DEVELOPMENTAL ORIGINS OF PHYSIOLOGICAL
STRESS REACTIVITY

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Academic dissertation to be publicly discussed,
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CONTENTS

CONTENTS .............................................................................................................................. 3

ABSTRACT .............................................................................................................................. 5

TIIVISTELMÄ ........................................................................................................................... 6

ACKNOWLEDGEMENTS ........................................................................................................ 7

LIST OF ORIGINAL PUBLICATIONS ..................................................................................... 9

ABBREVIATIONS .................................................................................................................. 10

1 INTRODUCTION ................................................................................................................. 11

   1.1 Developmental Origins of Health and Disease (DOHaD) ......................................... 11
   1.2 Programming of CV diseases ................................................................................... 12
   1.3 Prenatal growth, birth and early postnatal growth ..................................................... 15
   1.4 Anatomy and maturation ........................................................................................... 16
       1.4.1 CV system ...................................................................................................... 16
       1.4.2 HPAA ..................................................................................................................... 18
   1.5 Measuring CV and HPAA activity ............................................................................. 19
       1.5.1 Measuring blood pressure .............................................................................. 19
       1.5.2 Measuring sympathetic and parasympathetic nervous system activity .......... 20
       1.5.3 Measuring HPAA activity ................................................................................ 21
   1.6 Stress ........................................................................................................................ 21
       1.6.1 Measuring psychological stress in the laboratory environment ...................... 22
       1.6.2 Physiological hypo- or hyperreactivity of CV system and HPAA to stress ..... 23
       1.6.3 Physiological recovery from stress ................................................................. 24
   1.7 Effects of sex and age .............................................................................................. 24
   1.8 Animal studies in DOHaD ......................................................................................... 25

2 AIMS OF THE STUDY ....................................................................................................... 27

3 METHODS ......................................................................................................................... 28

   3.1 Study populations ..................................................................................................... 28
   3.2 Protocols ................................................................................................................... 30
       3.2.1 Trier Social Stress Test for Adults .................................................................. 30
       3.2.3 Trier Social Stress Test for Children ............................................................... 32
   3.3 Physiological measures ............................................................................................ 33
   3.4 Statistical analyses ................................................................................................... 34

4 RESULTS ........................................................................................................................... 36
4.1 CV and HPAA responses to stress (Studies I – IV) ..................................................36
4.2 Markers of prenatal environment and CV stress reactivity in late adulthood (Study I) ........................................................................................................................................36
4.3 Markers of prenatal environment and HPAA stress reactivity in late adulthood (Study II).....................................................................................................................................37
4.4 Markers of childhood growth and CV stress reactivity in late adulthood (Study III) ..39
4.5 Prenatal growth markers and CV stress reactivity and recovery in childhood (Study IV) ...................................................................................................................................41

5 DISCUSSION .....................................................................................................................44

5.1 Markers of prenatal growth and CV reactivity to stress in childhood and in late adulthood ........................................................................................................................................45
  5.1.1 Females ..........................................................................................................45
  5.1.2 Males ..............................................................................................................46
5.2 Markers of prenatal growth and late adulthood HPAA reactivity to stress ..........47
5.3 Markers of childhood growth and late adulthood CV reactivity to stress ..........48
5.4 Methodological considerations ..................................................................................50
5.5 Conclusions ..............................................................................................................51

6 REFERENCES ...................................................................................................................52

ORIGINAL PUBLICATIONS
ABSTRACT

The model of developmental origins of health and disease proposes that organisms during fetal period utilize cues that enable their adaptation in the postnatal environment they are likely to live, having short-term advantages when trying to survive in environment but simultaneously in the long run have costs for health. A large body of epidemiological research has found that low birth weight, a marker of intrauterine conditions, is associated with cardiovascular (CV) disease. Since the reported associations of birth weight with normal variation in the resting blood pressure (BP), a major predictor of CV disease risk, have been modest, a key candidate mediating the link has been CV and hypothalamus-pituitary-adrenal axes (HPAA) reactivity to stress. In addition, not only weight at birth but also gestational age and early postnatal growth may have independent associations to stress reactivity.

The aim of this thesis was to investigate whether pre- and postnatal growth and gestational age are associated with CV and HPAA activity before, during and after stress in childhood and in late adulthood. Altogether 287 men and women aged 60-70 and 299 boys and girls aged 7-9 underwent Trier Social Stress Test. Several indices of HPAA and CV were measured and birth size and gestational age were obtained from birth records.

Results showed that low birth weight was associated with low HPAA activity during psychosocial stress, and rapid gain in BMI during years 7-11 was related to heightened stress reactivity to psychosocial stress. Size at birth in children and gestational age and early postnatal (0-2 years) gain in height in adults were associated with CV stress responses; however, in a sex-specific manner. Given that CV stress responses and HPAA activity are markers of CV disease vulnerability, our results may partly explain the associations between early environment and later CV disease.

Tämän tutkimuksen tarkoituksena oli selvittää eri ikäryhmiin kuuluvilla henkilöillä syntymäkoon, raskauden keston ja varhaislapsuuden painoindeksin ja pituuden muutosten yhteys yksilön fysiologiseen aktiivisuuteen ennen stressiä, stressin aikana ja stressin jälkeen. 287 aikuista iältään 60-70 vuotta ja 299 lasta iältään 6-8 vuotta kävivät läpi Trierin Sosiaalisen Stressikokeen (TSST). Henkilöiltä mitattiin useita eri kardiovaskulaarisia ja HPAA –suureita.

Tulokset osoittivat, että 60-70 -vuotiailla miehillä ja naisilla matala syntymäpaino oli yhteydessä matalaan HPA -aktiivisuuteen ja nopea painoindeksin nousu vuosien 7 ja 11 välillä korkeaan verenpainereaktiivisuuteen psychososiaalisen stressin aikana. Tulokset osoittivat myös, että syntymäkoko lapsilla ja sekä raskauden kesto että pituuden kasvu kahden ensimmäisen elinvuoden aikana aikuisilla olivat yhteydessä useisiin kardiovaskulaarisisiin ja autonomisiin vasteisiin stressin aikana tai stressistä palaututtaessa, mutta näissä tuloksissa oli eroavaisuuksia sukupuolen välillä. Koska HPAA ja kardiovaskulaarinen aktiivtypically stressin aikana ja stressin jälkeen ovat sydän- ja verisuonitaudin riskitekijöitä, tulokset voivat osittain selittää varhaisen kasvuymppäristön vaikutusta riskiin sairastua sydän- ja verisuonitauteihin.
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Helsinki, 22.11.2010.  

