline measurement, the child was taken to another room, without the parent/caregiver, and introduced to a panel of two "judges" (Figure 2). The child was told that the panel would evaluate his/her performance in the upcoming tasks. The child was presented with different options of toys, of which she/he could choose the second favorite and the favorite one to be given to him/her as an award for excellent performance. The two toys were placed on a visible place during the completion of the tasks. The stress protocol consisted of a story-telling task, where the child had to complete a story after hearing its beginning played to him/her (the child prepared the story in the baseline room supported by the research nurse), right after the 5 minute story-telling task a 5 minute arithmetic task was conducted, both in front of a tape recorder and the panel. Recording of cardiovascular function was carried out during both tasks.

When the tasks were completed, each child was awarded with their favorite toy and taken back to the other room to continue watching the same movie as in the baseline period. After 13 minutes of watching the movie the child was asked to stand up and after 7 minutes a 5 minute recovery cardiovascular recording was conducted. Salivary

cortisol samples were obtained at arrival and at baseline, as described above, and 0, 10, 20, 30, and 45 minutes after the stress protocol.



Figure 2. Trier Social Stress Test for Children.

3.5 Cardiovascular function at 8 years of age

3.5.1 Ambulatory blood pressure

ABP was measured every 30 minutes between 8:00 and 10:00 h, and every hour between 22:00 and 8:00 h the following morning (41% on non-school days) using an oscillometric device (Spacelabs 90207, Spacelabs Healthcare, Washington, US), with an appropriate cuff size. The monitors met the standards of the Association for the Advancement of Medical Instrumentation and the British Hypertension Society for ABP measurement (E. O'Brien, Mee, Atkins, & O'Malley, 1992). Blood pressure cuffs were sited on the non-dominant upper arm.

Measurements were rejected for systolic ABP > 220 or < 60 mmHg, diastolic ABP > 120 or < 35 mmHg (Urbina et al., 2008), pulse pressure > 120 or < 20 mmHg, or heart

rate > 180 or < 40 beats/minute (Lurbe et al., 1999). On average, this yielded 24.8 (SD = 3.7, range 10 to 31) valid day and 9.8 (SD = 1.4, range 4 to 13) valid night readings. If data were available for less than 30% of the night or day, the recordings were excluded. Average 24-hour ABP level was calculated as the mean of average day and average night values. ABP load was calculated as the percentage of ABP values over a given period that exceeded the pediatric 95th percentiles (Wühl et al., 2002).

3.5.2 Cardiovascular reactivity to psychosocial stress

To assess cardiovascular reactivity to psychosocial stress, the children underwent the TSST-C protocol, as described above. This has been shown to produce strong and reliable autonomic responses in children of the same age (Jones et al., 2008). In a clinic setting, impedance cardiograph electrodes and a non-invasive Vasotrac® APM205A (MedWave Inc, MN) blood pressure monitor were attached and data were recorded for 5-minute epochs: with the children in a standing position; then during the speech and maths tasks of the TSST-C.

CO, PEP, and heart rate were measured using a BIOPAC MP150 (BIOPAC Systems Inc., Santa Barbara, CA) with impedance cardiography (NICO100C) and electrocardiography (ECG100C) modules, following published methodological guidelines (Sherwood et al., 1990). Signals were sampled at 1000 Hz and devices were calibrated according to manufacturer's instructions using Biopac AcqKnowledge software (v.3.8.1). Data were analysed using WinCPRS® 1.160 software (Absolute Aliens, Turku, Finland). HF HRV was determined according to current guidelines (Berntson et al., 1997). TPR was calculated as $(\text{mean arterial pressure}/\text{CO}) \times 80$ and expressed in $\text{dynes} \times \text{s} \times \text{cm}^{-5}$ (Feldt et al., 2011).

For each cardiovascular measure, the mental stress responses were calculated as the difference between means of the ten minutes of stress and the first five-minute baseline rest period, in accordance with established approaches (Jones et al., 2008; Kamarck & Lovallo, 2003). Because thoracic impedance cardiography may track stroke volume with acceptable accuracy, but requires calibration to an invasive standard for absolute accuracy, we used the ratio of mean stress and rest values as a measure of stress response in impedance-derived measures, as has been previously suggested (Sherwood et al., 1990).

3.6 HPAA activity at 8 and 12 years of age

Salivary cortisol (Salivette, Sarstedt, Nümbrecht, Germany) was measured at both 8 years of age (diurnal salivary cortisol and the TSST-C) and 12 years of age (diurnal salivary cortisol and the DST). Children and their parents/caregivers were shown how to collect salivary samples for determination of diurnal cortisol using the Salivette cotton swabs.

Salivary cortisol concentrations were determined by the use of a competitive solid-phase, time-resolved fluorescence immunoassay with fluorometric end point detection (DELFI; Wallac, Turku, Finland) (Dressendorfer, Kirschbaum, Rohde, Stahl, & Strasburger, 1992).

3.6.1 Salivary cortisol sampling and biochemical analyses at 8 years of age

At 8 years of age, diurnal salivary samples were obtained during a 1 day period, at awakening (mean = 07:53 h; SD = 50 min), 15 and 30 minutes thereafter, and at 10:30 h, 12:00 h, 17:30 h, and at bedtime (mean = 9:15 h; SD = 75 min). 81% of the children underwent the cortisol sampling during the physical activity assessment. The range of time between sampling and measurement of physical activity varied from 0 to 151 days.

The TSST-C protocol was used to measure HPAA responses to stress at 8 years of age. As described above, the salivary samples were obtained at arrival and at baseline and 0, 10, 20, 30, and 45 minutes after the TSST-C.

All saliva samples were collected between January 2006 and December 2006. The samples were stored at -20°C and were analyzed in August 2007. The intra-assay coefficient of variation was between 4.0 and 6.7%, and the interassay coefficients of variation were between 7.1 and 9.0%. Cortisol concentrations were measured in duplicate, and the mean coefficient of variation between duplicate analyses was 5.0%.

3.6.2 Salivary cortisol sampling and biochemical analyses at 12 years of age

At 12 years of age, salivary samples were obtained during two consecutive days, hereafter labeled as day A and day B. On both days, samples were collected upon awakening (day A: mean = 08:27 h, SD = 65 min; day B: mean = 08:26 h, SD = 71 min) and on day A also at 15, 30, 45 and 60 minutes after awakening, at 12:00 h, 17:00 h, and at bedtime (mean = 21:48 h, SD = 64 min). 30.7% of the children underwent the cortisol sampling during the physical activity assessment. The range of time between sampling and measurement of physical activity varied from 0 to 74 days.

Dexamethasone was administered after the bedtime saliva sample on day A (mean = 21:58 h, SD = 65 min) and a saliva sample was given at awakening the next morning (mean = 8:26 h, SD = 71 min). A low-dose of dexamethasone (3 µg/kg of weight) was used to detect the individual variation in HPA axis suppression. We used a much lower dose of dexamethasone (3 µg/kg of weight) than used in standard clinical endocrine practice to exclude Cushing's disease (e.g., 1 mg, or 20 µg/kg). The low-dose administered in this study has been used in population-based studies (e.g., Kajantie et al., 2003) to detect individual variation in HPA axis suppression, within the normal range of the function of the axis, as it aims for ~50% HPA axis suppression.

At 12 years of age, the saliva samples were collected between September 2009 and December 2011. The samples were stored at -20°C and analyzed in January 2012. The intra-assay coefficient of variation was between 4.0% and 6.7%. The inter-assay coefficients of variation were between 6.5% for low (3.7 nmol/l), 7.7% for medium (7.7 nmol/l) 6.9% for high concentration (18.4 nmol/l) control samples. Cortisol concentrations were measured in duplicate, and the mean coefficient of variation between duplicate analyses was 5.9%.

3.6.3 Cortisol parameters

Cortisol concentrations were log-transformed to attain normality. At 8 years of age diurnal variables were cortisol peak value after awakening (peak of values 15 and 30 min after awakening), cortisol awakening response (peak value after awakening minus value at awakening), awakening time-weighted area under the curve (AUC of 0, 15, and 30 min after awakening, calculated as the AUC above zero under trapezoidal rule),

awakening AUC increment (AUC minus awakening value), and nadir (minimum of diurnal values). TSST-C stressor variables were baseline, peak value after stress, increment (peak value after stress minus baseline value), time-weighted AUC (calculated as the AUC above zero under trapezoidal rule), and AUC increment (AUC minus baseline value).

At 12 years of age the following parameters were used: cortisol upon awakening, awakening time-weighted area under the curve (AUC) (AUC of 15, 30, 45, and 60 min after awakening, calculated as the AUC above zero under trapezoidal rule), and cortisol at bedtime, all from values on day A. Salivary cortisol response to the DST was the arithmetic difference between the log-transformed variables upon awakening (day A-day B), back-transformed after analyses to indicate the ratio day A/day B.