Kimmo Feldt
LIST OF ORIGINAL PUBLICATIONS

This review is based on the following original publications. The original articles are referred to in the text with their Roman numerals I - IV


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### ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tr>
<td>ACTH</td>
<td>Adenocorticotrophin</td>
</tr>
<tr>
<td>ANS</td>
<td>Autonomous Nervous System</td>
</tr>
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<td>AUC</td>
<td>Area Under the Curve</td>
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<td>BMI</td>
<td>Body Mass Index</td>
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<td>BP</td>
<td>Blood pressure</td>
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<td>CO</td>
<td>Cardiac Output</td>
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<td>CV</td>
<td>Cardiovascular</td>
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<td>DBP</td>
<td>Diastolic Blood Pressure</td>
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<tr>
<td>DOHaD</td>
<td>Developmental Origins of Health and Disease</td>
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<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
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<tr>
<td>HF HRV</td>
<td>High-Frequency Heart Rate Variability</td>
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<tr>
<td>HPAA</td>
<td>Hypothalamus Pituitary Adrenal –Axis</td>
</tr>
<tr>
<td>HR</td>
<td>Heart Rate</td>
</tr>
<tr>
<td>PEP</td>
<td>Pre-Ejection Period</td>
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<tr>
<td>PNS</td>
<td>Parasympathetic Nervous System</td>
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<tr>
<td>SBP</td>
<td>Systolic Blood Pressure</td>
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<tr>
<td>SNS</td>
<td>Sympathetic Nervous System</td>
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<tr>
<td>TPR</td>
<td>Total Peripheral Resistance</td>
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<tr>
<td>TSST</td>
<td>Trier Social Stress Test</td>
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<td>TSST-C</td>
<td>Trier Social Stress Test for Children</td>
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1 INTRODUCTION

During the past two decades, a large body of epidemiological evidence around the world has shown that small size at birth is linked with cardiovascular (CV) diseases such as heart disease and stroke (Barker, Winter, Osmond, Margetts, & Simmonds, 1989; Barker, Osmond, Forsen, Kajantie, & Eriksson, 2005; R. Huxley et al., 2007; Lawlor, Ronalds, Clark, Smith, & Leon, 2005; Osmond, Kajantie, Forsen, Eriksson, & Barker, 2007; Stein et al., 1996). However, the mechanisms behind these associations are unclear. The reported associations of size at birth with normal variation in resting blood pressure (BP) level have been inconsistent or surprisingly modest. (R. Huxley, Neil, & Collins, 2002; R. R. Huxley, Shiell, & Law, 2000; Kajantie, 2006; Law et al., 2002) and it has been suggested that rather than resting levels, the reactivity and recovery of both Hypothalamus Pituitary Adrenal –Axis (HPAA) and CV systems would link size at birth with CV diseases. It has also been recognized that developmental phases predisposing to adult CV outcomes include not only periods during fetal life but extend to infancy and childhood as well.

1.1 Developmental Origins of Health and Disease (DOHaD)

Many organisms during the fetal period are capable of developing in several ways by utilizing cues that enable their adaptation in the postnatal environment, in which they are likely to live. This “developmental plasticity” has probably evolved to facilitate survival and gain reproductive success. However, the problem is that the predictions may not be correct or the environment changes in time. Additionally, the developmental path that is selected may favour short-term survival, but still have damaging effects later in life. Being born small and having a slow metabolism might have short-term advantages when trying to survive in environments that are lacking in resources, but simultaneously in the long run have health disadvantages. Then again, being born large may benefit the individual development due to abundant resources early on, but simultaneously have adverse long-term consequences such as obesity, diabetes and cancer. (Gluckman, Hanson, Spencer, & Bateson, 2005)

Besides increasing the probabilities of successful development, this early plasticity of the organism also suggests that disease processes may have early origins. From
epidemiological studies we have learned that both slow prenatal and slow postnatal growth increases the risk of later chronic disease (Barker et al., 1989; Barker, 1992; J. G. Eriksson et al., 2007; J. G. Eriksson, Forsen, Kajantie, Osmond, & Barker, 2007; Osmond et al., 2007) and post-mortem studies have shown that there are signs of CV lesions already during early childhood (Berenson, Srinivasan, & Bao, 1997). The importance of early events in terms of disease development has since been confirmed both in experimental animal studies (Nuyt, 2008; Vieau et al., 2007) and in a number of different human populations (Jones et al., 2007; Raikkonen & Pesonen, 2009; Rich-Edwards et al., 1997; Stein et al., 1996). In the medical field, the idea of investigating the health and disease effects of early physical growth has been designated “Developmental Origins of Health and Disease” (DOHaD).

1.2 Programming of CV diseases

In the field of DOHaD the concept of “programming” signifies a process whereby an adverse environmental stimulus, experienced in utero, induces long-term structural or functional effects on the developing organism. Several mechanisms that affect the disease process in the course of human development have been unravelled. However, some of the epidemiological findings are complex and still to be solved. One of the best-known is the mismatch of small size at birth showing much stronger relationships to several CV diseases including CHD (Rich-Edwards et al., 1997), stroke (Lawlor et al., 2005) and overt hypertension (J. Eriksson, Forsen, Tuomilehto, Osmond, & Barker, 2000) than to their main risk-factors, resting BP level, which on average shows only 2 mmHg increase in systolic BP (SBP) per one kg decrease in birth weight (R. R. Huxley et al., 2000).