3.7 Psychiatric problems at 8 years of age

Mothers completed the Child Behavior Checklist 4–18 (CBCL) (Achenbach, 1991a) and teachers completed the Teacher's Report Form (TRF) (Achenbach, 1991b). Both questionnaires contain 120 symptom items assessed on a three-point scale ("not true," "somewhat true," and "often true"). We used the Achenbach software to obtain age- and sex-adjusted T-values for eight narrowband scales (anxious/depressed, withdrawn/depressed, somatic complaints, social problems, thought problems, attention problems, rule breaking behavior, aggressive behavior) and three broadband scales. The broadband scales are composites of the narrowband scales, of which internalizing refers to problems within the self (anxious/depressed, withdrawn/depressed, and somatic complaints); externalizing indicates conflict with others (rule breaking behavior and aggressive behavior); and the total problems scale is a composite of all eight narrowband scales (Achenbach, 1991a).

In addition, we used six Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)-oriented scales (DOS) aimed at covering common symptoms of childhood mental disorders (Krol, De Bruyn, Coolen, & van Aarle, 2006; Spatola et al., 2007). The DOS are based on 22 clinicians' ratings on the degree of consistency of CBCL or TRF items with corresponding DSM-IV criteria; items that were considered "very consistent" by at least 64% of the clinicians were then grouped into six separate DOS (affective

problems, anxiety problems, somatic problems, attention deficit/hyperactivity problems, oppositional defiant problems, and conduct problems). We used cutoffs at the 82nd percentile for all scales to indicate borderline clinically significant problems (0 = no problem, 1 = borderline clinically significant problem). The 82nd percentile cutoff has been reported to provide the most efficient discrimination in emotional, behavioral, and social problems in normative samples (Achenbach, 1991a).

3.8 Statistical analyses

Continuous outcome measures (Studies I, II, IV, and V) were tested with multiple linear regression analyses and dichotomized outcome measures with logistic regression analyses (Study III). All analyses were adjusted for the child's sex (when girls and boys were analyzed together), age, and body mass index (BMI; weight in kilograms divided by height in meters squared). Further study specific analyses are presented below.

3.8.1 Studies I and II

Associations of sleep measures with 24-hour ABP and cardiovascular stress response variables were tested with multiple linear regression analyses. In Study I, to test for the threshold effects, analyses were repeated with the sleep variables categorized (sleep duration was categorized into three groups contrasting the top and the bottom 10% with the middle 80% of the sample; sleep latency and fragmentation were dichotomized contrasting the top 10% with the rest of the sample; and sleep efficiency was dichotomized contrasting the bottom 10% with the rest of the sample).

Analyses were adjusted for the child's sex, age, height, BMI, maternal licorice consumption during pregnancy, and parental education (highest of either parent). To test whether the results differed between boys and girls, an interaction-term 'sex × sleep variable' was entered into the regression equation followed by the main effects. If an interaction was found to be significant, separate analyses were carried out for girls and boys to test for the sex-specific associations. Multiple statistical tests were accounted for by using Bonferroni-correction.

In Study II, additional adjustments were made for the start time of the baseline recording (in TSST-C analyses). Furthermore, a correction for body surface area (BSA,

$[(\text{cm} \times \text{kg})/3600]^{1/2}$ was carried out in the analyses of TPR and CO ($\text{TPR} \times \text{BSA}$, CO/BSA); a separate analysis was carried out where BMI replaced the BSA correction.

3.8.2 Study III

Overall physical activity was used as a continuous variable. MVPA was categorized into three groups, comparing the children with the highest amount of MVPA to the children with the lowest amount of MVPA.

The associations were adjusted for the child's sex, age, height, BMI, maternal licorice consumption during pregnancy, parental education (the highest of either parent), and sleep duration.

3.8.3 Studies IV and V

The salivary cortisol patterns in relation to physical activity were first analyzed by mixed random effects regression analysis (Kajantie et al., 2007). This analysis is designed for analyzing all available data and hence can handle missing data. It also takes into account that the repeated measures on the same individual are correlated. To test whether the salivary cortisol patterns varied according to physical activity, we included an interaction term 'physical activity \times sampling time', into the regression equation, followed by the main effects. In Study IV, physical activity was categorized into thirds by sex. In Study V, physical activity variables were used as continuous, and to facilitate the interpretation of the results, both physical activity and cortisol variables were standardized (mean = 0, SD = 1) in girls and boys separately.

In Study IV, analyses were adjusted for time at awakening, sex, age at testing, BMI, sleep duration, maternal occupational status, and maternal licorice consumption during pregnancy. Since obesity might be associated with physical activity and HPA function, all analyses were also performed after excluding children with obesity ($n = 10$) (T. J. Cole, Bellizzi, Flegal, & Dietz, 2000). However, as this did not affect any of the results, they are presented with these children included. Finally, because associations with salivary cortisol may vary according to sex (Kajantie & Phillips, 2006), we tested if sex moderated any of the associations.

As sex-specific differences in HPA function are known to increase towards adolescence (Ordaz & Luna, 2012), all analyses in Study V were studied in girls and

boys separately. In Study V, all associations were adjusted for the time at awakening (on day A for the analyses of diurnal salivary cortisol, and on days A and B for the analyses of salivary cortisol in response to DST) and for the time difference from taking dexamethasone on day A to awakening on day B (for analyses of salivary cortisol in response to DST), for age at testing, BMI, and pubertal status (model 1), and further for sleep duration, maternal occupational status, and maternal licorice consumption during pregnancy (model 2).

Level of pubertal maturation was measured in two different ways: by using the Pubertal Development Scale (PDS, a 5-item self-report scale: body hair, growth spurt, skin changes, and menarche and breast development for girls, and facial hair and voice change for boys rated on a scale of no changes yet (1) to clear changes (3) (Petersen, Crockett, Richards, & Boxer, 1988) and by drawing-based pubic hair development scale of Tanner staging (Tanner 1, prepubertal, to Tanner 5, postpubertal) (Marshall, W., A. & Tanner, 1969; Marshall, W., A. & Tanner, 1970). The model 2 analyses were first adjusted for the PDS scale, and then rerun by replacing the PDS by the Tanner pubic hair development scale.

4 RESULTS

4.1 Sleep and cardiovascular function

4.1.1 Objectively measured sleep and 24-hour ABP and cardiovascular reactivity to the TSST-C (Study I)

There were no significant associations between any measure of sleep quality and any parameter of ABP, when the sleep measures were treated as categorical variables or as continuous variables.

In response to the TSST-C, children with short in comparison to average sleep duration had almost significantly lower SBP (mean difference (MD), 3.0 mmHg; 95% confidence interval (CI), 6.0 to 0.0; $P = 0.051$). They also had lower TPR (MD, 11.5%; 95% CI, -18.3 to -4.6; $P = 0.001$), longer PEP (MD, 1.5 ms; 95% CI, 0.2 to 2.9; $P = 0.023$) (lower sympathetic activity), and higher CO (MD, 6.5%, 95% CI, 2.2 to 10.7; $P = 0.003$) reactivity to the TSST-C. However, when sleep quantity and quality were analyzed as continuous variables, none of these associations were significant. After correction for multiple testing, no association remained significant (P -values > 0.07), and there was no evidence that the associations differed by sex. Adjustment of PEP for heart rate made no difference to the results.

4.1.2 Parent-reported sleep problems and 24-hour ABP and cardiovascular reactivity to the TSST-C (Study II)

There were no significant associations between sleep problems and 24-hour ABP variables. In comparison to the children who were free from sleep problems, children with sleep breathing disorders had higher baseline TPR (MD, 416.6 dynes \times sec \times cm⁻⁵; 95% CI, 85.4 to 747.8; $P = 0.014$), as well as higher CO (11.0%; MD; 95% CI, 1.0 to 21; $P = 0.031$) and heart rate (MD, 5.7 beats/min; 95% CI, 0.2 to 11.2; $P = 0.044$) reactivity to the TSST-C. Children with disorders of excessive somnolence had 47.7% higher baseline HF HRV (95% CI, 7.3 to 103.4; $P = 0.016$).

There were no significant ‘sex \times sleep problem’ interactions in associations between sleep problems and 24-hour ABP variables. Significant ‘sex \times sleep problem’ interactions in associations between sleep problems and cardiovascular baseline values

and reactivity to the TSST-C were found (P-values for significant interaction terms were between 0.006 and 0.027) and sex-specific associations were analyzed. Based on these analyses girls with disorders of excessive somnolence had lower baseline SBP (MD, -4.2 mmHg; 95% CI, -8.3 to -0.1; P = 0.047), and DBP (MD, -3.3 mmHg; 95% CI = -6.4 to -0.3; P = 0.033), lower baseline TPR (MD, -141.6 dynes \times sec \times cm⁻⁵; 95% CI -279.4 to -3.8; P = 0.044), higher TPR reactivity (MD, 11.3%; 95% CI, 3.8 to 18.7; P = 0.003), and lower CO reactivity to the TSST-C (MD, -6.0%; 95% CI, -10.8 to -1.1; P = 0.016) than girls in the comparison group. Girls with sleep hyperhidrosis had lower baseline heart rate (MD, -15.3 beats/min; 95% CI, -25.6 to -4.9; P = 0.004) than girls in the comparison group. Boys with disorders of excessive somnolence had lower TPR reactivity to stress than boys in the comparison group (MD, -9.9%; 95% CI = -19.6 to -0.3; P = 0.044). All other associations were not significant in boys (P-values > 0.092).