When investigating early origins of CV disease risk factors using size at birth and BP level as their equivalents, several issues need to be taken into consideration. First, size at birth is determined by summarized intrauterine growth rate and gestational age. Size at birth is often controlled for gestational age in order to concentrate on the effects of growth and the availability of resources during the prenatal environment rather than the time the fetus spends in the womb. In addition, gestational age might have health effects also independent of size at birth. Leon et al. (Leon, Johansson, & Rasmussen, 2000) showed in a sample of 165 000 men aged 17-19 that when both gestational age at birth
and birth weight were included in the model as predictors of systolic BP level, the statistically significant effect of gestational age was not affected, though statistical strength for birth weight was decreased. In a sample of 3100 women, gestational age even showed a stronger association with BP at the age of 31 than birth weight (Jarvelin et al., 2004). Gestational age has also been linked with cerebrovascular disease (Koupil, Leon, & Lithell, 2005) and stroke (Lawlor et al., 2005). Therefore, size at birth may be insufficient in capturing the early influences that give rise to paths to high BP and CV disease.

Second, it has also been discovered that besides prenatal growth, growth during early postnatal life has major health effects. Especially slow growth during the prenatal period followed by rapid postnatal growth during infancy and childhood may be associated with heightened level of BP or a diagnosis of hypertension at an early age (Adair & Cole, 2003; Barker et al., 2005; Zhao et al., 2002). Then again, in an older cohort it was noticed that prenatal growth followed by a slow growth during infancy may also lead to an increased risk of developing CHD (Barker et al., 2005). Poor infant growth alone is also shown to predict coronary heart disease, and the effect has been stronger than for small size at birth (Fall, Vijayakumar, Barker, Osmond, & Duggleby, 1995; Forsen, Eriksson, Osmond, & Barker, 2004). In order to clarify the role of postnatal growth within the disease process, epidemiological studies in the Helsinki Birth Cohort Study (HBCS) have with more careful analyses found several suboptimal childhood growth patterns associated with adult diagnosis of hypertension (J. Eriksson et al., 2000), coronary heart disease (Barker et al., 2005; J. G. Eriksson et al., 1999) and type 2 diabetes (J. G. Eriksson, Osmond, Kajantie, Forsen, & Barker, 2006).

Third, associations of pre- and postnatal growth and gestational age with resting BP level are relatively modest compared to their associations with CV disease. It has therefore been suggested that the answer may not lie in pre- and postnatal predictors, but in the nature of the observed variable, i.e. the level of BP. Given that BP has great daily variations, and the highest strain to vessels occurs mostly when BP rises to its peak, investigations whether size at birth was linked to variation and pinnacles of BP started to appear. With a sample of 723 men, Koupil, Leon and Byberg (Koupil, Leon, & Byberg, 2005) showed that although weight at birth was not related to absolute level of BP, it was related to a relative increase in BP during working hours compared to the
usual daily level. Then again, in a sample of 104 men and 79 women aged 26 years, in women a one kg decrease in birth weight was associated with a 9 mmHg increase in SBP responses to cognitive stressors and a hypothetical confrontation scenario (Ward et al., 2004). In men, the association was not significant. In a sample of 721 men and women aged 58 years born at the time of the Dutch famine of 1944, in women a one kg decrease in birth weight was associated with a 5 mmHg increase in SBP response to psychosocial stress (de Rooij et al., 2006; Painter et al., 2006). Again, the association was not significant in men. Furthermore, in studies with adult women born preterm (Kistner, Celsi, Vanpee, & Jacobson, 2000; Kistner, Celsi, Vanpee, & Jacobson, 2005; Pyhala et al., 2009) it was shown that gestational age, rather than birth weight, predicts adult systolic BP reactivity measured by 24-ambulatory BP recordings over 130 mmHg. Pyhälä et al. (Pyhala et al., 2009) also showed that very low birth weight individuals have heightened diastolic BP responses to psychosocial stress at the age of 23 when compared to matched controls born full-term. Given all these results, it is suggested that the pathway from size at birth and gestational age to adulthood CV disease might be connected through the higher reactivity of the CV system.

Fourth, besides the activity of the CV system, the activity of HPAA has also been suggested as one of the key candidates in mediating the link between early growth and CV disease (Kajantie, 2006; Kajantie & Raikkonen, 2010; Seckl & Meaney, 2004). HPAA activity is related to precursors of CV disease, such as impaired glucose tolerance (Rosmond & Bjorntorp, 2000) and coronary calcification (K. Matthews, Schwartz, Cohen, & Seeman, 2006); however, the relationship between size at birth and postnatal HPAA activity is more complex. Size at birth has been associated both with hypocortisolism and hypercortisolism (Kajantie et al., 2002; Kajantie & Raikkonen, 2010; Reynolds et al., 2005; Reynolds, 2010). Several of these studies have, however, assessed cortisol at a state of rest or after a biochemical activation of the axes. As with CV system, it has been suggested that rather than the resting level, HPAA reactivity to stress may be determined during the fetal period (Phillips & Jones, 2006). Indeed, this hypotheses has gained support from results from animal studies: early life manipulations have dissimilar effects on HPAA function at a resting stage and during stress (S. G. Matthews, 2002). In humans, a study consisting of young healthy male twins showed a negative association between birth weight and cortisol responses to
psychosocial stress (Wust, Entringer, Federenko, Schlotz, & Hellhammer, 2005) and one other study consisting of singleton men and women found no association (de Rooij et al., 2006). However, in the latter study the response to stress was mild. Both the CV system and HPAA activity during stress may offer key links mediating the relationship between early growth and CV disease.

### 1.3 Prenatal growth, birth and early postnatal growth

Figure 1 depicts steps from conception to maturity by splitting growth into four additive and partly superimposed components, namely fetal period, infancy, childhood and puberty. The highest growth spurt can be witnessed during the fetal period, when growth velocity in relation to time makes an inverse u-shaped curve. There are also spurts of growth during early infancy and of puberty.

![Figure 1. Growth velocity throughout the human growth period (Kajantie 2003, with permission)](image-url)
Although the fetal genome signifies the prenatal (and postnatal) growth potential, the balance of evidence suggests that factors unrelated to the fetal genome determine 60-75% of the resulting birth weight and 70-85% of gestational age (Clausson, Lichtenstein, & Cnattingius, 2000; Lunde, Melve, Gjessing, Skjaerven, & Irgens, 2007). Non-genomic factors that determine pre- and postnatal growth are mainly maternal nutrition, endocrine factors, sex, parity, maternal growth, smoking, medical complications, maternal social conditions, childhood social conditions, placental functioning and several other factors.