Finally, we tested if any of the significant associations changed after adjusting for being diagnosed with any medical disorders, based on parental reports, and receiving medication. The results that were statistically significant remained so after these adjustments (P < 0.050), except for one: the difference in TPR reactivity among boys with disorders of excessive somnolence no longer reached our pre-determined significance level (P = 0.054). Similarly, when the BSA correction for CO and TPR was replaced by adjustment for BMI the results that were significant remained so. After the Bonferroni-correction was applied, all associations or interaction terms were no longer significant (corrected P-values > 0.071).

4.2 Physical activity and psychiatric problems (Study III)

All correlations between teacher- and mother-reported age and sex adjusted T-values of CBCL and TRF were significant (P-values < 0.03) with Pearson *rs* ranging from 0.15 for DOS-based affective problems to 0.46 for DOS-based attention deficit/hyperactivity problems. Figure 3 shows the adjusted odds ratios (ORs) and 95% CIs for borderline clinically significant problems per each 100 cpm increase in overall physical activity across the measurement days as rated by the mothers and teachers.

A higher overall physical activity was associated with lower odds for exhibiting withdrawn/depressed problems, somatic complaints, social, thought, attention, and

aggressive behavior problems; internalizing, externalizing, and total behavior problems; and DOS-based oppositional defiant and conduct problems as rated by the teachers (P-values < 0.049). A higher overall level of physical activity across the measurement days was associated with lower odds for aggressive behavior problems and DOS-based affective problems as rated by the mothers (P-values < 0.045). There were no other significant associations with maternal ratings.

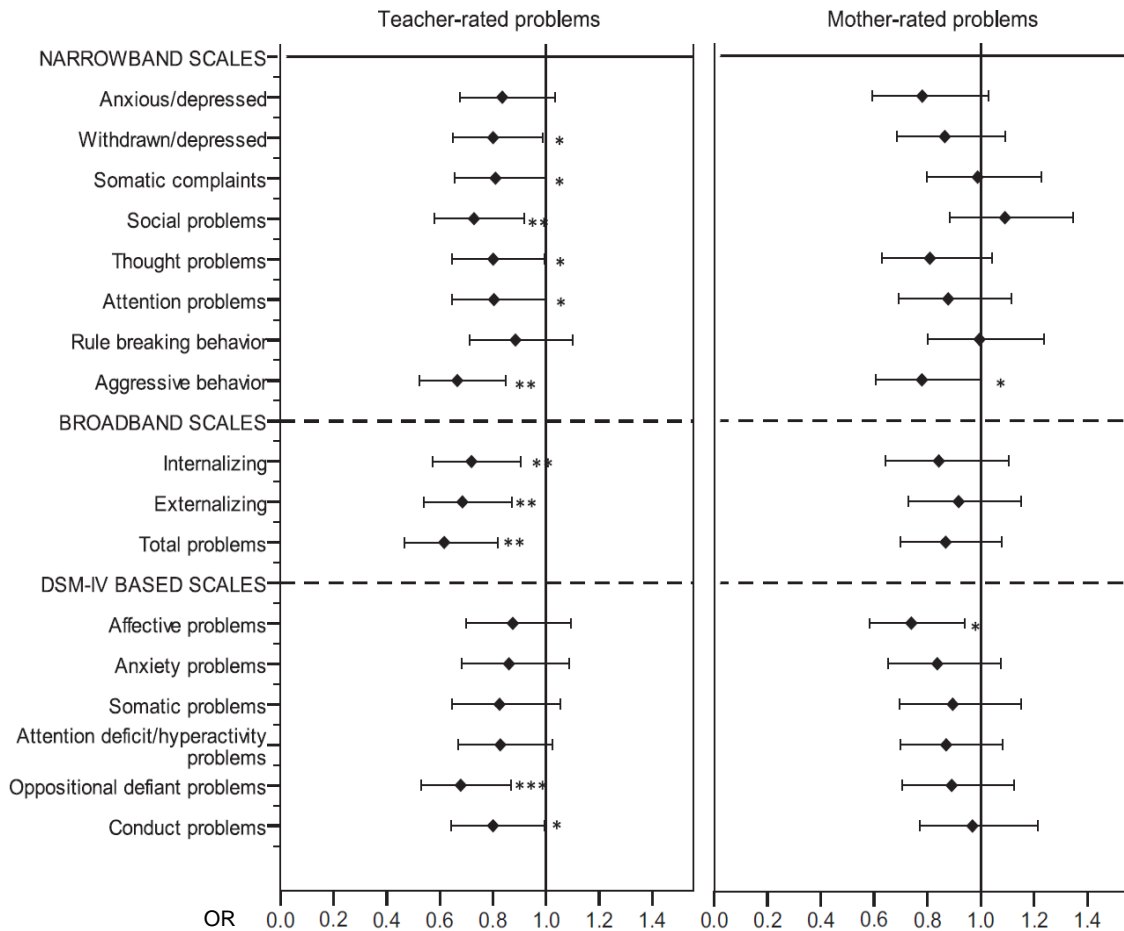


Figure 3. Associations between overall physical activity and psychiatric problems.

ORs indicate the change in the probability for borderline clinically significant psychiatric problems by every 100 cpm increase in physical activity, * P < 0.05; ** P < 0.01; *** P < 0.001.

(Martikainen et al., 2012. Physical activity and psychiatric problems in children. *Journal of Pediatrics*. 161, 160–162, reprinted with permission)

Table 2 shows that when compared to the children who spent the least amount of time in MVPA (the bottom tertile), the children who spent the most time in MVPA (the top tertile) had almost significantly lower odds for exhibiting withdrawn/depressed problems ($P = 0.050$), they also had significantly lower odds for aggressive behavior problems; internalizing, externalizing, and total behavior problems; and DOS-based oppositional defiant problems as rated by the teachers (P -values < 0.023). Regarding the maternal reports, they had lower odds for anxious/depressed, thought, and aggressive behavior problems; externalizing and total problems; and DOS-based affective, anxiety, and attention deficit/hyperactivity problems (P -values < 0.036). The children spending intermediate time in MVPA did not differ significantly from those spending the least amount of time in MVPA (P -values > 0.060).

When we reran our analyses by replacing the initial 2297 cutoff for MVPA (Heil, 2006) by the 1624 cutoff suggested for VPA (Ekblom, Nyberg, Ekblom Bak, Ekelund, & Marcus, 2012) the results remained essentially identical to those from the earlier analyses. Few differences emerged: when comparing the children in the highest third to the bottom third in VPA, the odds for teacher-reported somatic complaints became significant (OR, 0.2; 95% CI, 0.1 to 0.7), whereas the associations between VPA and mother-reported anxiety problems (OR, 0.3; 95% CI, 0.1 to 1.1), internalizing problems (OR, 0.4; 95% CI, 0.1 to 1.6), and anxious/depressed problems (OR, 0.3 95%; CI 0.1 to 1.0) declined to non-significant. No other differences between these two approaches were found.

Table 2. ORs for teacher- and mother-rated psychiatric problems by the level of MVPA.

Variable	High vs. Low level of MVPA						
	Teacher-rated problems			Mother-rated problems			
	OR	95% CI	P	OR	95% CI	P	
<i>Narrowband scales</i>							
Anxious/depressed	0.7	0.2, 2.3	0.58	0.2	0.1, 0.9	0.036	
Withdrawn/depressed	0.3	0.1, 1.0	0.051	0.4	0.1, 1.5	0.20	
Somatic complaints	0.3	0.1, 1.1	0.062	0.5	0.2, 1.7	0.26	
Social problems	0.4	0.1, 1.4	0.16	0.7	0.2, 2.1	0.53	
Thought problems	0.3	0.1, 1.1	0.072	0.1	0.0, 0.4	0.002	
Attention problems	0.8	0.2, 2.5	0.69	0.4	0.1, 1.3	0.12	
Rule breaking behavior	0.8	0.2, 2.5	0.66	0.6	0.2, 2.1	0.46	
Aggressive behavior	0.2	0.1, 0.7	0.010	0.2	0.0, 0.6	0.009	
<i>Broadband scales</i>							
Internalizing	0.2	0.1, 0.8	0.022	0.4	0.1, 1.8	0.24	
Externalizing	0.2	0.1, 0.7	0.011	0.3	0.1, 1.0	0.054	
Total problems	0.2	0.1, 0.8	0.019	0.3	0.1, 0.9	0.027	
<i>DSM-IV based scales</i>							
Affective problems	0.8	0.2, 3.0	0.80	0.1	0.0, 0.5	0.003	
Anxiety problems	0.4	0.1, 1.6	0.20	0.1	0.0, 0.6	0.007	
Somatic problems	0.4	0.1, 1.7	0.23	0.6	0.2, 2.3	0.47	
Attention/deficit hyperactivity problems	0.6	0.2, 2.0	0.45	0.3	0.1, 0.9	0.033	
Oppositional defiant problems	0.2	0.1, 0.8	0.015	0.3	0.1, 1.1	0.080	
Conduct problems	0.5	0.2, 1.6	0.26	0.5	0.1, 1.6	0.24	

An OR below 1 indicates lower probability of problems for children in the top third of MVPA when compared to the bottom third.

The associations are adjusted for the child's sex, age, height, BMI, sleep duration, maternal licorice consumption during pregnancy, and parental education (highest of either parent).

4.3 Physical activity and the HPAA

4.3.1. Physical activity and HPAA function at 8 years of age (Study IV)

Figure 4 shows that the overall physical activity level and time spent in VPA were not associated with the diurnal salivary cortisol level or pattern at 8 years of age (P-values > 0.07). There were no differences between groups in the traditional indices of diurnal

salivary cortisol (P -values > 0.10). Sex did not moderate the associations of overall physical activity and VPA with diurnal salivary cortisol levels (P -values > 0.06).

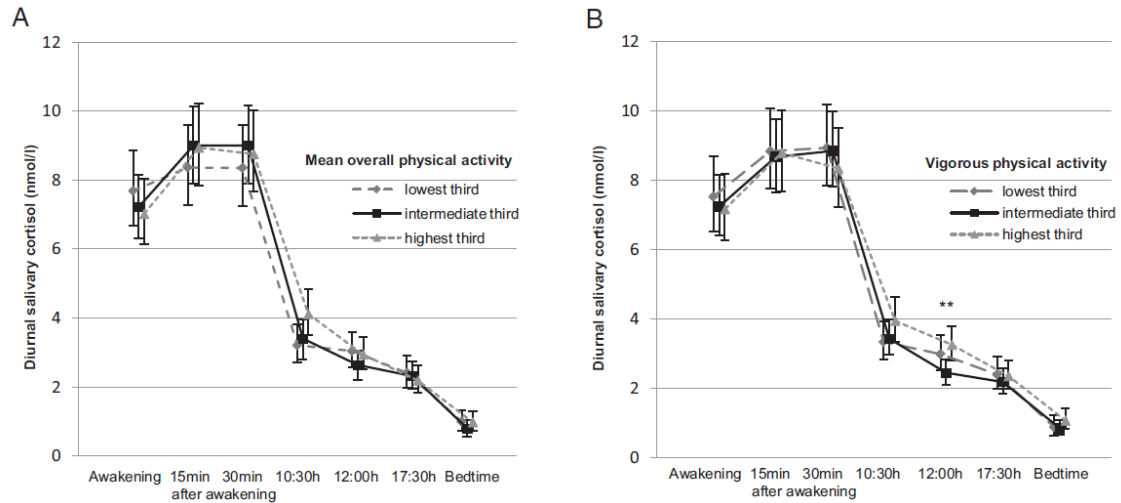


Figure 4. Diurnal salivary cortisol values in children by (A) thirds of mean overall physical activity and (B) thirds of time spent in VPA.

Values are geometric means, and error bars are 95% CIs adjusted for the time at awakening, sex, age, BMI, sleep duration, mother's occupational status, and licorice use during pregnancy.

** $P < 0.01$ for quadratic trend.

(Martikainen et al., 2013. Higher levels of physical activity are associated with lower hypothalamic-pituitary-adrenocortical axis reactivity to psychosocial stress in children. *Journal of Clinical Endocrinology and Metabolism*. 98, 619–627, reprinted with permission)

When the salivary cortisol responses to stress were assessed, overall physical activity interacted significantly with sampling time ('physical activity \times sampling time', $P = 0.013$). Figure 5A shows that children belonging to the lowest and intermediate thirds in overall physical activity showed a significant increase in salivary cortisol in response to stress (P -values < 0.001 for time). Children belonging to the highest third in overall physical activity did not show a significant increase in salivary cortisol in response to stress ($P = 0.10$ for time). In addition, salivary cortisol increment and AUC increment were lower in children with higher physical activity (P -values for linear trend < 0.017 , Table 3).

VPA also interacted significantly with sampling time ('VPA \times sampling time', $P = 0.003$). Figure 5B shows that salivary cortisol in response to stress increased significantly in children belonging to the lowest ($P = 0.002$) and intermediate ($P < 0.001$) thirds in VPA. While salivary cortisol also increased in children belonging to the highest third in VPA, the increase was smaller ($P = 0.034$). In addition, salivary cortisol increment and AUC increment were lower in children with higher VPA (P -values for linear trend < 0.025 , Table 3).

Sex did not moderate the associations of overall physical activity and VPA with salivary cortisol responses to stress (P -values > 0.10 for 'sex \times overall physical activity' / 'sex \times VPA' -interactions).

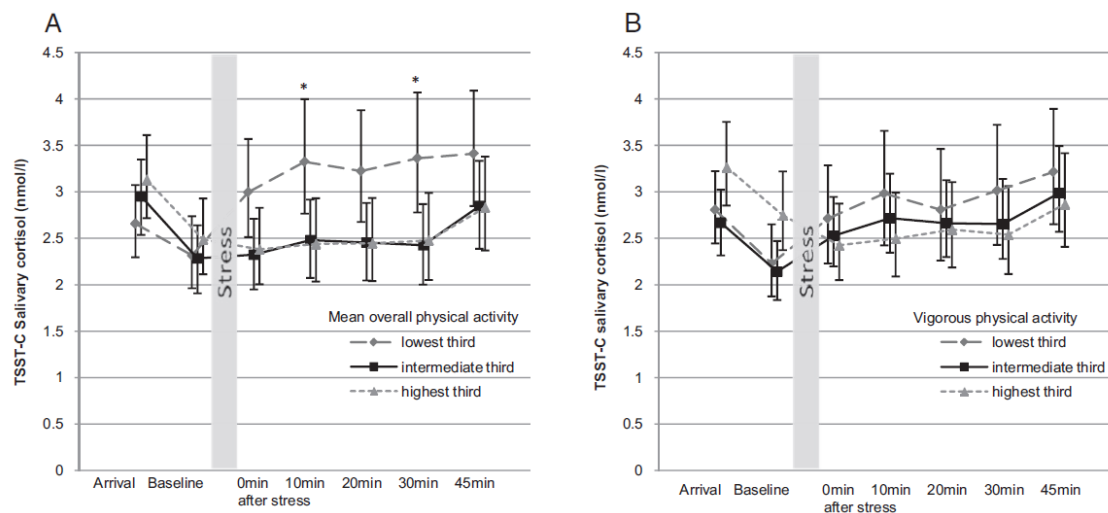


Figure 5. Salivary cortisol responses to TSST-C by (A) thirds of mean overall physical activity and (B) thirds of VPA.

Values are geometric means, and error bars are 95% CIs adjusted for the time at baseline, sex, age, BMI, sleep duration, mother's occupational status, and licorice use during pregnancy.

* $P < 0.05$ for linear trend.

(Martikainen et al., 2013. Higher levels of physical activity are associated with lower hypothalamic-pituitary-adrenocortical axis reactivity to psychosocial stress in children. *Journal of Clinical Endocrinology and Metabolism*. 98, 619–627, reprinted with permission)

Table 3. Geometric means and 95% CIs of salivary cortisol during the TSST-C according to the amount of overall physical activity and VPA.

Overall physical activity, thirds									
<i>Salivary cortisol</i> (nmol/l)	lowest		intermediate			highest		P-linear ¹	
	mean	95% CI	mean	95% CI	mean	95% CI			
Baseline	2.3	2.0, 2.7	2.3	2.0, 2.6	2.5	2.1, 2.9	0.57		
Peak after stress	4.8	4.0, 5.9	3.5	3.0, 4.2	3.7	3.0, 4.4	0.090		
Increment	2.1	1.7, 2.5	1.5	1.3, 1.8	1.5	1.2, 1.7	0.016		
AUC	3.1	2.6, 3.6	2.4	2.1, 2.8	2.5	2.1, 2.9	0.12		
AUC increment	1.3	1.2, 1.5	1.1	0.9, 1.2	1.0	0.9, 1.1	0.014		
Vigorous physical activity, thirds									
<i>Salivary cortisol</i> (nmol/l)	lowest		intermediate			highest		P-linear ¹	
	mean	95% CI	mean	95% CI	mean	95% CI			
Baseline	2.2	1.9, 2.6	2.1	1.9, 2.5	2.7	2.3, 3.2	0.089		
Peak after stress	4.3	3.5, 5.2	3.8	3.2, 4.5	3.9	3.2, 4.7	0.56		
Increment	1.9	1.6, 2.3	1.8	1.5, 2.0	1.4	1.2, 1.7	0.024		
AUC	2.8	2.4, 3.3	2.6	2.2, 3.0	2.6	2.2, 3.0	0.59		
AUC increment	1.3	1.1, 1.4	1.2	1.1, 1.4	0.9	0.8, 1.1	0.007		

Associations are adjusted for time at baseline, sex, age, BMI, sleep duration, mother's occupational status and licorice use during pregnancy

¹ P-values are for linear trend, all P-values for quadratic trend were nonsignificant (P-values > .09)

4.3.2. Physical activity and HPA function at 12 years of age (Study V)

Figure 6 shows that in girls the interactions between overall physical activity and sampling time from awakening to 60 minutes after awakening (Panel A) ('overall physical activity × sampling time', P = 0.014 in model 1, P = 0.014 in model 2) and between VPA and sampling time from awakening to 60 minutes after awakening (Panel B) ('VPA × sampling time', P = 0.026 in model 1, P = 0.026 in model 2) were significant in the analyses of salivary cortisol on day A. Sub-analyses with physical activity grouped into thirds showed that while the effect of time on morning salivary cortisol concentrations was significant in all three groups, the response was significantly greater in girls belonging to the lowest and middle thirds of overall physical activity and VPA (P-values < 3.15×10^{-7}) when compared with girls belonging to the highest third in overall physical activity (P = 0.004) and VPA (P = 0.002).