Unlike pre- and postnatal growth, the regulation of the time of delivery in term pregnancies is not a well-known phenomenon. One of the key candidates is corticotropin-releasing hormone (CRH), which plays an important role in the etiology of preterm delivery associated with maternal or fetal stress (Lockwood, 1999) and also in parturition regulation in the case of primates (Bowman et al., 2001). In humans, a few studies suggest CRH as the likely determinant of the timing of human birth (McLean et al., 1995; Wadhwa, Porto, Garite, Chicz-DeMet, & Sandman, 1998), but the exact pathways still remain unclear. CRH and most of the non-genomic growth factors, such as nutrition and hormones, participate in the development of the CV system and HPAA. Therefore, all these factors offer several potential mechanisms that may underlie the development of CV disease.

1.4 Anatomy and maturation

1.4.1 CV system

The CV system is made up of the heart and the blood vessels, such as the veins and arteries, which by upholding BP move the blood around the body. BP is a product of cardiac output (CO) and peripheral resistance. The former is the amount of blood pumped by the heart during one minute and peripheral resistance a combination of elements that create resistance to regulate blood flow distribution in the periphery. Resistance in the periphery consists in a high degree of inherent constrictor tone in arterioles, which is called basal tone. Basal tone is mainly accounted for by an intrinsic property of vascular smooth muscle that is independent of neural or humoral influences and is caused by rhythmic contractions that are propagated from cell to cell. Basal tone
may be thought of as a (conceptual) reference point on which various vasomotor influences (neural and humoral) are expressed. Besides basal tone, peripheral resistance comprises a summation of vascular reactivity to several different contractile agonists.

One of the most important regulators of the CV system is the autonomic nervous system (ANS). It is mainly efferent, transmitting signals from the central nervous system to peripheral organs. The ANS controls heart rate (HR) and the force of heart contraction, the constriction and dilatation of blood vessels, and the contraction and relaxation of smooth muscle in various organs. It is divided into two separate divisions, parasympathetic and sympathetic, based on both anatomical and functional differences.

The ANS has the capability to cause rapid increases in arterial pressure. For this purpose, the entire vasoconstrictor and cardiac accelerating functions of the sympathetic nervous system (SNS) are stimulated as a unit. At the same time, there is a reciprocal de-activation of the parasympathetic vagal inhibitory signals to the heart. In consequence, arterioles, veins and other large vessels constrict and the heart itself is directly stimulated further enhancing cardiac pumping. With this short-term regulation of BP, vasomotor fibres from SNS, renal sympathetic nerves and circulating humoral agents play important roles in the regulation of organ blood flow.

During the fetal period, all elements of the human ANS and peripheral nervous system are developed from the neural crest, which is an embryonic structure formed during the third and fourth week of fetal development. Neural crest cells migrate to several specific regions to form the basis of the sympathetic nervous system, and later on the parasympathetic nervous system. Morphological maturation of sympathetic ganglion cells emerges near twelve weeks of development, which then gives rise to the adrenal medulla, the principal site of the amino-acid tyrosine conversion to the catecholamines epinephrine and norepinephrine.

Parasympathetic cholinergic nerves appear in human fetal atria from week 8 onwards and sympathetic-adrenergic nerves in the fetal heart in weeks 9 to 10 of development. However, it is suggested that the cardiac activity regulating parasympathetic and cholinergic tones emerges in weeks 15-17 and sympathetic tone even later during weeks 23-28 (Papp, 1988). After birth, sympathetic and parasympathetic innervations and cardiac regulatory systems continue to develop late into postnatal life (Robinson, 1996).
1.4.2 HPAA

HPAA is an important neuroendocrine system, which involves parts of the hypothalamus, the anterior lobe of the pituitary gland and the adrenal cortices. Figure 2 describes the functioning of the main parts of the axes in men and women. In general, hypothalamus releases corticotrophin-releasing hormone (CRH), which stimulates adrenocorticotrophic hormone (ACTH). ACTH is then transported by the blood to the adrenal cortex of the adrenal gland, where it stimulates the biosynthesis of corticosteroids (such as cortisol).

HPAA maturation during the fetal period starts early on and fetal hypothalamus can be seen by 7 weeks of gestation and HPAA hormonal activity by eight to twelve weeks of gestation (Mesiano & Jaffe, 1997). Hypothalamic CRH can be identified by 16 weeks in the paraventricular nucleus and in other sites such as the hippocampus (Petraglia, Sutton, & Vale, 1989). CRH is the primary hypothalamic releasing factor regulating adrenocortical steroidogenesis and the growth of pituitary corticotrophs (a cell secreting ACTH) of the fetal HPAA (Rose et al. 1998), acting as a vasodilator of the fetoplacental circulation (Clifton et al., 1994) and also mediating the stress response. Although placental CRH is identical to hypothalamic CRH in structure and immunoreactivity, expression and secretion of placental CRH are increased and hypothalamic CRH decreased by glucocorticoids.

**Figure 2.** The function of HPAA.
Another part of the HPAA is the adrenal cortex, which secretes an important homeostasis-maintaining hormone cortisol. Functional development of the adrenal cortex starts from four weeks of development and the precise onset of biosynthesis and production of cortisol has been only recently discovered. De novo cortisol production is available at 8 weeks of gestation (Goto et al., 2006), which influences the structural and functional development of a wide variety of fetal tissues, and is essential for the antepartum maturation of organ systems including the lungs, gastrointestinal tract, liver, and central nervous system. In addition, the largest part (appr. 80-90%) of the adrenal cortex consists of the “fetal zone” producing dehydroepiandrosterone (dhea), which serves as a precursor to male and female sex hormones and affects on the development of CV disease (Ebeling & Koivisto, 1994).