In girls the amount of sedentary time did not interact with sampling time from awakening to 60 minutes after awakening (Figure 6C) (P-values > 0.097) and overall physical activity, VPA and sedentary time did not interact with sampling time from noon to bedtime in the analysis of salivary cortisol on day A (P-values > 0.31) (Figure 6). Table 4 shows that girls with higher overall physical activity and who spent more time in VPA had lower salivary cortisol values upon awakening and a lower awakening AUC on day A (P-values < 0.039). Girls with less sedentary time had a lower awakening AUC on day A (P = 0.035). Associations between overall physical activity and sedentary time with awakening AUC were significant in model 2 only. In girls physical activity was not associated with the suppression of salivary cortisol after the DST on day B (P-values > 0.11).

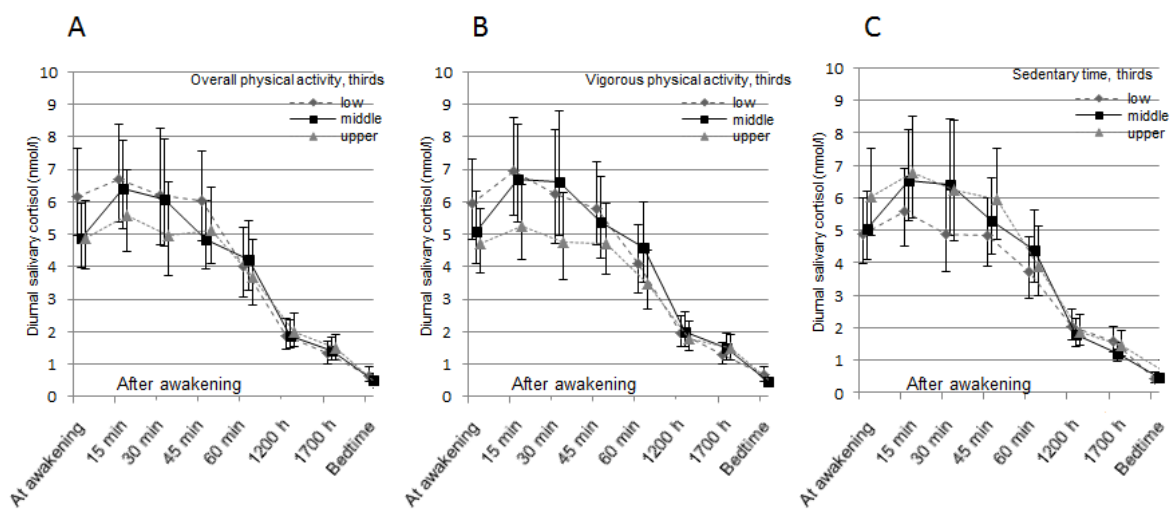


Figure 6. Diurnal salivary cortisol concentrations according to overall physical activity (panel A) and time spent in VPA (panel B) and sedentary time (panel C) categorized into thirds in girls.

Values are geometric means and error bars are 95 % CIs (back-transformed from log transformed values) adjusted for time at awakening, age, BMI, stage of pubertal development, sleep duration, maternal occupational status, and maternal licorice use during pregnancy.

(Martikainen et al., 2014. Physical activity and hypothalamic-pituitary-adrenocortical axis function in adolescents. *Psychoneuroendocrinology*, 49, 96–105, reprinted with permission)

In boys physical activity did not interact with sampling time from awakening to 60 minutes thereafter (P-values > 0.16) or with sampling time from noon to bedtime in the analyses of salivary cortisol on day A (P-values > 0.59) (Figure 6). Table 5 shows that in boys physical activity was not associated with the indices of diurnal salivary cortisol either (P-values > 0.065). However, boys with higher overall physical activity and who had less sedentary time had more suppressed salivary cortisol values upon awakening after the DST on day B (P-values < 0.012).

Finally, we tested if any of the associations changed after adjusting for Tanner stage instead of the PDS. The results that were statistically significant remained so after these adjustments (P-values < 0.047) except for one: in girls the association between overall physical activity and salivary cortisol upon awakening was rendered non-significant (P = 0.056 and P = 0.055 in models 1 and 2).

In a series of supplementary analyses we tested if the results changed when time spent in VPA was replaced with time spent in MVPA. In girls the results remained the same except that more time spent in MVPA was associated with lower awakening AUC on day A in model 2 only (-0.13 SD per SD; 95% CI, -0.29 to 0.03; P = 0.11 in model 1 P = 0.041 in model 2). In boys the association between more time spent in MVPA with higher diurnal salivary cortisol upon awakening on day A became significant in model 2 (0.16 SD per SD; 95% CI, -0.01 to 0.33; P = 0.061 in model 1 P = 0.042 in model 2), and it was also associated with more suppressed salivary cortisol values upon awakening after the DST on day B (0.23 SD per SD; 95% CI, 0.05 to 0.40; P = 0.013 in model 1 P = 0.022 in model 2). Supplementary analyses on light physical activity showed that in boys it was associated with more suppressed cortisol values after the DST (0.18 SD per SD; 95% CI, 0.016 to 0.35; P = 0.032 in model 1; P = 0.032 in model 2). All other associations with light physical activity were nonsignificant (P-values > 0.12).

Table 4. Partially and fully adjusted associations between diurnal salivary cortisol and physical activity in girls.

	Overall physical activity			Sedentary time			Vigorous physical activity		
	SD per SD ^a	95% CI	P	SD per SD ^a	95% CI	P	SD per SD ^a	95% CI	P
Diurnal salivary cortisol on day A (n=150)									
Upon awakening									
Model 1	-0.17	-0.34, -0.01	0.038	0.13	-0.02, 0.29	0.086	-0.22	-0.40, -0.04	0.015
Model 2	-0.19	-0.38, -0.01	0.036	0.15	-0.02, 0.31	0.085	-0.24	-0.43, -0.05	0.012
Awakening AUC									
Model 1	-0.15	-0.31, 0.02	0.081	0.12	-0.03, 0.28	0.12	-0.19	-0.37, -0.01	0.036
Model 2	-0.22	-0.40, -0.04	0.018	0.18	0.01, 0.34	0.035	-0.25	-0.44, -0.06	0.009
Bedtime									
Model 1	-0.04	-0.21, 0.14	0.67	0.04	-0.13, 0.20	0.67	-0.07	-0.26, 0.11	0.44
Model 2	-0.13	-0.31, 0.06	0.18	0.11	-0.06, 0.28	0.21	-0.15	-0.34, 0.05	0.13
Salivary cortisol in response to DST suppression^b (day A-day B) (n = 146)									
Upon awakening									
Model 1	-0.12	-0.28, 0.03	0.12	0.06	-0.08, 0.21	0.39	-0.13	-0.30, 0.03	0.12
Model 2	-0.13	-0.30, 0.04	0.12	0.07	-0.09, 0.22	0.38	-0.14	-0.31, 0.04	0.13

Physical activity and salivary cortisol variables are standardized (mean = 0, SD = 1).

^a Indicates the change (in SD scores) in salivary cortisol for every 1 SD increase in physical activity or sedentary time.

^b In salivary cortisol upon awakening the day before (day A) minus the day after (day B) the DST, higher values indicate more suppression.

Model 1 refers linear regression analyses adjusted for time at awakening (diurnal cortisol), time at awakening the day before and the day after and time difference between taking dexamethasone on the day before and time at awakening the day after the dexamethasone suppression test, age at testing, BMI, and pubertal status.

Model 2 refers to Model 1 adjustments and additional adjustments by sleep duration, maternal occupational status at testing, and maternal licorice consumption during pregnancy.

Table 5. Partially and fully adjusted associations between diurnal salivary cortisol and physical activity in boys.

	Overall physical activity			Sedentary time			Vigorous physical activity		
	SD per SD ^a	95% CI	P	SD per SD ^a	95% CI	P	SD per SD ^a	95% CI	P
Diurnal salivary cortisol on day A (n=133)									
Upon awakening									
Model 1	0.14	-0.03, 0.32	0.11	-0.15	-0.32, 0.02	0.081	0.12	-0.05, 0.29	0.16
Model 2	0.14	-0.03, 0.31	0.11	-0.16	-0.33, 0.01	0.066	0.14	-0.03, 0.31	0.11
Awakening AUC									
Model 1	0.02	-0.13, 0.18	0.75	0.00	-0.14, 0.15	0.95	0.07	-0.07, 0.21	0.34
Model 2	0.10	-0.05, 0.24	0.19	-0.02	-0.17, 0.13	0.79	0.10	-0.05, 0.24	0.19
Bedtime									
Model 1	-0.06	-0.22, 0.09	0.44	0.06	-0.09, 0.21	0.41	-0.05	-0.19, 0.10	0.53
Model 2	-0.03	-0.18, 0.12	0.66	0.04	-0.11, 0.19	0.58	-0.03	-0.18, 0.12	0.66
Salivary cortisol in response to DST suppression^b (day A-day B) (n = 126)									
Upon awakening									
Model 1	0.25	0.07, 0.43	0.007	-0.27	-0.44, -0.09	0.003	0.17	-0.01, 0.34	0.063
Model 2	0.24	0.06, 0.42	0.011	-0.26	-0.44, -0.08	0.004	0.16	-0.02, 0.33	0.086

Physical activity and salivary cortisol variables are standardized (mean = 0, SD = 1).

^a Indicates the change (in SD scores) in salivary cortisol for every 1 SD increase in physical activity or sedentary time.

^b In salivary cortisol upon awakening the day before (day A) minus the day after (day B) the DST, higher values indicate more suppression.

Model 1 refers to linear regression analyses adjusted for time at awakening (diurnal cortisol), time at awakening the day before and the day after and time difference between taking dexamethasone on the day before and time at awakening the day after the dexamethasone suppression test, age at testing, BMI, and pubertal status.

Model 2 refers to Model 1 adjustments and additional adjustments by sleep duration, maternal occupational status at testing, and maternal licorice consumption during pregnancy.

5 DISCUSSION

This study was designed to explore the associations of sleep and physical activity with stress system functioning, and the associations of physical activity with psychiatric problems, which have received limited attention among children and youth in previous studies

First, it was shown that poor sleep in healthy prepubertal children (at 8 years of age) was not associated with an unhealthy cardiovascular phenotype, although these links have been reported in adults (Studies I and II). Second, it was shown that higher levels of physical activity were associated with lower odds for psychiatric problems (Study III). And third, it was shown that prepubertal children with higher levels of physical activity demonstrated a lower HPA axis reactivity to psychosocial stress (Study IV). Furthermore, when the children reached early adolescence (12 years of age) the associations between physical activity and HPA axis function were more sex-specific, showing lower morning cortisol levels in girls and higher HPA axis feedback inhibition in boys (Study V).

As further discussed below, the results emphasize the importance of sustaining and supporting high physical activity levels throughout childhood and adolescence and also provide evidence for possible mechanisms explaining the associations between physical activity and well-being in youth.

5.1 Sleep and cardiovascular function in children

5.1.1 Objectively measured sleep

Study I showed that sleep quantity and quality, in a community sample of 8-year-old children without sleep breathing disorders, treated either as categorical or continuous variables, were not associated with ABP. It was also shown that, in comparison to average sleepers, children with short sleep duration had almost significantly lower SBP, lower TPR and PEP and higher CO responses to the TSST-C. This suggests lower sympathetic nervous system activation and higher cardiac activation under stress for children whose sleep is shorter.

Other studies using actigraphy are not in agreement with these findings. One study reported that low sleep efficiency was associated with elevated SBP and DBP and with hypertension and that short sleep duration was associated with hypertension in a sample of 13- to 16-year-old adolescents ($n = 238$) (Javaheri et al., 2008). Another study showed that

short sleep duration, but not poor sleep efficiency, was associated with elevated 24-hour SBP, DBP, and prehypertension in 14- to 19-year-olds ($n = 246$) (Mezick et al., 2012). Possibilities for the differences between these findings are further discussed below (section 5.1.3).

5.1.2 Parent-reported sleep problems

Similarly to the findings on objectively measured sleep, the findings regarding parent-reported sleep problems in Study II did not form a consistent pattern of expected higher ABP level and load, and higher cardiovascular and autonomic reactivity to stress in children with sleep problems. The findings indicated higher baseline parasympathetic (HF HRV) activity in children with disorders of excessive somnolence and lower SBP and DBP reactivity in children with sleep wake transition disorders. Only children with sleep breathing disorders had higher baseline vascular sympathetic activity (TPR) and higher cardiac sympathetic reactivity to stress (CO), however, the number of these children was low ($n = 5$), which might compromise the external validity of the finding.

Some of the findings also showed sex-specificity; girls with disorders of excessive somnolence had lower baseline SBP and DBP, and lower baseline vascular sympathetic activity (TPR), as well as higher vascular sympathetic reactivity (TPR) and lower cardiac sympathetic reactivity (CO) to stress. Girls with sleep hyperhidrosis had lower baseline heart rate. The possible sex-specific associations between sleep problems and cardiovascular function have not been studied extensively in previous research in children.

These results disagree with previous studies in children with clinically-diagnosed sleep disordered breathing (with ages ranging from 3 to 17) who exhibited higher 24h day- and night-time ABP levels (Amin et al., 2008; Kohyama et al., 2003; Leung et al., 2006; Li et al., 2008). These results are also in disagreement with another study in 6- to 13-year-olds who displayed higher daytime SBP and night-time SBP and DBP if their parents reported they snored and had a higher apnea-hypopnea index, or higher night-time DBP if they snored without having high apnea-hypopnea index. These findings, however, agree with one community-based study in 4- to 14-year-olds showing that parent-reported habitual snoring was not associated with SBP or DBP measured once in the morning (Kaditis et al., 2005).

The finding that children with sleep breathing disorders had higher baseline vascular sympathetic activity (TPR) and higher cardiac sympathetic reactivity to stress (CO) is in line with studies showing altered autonomic function in response to various challenges, including breathing tests (Montesano et al., 2010; L. M. O'Brien & Gozal, 2005), the head-up tilt test

(Montesano et al., 2010), and the cold-pressor test (L. M. O'Brien & Gozal, 2005). However, these findings were not significant after correction for multiple testing.

5.1.3 Potential mechanisms

Previously, various mechanisms have been proposed to explain the links between sleep disturbances and cardiovascular risks. Obstructive sleep apnea has been linked with increased blood pressure in children through hypoxemia and recurrent arousals during the night (Li et al., 2008), whereas depressive symptomatology and chronic stress have been proposed as mechanisms explaining the links between other sleep disturbances and cardiovascular risks in adults (Schwartz et al., 1999). For instance, Ogawa et al. (2003) found that sleep deprivation causes arterial baroreflex resetting towards an increased blood pressure and hypothesized that the same mechanisms within the central nervous system might cause increased blood pressure in both sleep deprivation and mental stress states. Also waking after too little sleep can be considered as a stressful condition itself, and therefore is associated with a greater sympathetic activation (Lusardi et al., 1996). Altogether, associations between sleep and stress are expected to be bidirectional, resulting in a self-reinforcing vicious cycle of decreased well-being (Garde, Albertsen, Persson, Hansen, & Rugulies, 2011).

The discrepancy between Study I and the other studies using actigraphy may relate to methodological differences. In both of the other studies the participants came from a more varied ethnic background (Javaheri et al., 2008; Mezick et al., 2012). Additionally the study by Javaheri et al. (2008) was based on participants of whom 57% were born premature, and 21% were obese at the time of testing. Previously, these characteristics have been associated with elevated blood pressure (Hovi et al., 2010; Sorof & Daniels, 2002; Winkleby, Robinson, Sundquist, & Kraemer, 1999), thus the risk of confounding is likely to have been greater when compared to Study I.

The participants in the previous studies using parent-reported or actigraphy-based sleep measures also differ from the Study I participants in age-range. In the previous studies the samples have included both pre-pubertal and pubertal children (Amin et al., 2008; Javaheri et al., 2008; Kaditis et al., 2005; Kohyama et al., 2003; Leung et al., 2006; Li et al., 2008; Li et al., 2009; Mezick et al., 2012; Montesano et al., 2010; L. M. O'Brien & Gozal, 2005). Participants in Study I were pre-pubertal and within a narrow age-range. A wider age-range of the previous samples may introduce confounding by sexual maturation as prepubertal and pubertal children are known to vary in their biological need for sleep (Sadeh et al., 2009).

Furthermore, also blood pressure and cardiovascular function depend on age (Wühl et al., 2002).

Most existing studies on specific sleep problems have been carried out in children with a clinical diagnosis of sleep disordered breathing. In Study II, we used parental reports of their children's sleep problems and covered a wide range of problems that are relatively common even in otherwise healthy children (Spruyt et al., 2005). In healthy children, the occurrence of sleep problems varies depending on the disorder (Spruyt et al., 2005). Among the Study II participants only 1.8% (n = 5) were reported as having sleep breathing problems occurring at least three times per week. In this community-based sample, the association between cardiovascular function and sleep breathing disorders might be underestimated because of their low prevalence.

24-hour ABP is regarded as a better approach to the characterization of blood pressure status at rest than isolated blood pressure measures due to the highly labile and stress-responsive 'white-coat' nature of the measure (Wühl et al., 2004). In addition to resting blood pressure characterization, an extensive approach to characterization of the cardiovascular responses to a standardized psychological stressor (TSST-C) was used in studies I and II (Cua et al., 2005; Sherwood et al., 1990). This has been shown to elicit significant cardiovascular stress responses in pediatric populations (Feldt et al., 2011; Jones et al., 2008).