Besides placental CRH, adrenocorticotropic hormone (ACTH) is one of the prime trophic hormones controlling and stimulating fetal adrenocortical growth and differentiation. It is produced in the anterior pituitary gland and acts via local mediators or growth factors in synchronizing fetal adrenocortical growth and angiogenesis. Hypothalamic CRH stimulates pituitary ACTH release by 14 to 20 weeks (Blumenfeld & Jaffe, 1986).

1.5 Measuring CV and HPAA activity

1.5.1 Measuring blood pressure

In 1905, Korotkoff described the auscultatory sounds which became the foundation for the BP measurement techniques. It is still the most common method of BP measurement today. An air-filled cuff is wrapped around the patient's upper arm and it is inflated to occlude the brachial artery. As the cuff is allowed to deflate, a stethoscope is placed over the patient's brachial artery (distal to the cuff). The auscultatory technique is based on the ability of the human ear to detect and distinguish sounds. This is a great advantage since it allows the clinician to determine the quality of each measurement. However, inherent in this is the possibility for measurement error due to differences in hearing acuity from clinician to clinician. In an attempt to increase reproducibility, some automated devices have replaced the human ear with a microphone.
Unlike auscultatory techniques, which measure systolic and diastolic BP but estimate mean arterial pressure, oscillometric devices often measure the mean BP but estimate systolic and diastolic BP (Park, Menard, & Yuan, 2001). The term "oscillometric" refers to any measurement of the oscillations caused by the arterial pressure pulse. An air-filled cuff is wrapped around the patient's arm or finger and the cuff is inflated to occlude the blood flow. As the cuff is allowed to deflate, pressure data is recorded by the device.

During the early 1970’s, a method which relied on the principle of the "unloaded arterial wall" was introduced. Arterial pulsation was detected by a photoplethysmograph from a finger under a pressure cuff. The output of the plethysmograph is used to drive a “servo-loop”, which rapidly changes the cuff pressure to keep the output constant, so that the artery is held in a partially opened state. The oscillations of pressure in the cuff are then measured. By exploiting this method, the Finometer BP measurement device (used in studies I & III) gives an accurate and continuous estimate of the changes in systolic and diastolic BP, and also estimates cardiac output and peripheral resistance with the Modelflow method (Bogert & van Lieshout, 2005; Guelen et al., 2003).

Another non-invasive BP measurement technique is called the tonometry, in which the radial artery is compressed against radial bone. Pulsations are then proportional to the intra-arterial pressure. The technique is based on an assumption that, under proper conditions, the artery wall does not influence the transmission of arterial pressure to a sensor applied to the skin. The technique is used for example in the Vasotrac BP measurement device applied in study IV. Vasotrac provides semi-continuous BP measurement and is well-validated against invasive arterial monitoring (Cua, Thomas, Zurakowski, & Laussen, 2005).

1.5.2 Measuring sympathetic and parasympathetic nervous system activity

Components of the autonomic nervous system (ANS), the SNS and parasympathetic nervous system (PNS), control cardiac and vascular activity. During recent decades, a few non-invasive measurement techniques have been developed to analyse both components separately. Especially the time-interval between ventricular depolarization to the beginning of left ventricular ejection, defined as pre-ejection period (PEP), is
used as an index of cardiac sympathetic activation due to its dependence of β-adrenergic
inotropic drive to the left ventricle of the heart (Berntson et al., 1994). Then again, high
frequency (0.12 – 0.40 Hz) fluctuations of heart rate (HF HRV) indicate vagal influence
on the heart and work as an index of parasympathetic activity (Berntson et al., 1997).
This index can be obtained by using a computational technique called Fast Fourier
Transform (FFT) to the detrended and appropriately resampled time series of heart rate
data. Besides CV markers, salivary alpha-amylase levels have also been found to
correlate with norepinephrine levels and may be used as a proxy for SNS activity
(Raikkonen et al., 2010; Rohleder, Nater, Wolf, Ehlert, & Kirschbaum, 2004). These
markers are widely used and offer simple and indirect indices of ANS activity.

1.5.3 Measuring HPAA activity

Markers of HPAA activity, ACTH and cortisol concentrations, are often measured
directly from blood. Cortisol may also be assessed from saliva or urine. However,
cortisol in the blood stream is bound to circulating proteins, whereas in saliva-bound
hormone components are too large to pass through when blood filters through the
salivary glands. Therefore, salivary cortisol measurement is a reliable indicator of
biologically active cortisol or “free” cortisol (Hellhammer, Wust, & Kudielka, 2009),
whereas cortisol derived from blood indicates total cortisol, both bound and free.

1.6 Stress

Stress is an ambiguous concept that is used in different occasions to denote positive or
negative strain in a physical or psychological context. Stress responses are adaptive and
enable us to both survive and to recover from life-threatening physical demands. In
1936, endocrinologist Hans Selye defined stress as the nonspecific response of the body
to any demand (Selye, 1936). This nonspecificity meant that exposure to any stressor
elicit same type of pituitary adrenocortical and sympathoadrenomedullary response.
Although popular, this concept has since subsequently been refined and it has been
found that different types of stressors have their own unique central neurochemical and
peripheral pattern of responses (Pacak et al., 1998).

Activation of the stress system leads to behavioral and peripheral changes that
improve the ability of the organism to adjust to environmental demands and increase
its chances for survival. This concept of maintaining bodily homeostasis has been termed “allostasis”. When stress is chronic or physiological responses to stress are exaggerated or the stress system does not perform normally, various pathophysiological states may arise (Chrousos & Gold, 1992) and lead to allostatic load on the price of adaptation (McEwen & Gianaros, 2010).

In the modern society, many of the demands one faces that are mental lead to increased physical stress reactivity compared to bodily needs. A wide body of evidence from a diversity of disciplines has shown that especially the psychosocial factors and modern-day psychological stress (Dimsdale, 2008) are related to mortality and morbidity due to CV diseases (Everson-Rose & Lewis, 2005). Psychosocial factors that relate to mortality and morbidity are mainly chronic and acute psychosocial stressors, social ties, social support, social conflict and negative emotional states (Everson-Rose & Lewis, 2005).

### 1.6.1 Measuring psychological stress in the laboratory environment

Individual differences in psychological stress reactivity are often measured by examining changes in physiological functioning elicited by aversive, challenging, or engaging laboratory tasks, such as mental arithmetic, cold pressor, or public speaking tasks. Given that each of these has their own unique pattern of responses, we can define our challenge by the strain to which we are interested in.

During psychosocial stress, the human body maintains homeostasis by regulating CV, autonomic, endocrine, neurophysiological, metabolic and immunological activity, all of which interact and covary depending on the context. Moreover, both hyperreactivity and hyporeactivity of these systems may lead to the development of several CV disease states. The present studies have focused on responses of the CV system and HPAA to psychosocial stress.

In order to achieve the highest ecological validity when studying stress in the laboratory environment, it is common to use different types of psychosocial stress tasks. Psychosocial stress tests, especially public speaking tasks, give a reliable and robust responses and activate both CV system and HPAA (Burleson et al., 2003; Dickerson & Kemeny, 2004). Furthermore, under psychosocial stress, BP is mainly driven by increased vascular resistance but also increased cardiac output. Higher cardiac output
during psychosocial stress is less evident in children (Jones et al., 2008), but in older individuals it is suggested to result from increased myocardial contractility (Uchino, Uno, Holt-Lunstad, & Flinders, 1999). Furthermore, evaluative observation results in increased beta-adrenergic activity (Kelsey et al., 2000), increased cortisol production (Dickerson & Kemeny, 2004) and robust vascular and myocardial responses (Christian & Stoney, 2006; Schommer, Hellhammer, & Kirschbaum, 2003). A meta-analysis of over 200 stress studies (Dickerson & Kemeny, 2004) suggested that by including social evaluative threat, unpredictability and by using a combination of speech tasks and cognitive tasks with a presence of evaluative observation, the most robust HPAA stress response is achieved. Therefore, the present studies applied Trier Social Stress Test (TSST), which is designed as a combination of each of these factors and offers a comprehensive activation of various physiological stress systems.

1.6.2 Physiological hypo- or hyperreactivity of CV system and HPAA to stress

Although the responses of both the CV and HPAA axes react to and are important during stressful situations, both the hypo- and hyperreactivity of these systems have major health outcomes, especially when they are considered chronic. Heightened BP reactivity to stress predicts the future resting level of BP (Carroll, Ring, Hunt, Ford, & Macintyre, 2003), and it has been linked with adult hypertension (K. A. Matthews et al., 2004), increased left ventricular mass (Treiber et al., 2003) carotid atherosclerosis (Jennings et al., 2004) and all-cause mortality (Strandberg & Salomaa, 2000). Then again, chronic hypersecretion of cortisol is linked with central obesity, systemic arterial hypertension and impaired glucose tolerance (Arnaldi et al., 2003) and hypoactive HPAA has been associated with fibromyalgia (Wingenfeld et al., 2008) and chronic fatigue syndrome (Roberts, Wessely, Chalder, Papadopoulos, & Cleare, 2004). It has been suggested that this hypoactivity is a bodily defence mechanism after a long period of hyperactivity (Fries, Hesse, Hellhammer, & Hellhammer, 2005).
1.6.3 Physiological recovery from stress

In addition to the magnitude of the rise during stress, prolonged elevation of CV activity after the end of the stressor has also been found to be an independent predictor of future BP level (Steptoe & Marmot, 2005), and the onset of hypertension (Singh, Petrides, Gold, Chrousos, & Deuster, 1999). In addition, prenatally malnourished (6% casein diet) rats have elevations in BP that persist for 15 minutes after an olfactory stressor had ended.(Tonkiss, Trzcinska, Galler, Ruiz-Opazo, & Herrera, 1998) Although mounting human evidence suggests that reduced growth during prenatal life is associated with the biology of stress response in adulthood, we do not know whether this phenomenon is reflected by a slow post-stress recovery of BP.

1.7 Effects of sex and age

Several studies that have investigated the programming of CV stress system have reported sex-specific results. Two studies found that low birth weight was associated with increased BP stress reactivity only in women (Jones et al., 2007; Ward et al., 2004) and one study found opposite associations between the sexes (Painter et al., 2006). The reasons behind the sex-specificity have remained unclear. Then again, the programming of HPAA activity has not had support for sex-specificity (Reynolds et al., 2005). However, there are only few human studies investigating the programming of HPAA reactivity and responses to stress. One study found an inverse association between birth weight and salivary cortisol response to stress only in 7-9 year old boys, but not in girls (Jones et al., 2008) and one study found no associations in either men or women (de Rooij et al., 2006). In the latter study, however, the HPAA stress response was mild.

Both sex and age have several effects on both CV and HPAA dynamics during acute stress. Increasing age is accompanied by increased BP responses to stress especially in women (Kajantie & Phillips, 2006), and parasympathetic withdrawal (Uchino, Holt-Lunstad, Bloor, & Campo, 2005) as well as increases in plasma norepinephrine spillover (Esler et al., 1995) in both women and men. Elderly individuals also have reduced sympathetic influence on BP possibly due to reduction in vasomotor sympathetic responsiveness (Barnett et al., 1999). There are sex differences also in several mechanisms that underlie BP regulation and HPAA activity.
HPAA responses to psychosocial stress after puberty and before menopause are lower in women compared to men (Kajantie & Phillips, 2006) and it has been hypothesized that the sex differences to stress responses might be due to the evolutionary effect protecting the fetus from maternal stress responses (Kajantie & Phillips, 2006). Therefore, it is important to conduct several of the analyses in different age groups and separately for both sex, especially in studies of CV programming.