Thus, Studies I and II have a number of methodological strengths in comparison to other existing studies that have generally relied only upon parent or teacher reports of children's sleep (Bayer et al., 2009; Sampei et al., 2006; Sung et al., 2008), and infrequent or single blood pressure measures (Bayer et al., 2009; Javaheri et al., 2008; Sampei et al., 2006; Sung et al., 2008).

When we took into account the possible Type 1 errors, arising from multiple testing and applied Bonferroni-correction, none of the associations or interaction terms remained statistically significant. Although this could be considered an overly conservative measure, possibly increasing the risk of type 2 errors, it weakens the confidence in the validity of our positive findings. Therefore, further research is needed to confirm our results and further research is also needed to make conclusions about the possible mechanisms behind them.

In sum, an association between sleep and unhealthy cardiovascular function was not found in Studies I and II. However, in line with the hypothesized association between poor sleep and increased stress, it has been reported among the same participants that poor sleep is associated with altered activity of the endocrine stress systems: the HPA and the SAM (Pesonen et al., 2012; Räikkönen et al., 2010). It is known that the activation of the HPA

promotes hypertension (Brown et al., 2004). Thus there is a possibility that, if prolonged, the elevated HPA activity might result in increased cardiovascular risks later on in the development of these children, which is a question for future studies.

5.2 Physical activity and psychiatric problems

Study III showed that higher levels of overall daytime physical activity and more time spent in more vigorous physical activity were associated with lower odds for psychiatric problems in a community-based sample of 8-year-old children.

In line with the results from Study III, studies using pedometers in 10-year-olds (Parfitt & Eston, 2005) ($n = 70$) and hip-worn accelerometers in 9- to 10-year olds (Parfitt et al., 2009) ($n = 57$) (for a seven-day period) found that higher step count as well as a longer time in accumulated vigorous activity were associated with less self-reported symptoms of anxiety and depression (Parfitt & Eston, 2005; Parfitt et al., 2009). Apart from anxiety and depression, these studies did not measure other psychiatric problems, thus precluding comparison with the findings of our study. Findings from Study III are in contrast with those of Strauss et al. (2001), who did not find associations between physical activity (measured with hip-worn accelerometers for seven days) and anxiety symptoms in 10- to 16-year-olds ($n = 92$) and with those of Johnson et al. (2008), who found no association between physical activity (measured with hip-worn accelerometers over six days) and depression in 12-year-old girls ($n = 1397$). The older age of the participants in these studies and the wider age-range in the sample of Strauss et al. (2001), as compared to ours, may explain the disagreement in the findings, since aging is shown to alter physical activity (Nyberg et al., 2009) as well as expression of psychiatric problems in children (Oldehinkel et al., 2011).

As in various prior studies (Achenbach, McConaughy, & Howell, 1987) the correlations between the teachers' and mothers' ratings of psychiatric problems were modest, albeit significant in Study III. It has been suggested that this relates to the different environmental contexts in which the child's behavior is observed (Achenbach et al., 1987). Yet, both teachers' and mothers' ratings have been shown to predict future maladjustment, independent of each other (Verhulst, Dekker, & van der Ende, 1997). And even though there were some differences among the associations of physical activity with maternal and teacher's ratings of psychiatric symptoms, the findings between the two observers were convergent.

In sum, these findings add to previous knowledge by showing (1) that higher overall physical activity and time spent in more vigorous physical activity are not only associated with a lower probability for exhibiting emotional problems (anxiety and depression), but are also associated with lower likelihood for exhibiting other forms of social and behavioral problems; and (2) that the higher level of overall physical activity and not only the higher intensity of physical activity is associated with lower likelihood of having psychiatric problems.

While the mechanisms behind the associations of physical activity and psychiatric problems are still poorly understood, intervention studies provide some evidence that by increasing participation in sports a decrease can be achieved in the level of anxiety and depression (Larun, Nordheim, Ekeland, Hagen, & Heian, 2006). It remains unknown, however, how stable the potential benefits of such interventions are. There is a need for longitudinal controlled studies to tackle the question of causality and to further focus on the possible effects of confounding variables such as more supportive parents, higher socio-economic status or absence of family stressors, which might all encourage children to be more physically active as well as account for the absence of psychiatric problems.

5.3 Physical activity and the HPA

5.3.1 At 8 years of age

Study IV showed that physical activity levels in healthy 8-year-old children were associated with altered HPA reactivity to stress. Both the overall habitual level of physical activity as well as the amount of VPA associated with HPA reactivity of our participants. Children with the highest levels of objectively measured overall daytime physical activity or VPA showed no or only small increases in salivary cortisol levels in response to stress. In contrast, children with less physical activity showed a significant increase in salivary cortisol levels after stress. This finding was also reflected in the higher levels of salivary cortisol increment and AUC increment in response to stress, which suggests that stress reactivity was higher for individuals with lower physical activity, although the baseline and peak after stress did not vary between the groups. The diurnal salivary cortisol pattern did not differ according to the level of overall daytime physical activity and VPA.

The association between physical activity and HPAA function was similar in girls and boys although the level of their activity differed. This indicates that sex does not moderate the association between physical activity and HPAA reactivity at this age.

As we have reported earlier on the same participants (Räikkönen et al., 2010), the children's salivary cortisol response to the TSST-C stressor was significantly lower than that seen in a similarly aged and sized study of healthy children in the UK (Jones et al., 2006). It has been recognized recently that many typically developing 'low-risk' children have relatively low HPAA responses to a variety of stressors, including the TSST-C (Gunnar, Frenn, Wewerka, & Van Ryzin, 2009). In some children, salivary cortisol levels may even decrease in response to stress (Gunnar et al., 2009). In our cohort, the children with higher levels of physical activity might also represent a more optimally developing group of children, who demonstrate a hyporesponsivity to stress typically found in the prepubertal period of development in both animals and humans (Lupien et al., 2009).

5.3.2 At 12 years of age

In Study V, higher levels of overall physical activity and VPA were associated with lower morning salivary cortisol values in adolescent girls. Whereas in adolescent boys, higher overall physical activity and lower sedentary time were associated with higher HPAA feedback inhibition. No associations were found between these physical activity measures and HPAA feedback inhibition in girls or the diurnal salivary cortisol pattern in boys.

The associations between HPAA activity and objectively measured physical activity levels have not been studied earlier during the developmental transition to adolescence. Among 8 to 13-year-olds (n = 111) Dockray et al. (2009) did not detect an association between parent-reported physical activity and salivary cortisol responses to the TSST-C; however, diurnal cortisol patterns were not studied. Study IV showed that both boys and girls with higher levels of objectively measured physical activity had lower reactivity to the TSST-C, whereas neither boys nor girls had different diurnal cortisol patterns according to physical activity. However, the response to DST was not studied at 8 years of age, thus the results are not comparable in this respect.

Additional analyses replaced VPA with MVPA. One difference was found in girls and two in boys. In girls, MVPA associated with lower cortisol AUC upon awakening on day A in the fully adjusted model only, whereas the association of VPA with cortisol AUC was significant in both models. In boys, the association between MVPA with higher cortisol at awakening on day A became significant in the partially adjusted model, while it was not significant in either

model when we examined VPA. Furthermore, in boys MVPA was associated with more suppressed cortisol in response to the DST across partially and fully adjusted models, whereas for VPA the associations did not reach conventional levels of significance. The findings of MVPA should be interpreted with caution as the threshold of 3 METs for MVPA is relatively low. This threshold may not discriminate between moderate and lower level physical activity intensities and hence the group may become too heterogeneous (Mattocks et al., 2007). Yet, the cpm cutoff for 4 METs, which is recommended to identify moderate activities (Mattocks et al., 2007) for wrist-worn Actiwatch, is not available (Ekblom et al., 2012).

5.3.3 Potential mechanisms

These findings contribute to the existing literature on the suggested role of physical activity as both a stressor and a modifier of stress (Hackney, 2006). The lower reactivity of HPA to the psychosocial stress protocol in children with a higher level of physical activity in Study IV indicates that physical activity might modify the HPA responses to psychosocial stress.

This finding is in line with other existing findings from adults, where physically trained men exhibited significantly lower cortisol responses to the TSST when compared to their untrained counterparts (Rimmele et al., 2007), older physically fit women showed lower cortisol responses to another psychosocial stress test when compared to unfit older women (Traustadottir et al., 2005) and among 18- to 23-year-old women, self-reported physical activity levels were associated with lower cortisol responses to a TSST for groups protocol (Klaperski, 2013). Consequently, physical activity might serve as a protective factor in stressful day-to-day experiences, which may be one explanatory mechanism behind the association of higher physical activity and better psychological well-being in children and youth.

To study the suggestion that physical activity might modify HPA responses to stress also in prepubertal children, future research is needed to answer, whether a lower cortisol response to acute physical activity can be found in more active children. At present, the results are contradictory. One study has previously found that acute physical activity was not associated with later cortisol levels in 53 prepubertal (9-year-old) girls and boys (Budde, Windisch, Kudielka, & Voelcker-Rehage, 2010). However, another study on 38 prepubertal (10-year-old) boys found this association for highly fit participants, but not for those with average fitness (Benitez-Sillero et al., 2009).