1.8 Animal studies in DOHaD

Underlying causal pathways in the field of DOHaD have mainly been referred from animal studies due to the possibility of manipulating various variables. Experiments with rats, which had prenatal malnutrition by 6% casein diet during pregnancy, were found to have a higher diastolic BP response to olfactory stress (Tonkiss et al., 1998), reduced beta1-adrenergic receptor expression in the heart (Fernandez-Twinn, Ekizoglu, Wayman, Petry, & Ozanne, 2006) and increased predisposition to cardiac arrhythmias (Hu et al., 2000) in later life. In addition, low birth weight in female rats is associated with high plasma epinephrine level activity at the age of 3-4 months (Jansson & Lambert, 1999) and restrictions in both prenatal and postnatal growth result in increased BP and reduced nephron number in male rat offspring (Wlodek, Westcott, Siebel, Owens, & Moritz, 2008). One study also showed that rats with intra-uterine growth restriction do not have higher BP reactions to sound stress than control rats, but they do have a higher overall BP level (Schreuder, Fodor, van Wijk, & Delemarre-van de Waal, 2006).

Then again, prenatal stress may lead to impaired prenatal growth and the subsequent exposure to excess glucocorticoids during critical windows of neuroendocrine development have several long-term health effects (Glover, O'Connor, & O'Donnell, 2010; S. G. Matthews, 2002). Administration of exogenous corticosteroids to pregnant rats decreases the birth weight and raises the BP of their offspring in later life (Benediktsson, Lindsay, Noble, Seckl, & Edwards, 1993). Prenatal stress near term is associated with elevated plasma cortisol responses to acute stress (30 minute exposure to strobe light) (Kapoor, Dunn, Kostaki, Andrews, & Matthews, 2006). There is also good evidence that prenatal glucocorticoid exposure alters not only the development of
the HPAA but also sympathetic innervations (Bian, Seidler, & Slotkin, 1993), cardiac noradrenergic and sympathetic processes (Seckl & Meaney, 2004), and induces long-term effects for ACTH, corticosteroid-binding globulin, BP and BP variability (Igosheva, Klimova, Anishchenko, & Glover, 2004; McCormick, Smythe, Sharma, & Meaney, 1995; Weinstock, Poltyrev, Schorer-Apelbaum, Men, & McCarty, 1998). Therefore, prenatal stress may underlie prenatal growth restrictions and lead to altered cardiac and HPAA activity in later life.

In sum, animal models offer insight and suggest hypotheses for human programming of physiological activity during stress and also to its underlying mechanisms. We decided to investigate whether pre- and postnatal growth is associated with CV and HPAA activity before, during and after stress in childhood and late adulthood in both men and women.
2 AIMS OF THE STUDY

1. To study whether prenatal growth and length of gestation are associated with CV reactivity to and recovery from psychosocial stress in childhood and in late adulthood (Studies I & IV)

2. To examine whether prenatal growth and length of gestation are associated with HPAA reactivity to psychosocial stress in late adulthood (Study II)

3. To study whether childhood growth is associated with CV reactivity to psychosocial stress in late adulthood (Study III)
3 METHODS

3.1 Study populations

Participants in the present studies came from two cohorts. Figure 3 depicts a flowchart for both cohorts. The participants in Studies I, II and III came from the Helsinki Birth Cohort Study, which consists of men (n=4630) and women (n=4130) who were born at Helsinki University Central Hospital during 1934–1944, attended child welfare clinics in the city of Helsinki, and were still resident in Finland in 1971, when personal identification numbers were allocated to all residents of the country. During the years 2001–2004, at the average age of 61.5 years (SD = 2.9, range = 56.7–69.8), a subset of 2003 women (n=1075) and men (n=928) participated in a clinical examination. They were selected from the initial study population using random number tables as described elsewhere (Barker et al., 2005). From those who had attended the clinical examination and who had appropriate early life data including length of gestation and measurement of body size at birth available, 287 women and men participated in an experimental stress protocol between 2004 and 2005. CV measurements were obtained from 153 persons. Because of our focus on the life span consequences of slow intrauterine growth, we overrepresented by 33% participants whose birth weight adjusted for gestational age was below the 10th percentile of the entire birth cohort. The subjects were invited in random order.

Data on the newborn’s date of birth, weight (g), length (cm), head circumference (cm), and the date of the mother’s last menstrual period, as well as childhood social class (lower, 79.1%, lower middle, 16.3%, upper 4.6%) based on the father’s occupation, were extracted from birth records. Ponderal index (PI) was calculated as \( \frac{\text{birthweight}}{\text{birthlength}^3} \).

Participants in study IV came from the GLAKU cohort. They were recruited from a secondary birth hospital used by residents of a specific geographical area, with the exception of deliveries requiring tertiary level care. This cohort comprised initially 1049 mothers and their infants born between March and November 1998 in Helsinki, Finland. In 2006, children and their parents were invited to participate in a follow-up with a focus on individual differences in psychophysiological development. 912 (86.9%)
mothers of the initial cohort agreed to be included in the follow-up and 890 (84.8% of the initial cohort) were traced. Because one of the original study objectives, which was however not focused on in this thesis, was to examine developmental consequences of maternal licorice consumption during pregnancy, the sample was weighed according to the mother’s licorice intake during pregnancy (Raikkonen et al., 2010; Strandberg, Jarvenpaa, Vanhanen, & McKeigue, 2001), as follows.

We invited all 88 children belonging to the group whose mothers consumed high levels of licorice during pregnancy and 64 participated. The other invited children had to live within a 35-mile radius of Helsinki to manage costs relating to participant and researcher travel and accommodation. We invited 271 children whose mothers had consumed zero or low amounts of licorice and 54 children whose mothers consumed moderate levels of licorice. 211 and 46 participated, respectively. Of the 321 children who agreed to participate in the follow-up, 299 participated in the stress study (72.4%).

We obtained weight (kg) and length (cm) at birth, date of birth and gestational age confirmed by ultrasound before 20 weeks of gestation, from birth records. The ponderal index was determined as the ratio of weight (kg) to the cube of length at birth (cm³). To better describe intrauterine growth, birth weight and birth length were transformed into z-scores (birth weight and birth length SD scores) for gestational age and sex based on Finnish standards (Pihkala, Hakala, Voutilainen, & Raivio, 1989). The socioeconomic status of the family was classified according to the self-reported occupation of the mothers in 2006 (lower, 8%; middle, 32.4%; upper, 59.5%).
3.2 Protocols

3.2.1 Trier Social Stress Test for Adults

In the first three studies we used TSST as a stress test. The training for TSST was done under the supervision of Professor Hellhammer in the Department of Psychobiology at the University of Trier, where the protocol has been developed.