The findings at 12 years of age (Study V) were in line with the findings at 8 years of age (Study IV) by showing that, in early adolescent boys, higher levels of overall physical activity (and lower sedentary time) were associated with higher HPAA suppression in response to the DST. This association was not observed in girls, although morning cortisol concentrations were lower in girls engaging in higher levels of physical activity. Animal models have shown that the DST affects HPAA feedback inhibition especially by increasing glucocorticoid receptor activity at the level of the pituitary (M. A. Cole, Kim, Kalman, & Spencer, 2000). Thus, physical activity could associate with dissimilar aspects of the HPAA in adolescent girls and boys. Future studies with more detailed methods assessing HPAA function and feedback inhibition could elaborate the understanding of these differences.

When compared to girls, the 12-year-old boys' pubertal development in our study cohort was less advanced (Pesonen et al., 2014). As HPAA activity increases with age and pubertal development (Gunnar et al., 2009), it is possible that our findings in boys are closer to the findings reported in Study IV at the age of 8 years. The sex-specific findings could also result from the sex-specific differences in HPAA function emerging towards mid-adolescence (Ordaz & Luna, 2012), which are likely to be mediated by hormonal changes (A. M. Bao et al., 2005), although especially in youth, the results on the direction of the sex-differences have not been consistent (Adam et al., 2010; Bouma et al., 2009; Gunnar et al., 2009; Reynolds et al., 2013).

Together these two studies (Studies IV and V) suggest that physical activity might promote well-being by modifying the HPAA activity and reactivity to different stressors in children and youth, although sex-differences are likely to advance during adolescence. In adolescence, the environmental factors could have different influences on HPAA functioning in girls and boys, and also the health impacts of these environmental factors could vary. With this in mind, especially prospective experimental studies are still needed to draw a consistent picture of the possible influence of physical activity on HPAA functioning in men and women at different ages. Also the possible health implications of these findings should be tested in further follow-up studies.

5.4 Methodological considerations

It should be noted that owing to its cross-sectional nature, the causality of the reported effects cannot be identified in this study. Prospective controlled studies are needed to answer the

questions on causal relationships. Further central methodological considerations are outlined below.

5.4.1 Study population

The study population has a number of beneficial characteristics. Birth anthropometry, length of gestation and health at birth were all within the normal range. Participants were either prepubertal (Studies I to IV) or in early adolescence (Study V) and drawn from a narrow age-range. They had normal body weights and were healthy at the time of testing. They all came from an ethnically homogeneous Northern European population and at the age of 8 years 61% had at least one parent who had completed tertiary education. Although these characteristics limit the generalizability of our findings, they also reduce the possibility of confounding effects such as ethnicity, birth characteristics, or pubertal status.

It should be noted that although we did measure the level of the children's pubertal development at 12 years of age, we could not account for the menstrual phase, which can affect HPA function (Kajantie & Phillips, 2006), however only 26% of the girls had menstruation.

5.4.2 Sleep

The validity of actigraphy is well-established as a method for assessment of sleep quantity and quality over multiple consecutive nights (Acebo & LeBourgeois, 2006) with high levels of agreement with polysomnography measures (Meltzer et al., 2012; Tonetti, Pasquini, Fabbri, Belluzzi, & Natale, 2008). Furthermore, actigraphy has the benefit of being an ecologically valid sleep-assessment option for studying sleep patterns over many consecutive nights (Morgenthaler et al., 2007; Ohayon, Carskadon, Guilleminault, & Vitiello, 2004). Good reliability is reached when the assessment lasts for at least 5 consecutive nights (Acebo et al., 1999), as in our study. However, as actigraphy is based on movement data, it is possible that sleep duration estimates are exaggerated in more stationary individuals. Also as individual variability in sleep duration is high (Matricciani et al., 2013), averaged sleep duration values might not provide adequate information on whether the participants are receiving adequate amount of sleep.

The use of parent-reports of their children's sleep problems in the current study may be subject to some criticism. Parent-reports are obviously different from clinically diagnosed sleep problems and from a combination of parent- and polysomnography-based measurements. The range of parent-reported sleep behaviours that may be considered a

problem is wide and the definitions across studies vary. However, although studies using polysomnography are considered as the gold standard in measuring sleep, the questionnaire-based studies are of practical importance as they can be used in larger populations and are easily applicable in clinical practice. The inclusion of various types of sleep problems in a community sample of children may, thus, give us a better possibility to unravel the developmental pathways that may underlie these associations in adults. Furthermore, the literature in adults does show that both clinically-diagnosed sleep disorders and subjective sleep complaints are associated with increased risk of hypertension and cardiovascular diseases (Foley, Ancoli-Israel, Britz, & Walsh, 2004; Gangwisch et al., 2006; Gottlieb et al., 2006; Loponen, Hublin, Kalimo, Mänttari, & Tenkanen, 2010; Phillips & Mannino, 2007). To prevent overestimation of sleep problems, we used a strict cutoff in the definition of the six sleep problem subscales, which corresponded with previous studies (Spruyt et al., 2005).

5.4.3 Physical activity

When measuring physical activity with accelerometers, defining valid cutoff points for different physical activity intensities is of crucial importance. However, differences in cutoff points are common in the measurement of physical activity. This is shown, for instance, in a cross-validation study (Troost, Loprinzi, Moore, & Pfeiffer, 2011), where cutoff points for defining MVPA for ActiGraph accelerometer ranged from 2220 (Freedson, Pober, & Janz, 2005) to 3581 (Mattocks et al., 2007). Moreover, both 3 and 4 METs have been used as cutoff points for MVPA, while 4 METs has been considered superior in discriminating MVPA from lower intensity activities than 3 METs (Mattocks et al., 2007).

One clear methodological limitation in Study III is that the physical activity intensity cutoff points were derived from a study using Actical accelerometer, which might lead to inaccuracies when Actiwatch devices are used. Our study with a cutoff point of 2297 cpm for measuring MVPA above 4 metabolic equivalents (METs) also differed from the recent study, suggesting cutoff points of 1048 for 3 METs and 1624 for 6 METs (Ekblom et al., 2012), which we used in Studies IV and V.

The cutoff points by Ekblom et al. (Ekblom et al., 2012) are the only device-specific thresholds for the wrist-worn Actiwatch published so far. However, when Study III was under preparation, these cutoff points were not yet published. Furthermore, we used 4 METs as the cutoff point for MVPA, whereas Ekblom et al. (2012) provided a cutoff point for 6 METs for VPA, namely 1624 cpm. This indicates that the cutoff used in our study might be closer to VPA than MVPA. When the analyses were rerun by replacing the initial 2297 cpm

cutoff for MVPA by the 1624 cpm cutoff suggested by Ekblom et al. (5), the results remained essentially identical to those from the earlier analyses as discussed in the results section.

A further limitation in study V is that the calibration study for Actiwatch was conducted in 8-year-olds (Ekblom et al., 2012). For wrist-worn Actiwatch the study by Ekblom et al. (Ekblom et al., 2012) is currently the only calibration study using this device and location, and using the same cutoffs increases the comparability of our current findings at 12 years of age to our earlier study at 8 years of age.

In addition, the physical condition of the participants was not assessed. Not being able to adjust the data for physical fitness is a limitation as it might affect the cortisol responses of the participants. Finally, it would have been beneficial to also collect self-reported information on physical exercise, in addition to the accelerometer-based assessment of physical activity. This would have clarified whether the amount of exercise per se, as separated from habitual physical activity, shows similar associations with psychiatric problems.

5.5 Conclusions

In sum, these studies provide evidence on the associations of sleep and physical activity with stress system function and on physical activity with psychiatric problems in children. In contrast with a wealth of evidence especially from adults, the results showed that sleep in healthy 8-year-old children was not associated with an unhealthy cardiovascular phenotype. Higher physical activity levels were associated with a lower probability for psychiatric problems in children as well as lower HPAA reactivity to psychosocial stress at 8 years of age. In addition, in early adolescence (12 years of age) physical activity was associated with lower morning cortisol levels in girls and higher HPAA suppression in response to the DST in boys.

The results support the hypothesis that higher levels of physical activity are associated with lower odds for psychiatric problems, and that the adaptation of the HPAA caused by physical activity could generalize to psychosocial stressors as well (Hackney, 2006). These differences in HPAA function can be considered as one explanatory mechanism behind the associations of physical activity and psychological well-being, and furthermore, low physical activity levels can be considered as a risk factor increasing vulnerability to different daily stressors.

These results stress the importance of maintaining adequate physical activity levels in childhood and adolescence. Supporting physical activity can be viewed as a cost-efficient method of promoting health and possibly preventing stress-related illnesses further on in life. In a societal level, practices enhancing physically active lifestyle should be supported. This is especially important as it is known that children from different socioeconomic backgrounds have unequal possibilities to participate in physical activity (Currie et al., 2012; Kantomaa, Tammelin, Näyhä, & Taanila, 2007). Physical exercise and enjoyable physical activities should be accessible, and for example schools should be encouraged and financially supported in providing these activities to children and youth.

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