At the start of the TSST, the subject was asked to convince in five minutes a committee of two persons (Figure 4. - one man and one woman, who are dressed in white medical jackets) that he/she is the best candidate for a self-selected confidential post. To maximize ego involvement, the subject was specifically asked to focus on his/her personal abilities and not on any objectively measurable quantities such as work experience. The assistant showed the subject a video camera and tape recorder and told
the subjects that their performance is to be videotaped and recorded for further expert analysis of their behaviour and success in the task. The subject was told to prepare the speech for 3 min. The subject stood in front of the seated committee who were instructed to minimize all verbal and non-verbal communication during the preparation period and the speech task. A mental arithmetic task followed immediately after the speech task. The subject remained standing and was asked to perform serial subtractions, starting from 509 and subtracting seven. The subtractions were asked to be performed as quickly as possible. If a mistake occurred, the committee notified the subject by saying ‘error’ and asked him/her to start again from 509. Although the arithmetic task and speech task both lasted for 5 min, the durations of the tasks were not revealed to the subject in advance. After the completion of both tasks, all monitoring devices were removed and the subject was led to another room for the recovery period. As TSST is a very powerful stressor, all the subjects underwent a brief debriefing session after the task with a trained psychology student, who was also a committee member.

![Figure 4. Trier Social Stress Test for Adults. The committee.](image)

Before the experiment, the subject filled in all the questionnaires, rested for a total of 45 min and was led to the laboratory. The subject remained standing throughout the baseline and the experimental stress protocol and the time in between them.
The study protocol was approved by the Ethical Committee of Epidemiology and Public Health Research at the Helsinki University Central Hospital. Written informed consent was obtained from each participant.

### 3.2.3 Trier Social Stress Test for Children

In the last study we applied Trier Social Stress for Children (TSST-C). Training was carried out by Dr Alex Jones from Southampton University, who had developed the protocol to suit the purposes of CV measurement (Buske-Kirschbaum et al., 1997; Jones et al., 2008). Prior to the stress experiment, the subject completed a five-minute baseline recording in a standing position watching a relaxing movie next to a parent. The child was brought to another room without his/her parent and was introduced to a committee of two ‘judges’ (Figure 5). A selection of toys was presented and the child was asked to pick up the favourite and second favourite toy, and the favourite toy was to be a reward if the tasks were performed extremely well (at the end each child received this toy). These toys were placed and visible on a table between the child and the committee. The beginning of a story was played, and the child was asked to complete it in front of the committee and a tape recorder. The child was taken back to the baseline room, where the story was prepared with support and encouragement from a research nurse. Following this, the child was again taken in front of the committee to present the five-minute story, which was followed by a five-minute mental arithmetic task. After completion of the task, the child was given his/her favourite toy for an excellent performance, and was led to another peaceful room to continue watching the comforting movie started during baseline. After 13 minutes of watching the film, the child was asked to stand up. During a total of 12 minutes of standing, the last 5 minutes was determined as the post-stress recovery period.

The Ethical Committee of the City of Helsinki Health Department and the Ethical Committee of Children’s and Adolescents’ Diseases and Psychiatry at Helsinki and the Uusimaa Hospital District had approved the protocol.
3.3 Physiological measures

In Studies I and III, a continuous beat-to-beat monitoring of BP and HR during the baseline and the task was conducted by Finometer (FMS, Amsterdam, The Netherlands), non-invasive finger photoplethysmograph. On average, systolic BP (SBP) and diastolic BP (DBP) measured by Finometer differ 2 mmHg from those measured by a mercury sphygmomanometer, whereas the Association for the Advancement of Medical Instrumentation criteria for the reliability of BP measurements require a bias of 5 mmHg and a variability of 8 mmHg against a mercury sphygmomanometer (Schutte, Huisman, van Rooyen, Malan, & Schutte, 2004). Finometer also estimates systemic haemodynamic function by the Modelflow method (Sugawara et al., 2003), which computes an aortic flow waveform by simulating a non-linear three-element model of the aortic input impedance. This provides an estimate of left ventricular stroke volume, cardiac output (CO; calculated as stroke volume * instantaneous HR and expressed as l/min) and total peripheral resistance (TPR; calculated as (mean arterial pressure/ CO) * 80 and expressed as dynes s cm⁻⁵). Rather than absolute values, in particular, relative changes in BP and stroke volume levels within an individual over time are most reliably measured by the Finometer device (Schutte, Huisman, Van Rooyen, Oosthuizen, & Jerling, 2003).
In Study II, we measured the activity of HPAA. Salivary cortisol concentrations were determined using a competitive solid-phase, time-resolved fluorescence immunoassay with fluorometric end point detection (DELFIA; Wallac, Turku, Finland). Plasma cortisol concentrations were determined by ELISA (ImmunoBiological Laboratories, Hamburg, Germany) and ACTH by chemiluminescence immunofluorometric assay (Nichols Institute Diagnostics, San Clemente, CA).

In Study IV, BP was monitored using Vasotrac APM205A (MedWave Inc, St. Paul, MN, USA) tonometer. Vasotrac performs well within Association of the Advancement of Medical Instrumentation (AAMI) criteria, when validated against intra-arterial measurement in a pediatric sample (Cua et al., 2005), and it allows semi-continuous (every 12-15 heartbeats) BP measurements by applying pressure to the radial artery of the non-dominant hand. CO, PEP and HR were measured with impedance cardiography (NICO100C; Santa Barbara, CA) and ECG (ECG100C; Santa Barbara, CA) using methodological guidelines by Sherwood et al. (Sherwood et al., 1990). All PEP values were corrected for respective heart rate value. High-frequency heart rate variability (HF HRV) was determined according to current guidelines (Berntson et al., 1994). Total peripheral resistance (TPR) was calculated as (mean arterial pressure/CO) * 80 and expressed as dyne * s * cm⁻⁵. With this pattern of autonomic parameters we were able to investigate underlying vascular (TPR) and cardiac (CO) mechanisms for BP, and also autonomic activity (PEP&HF HRV), which relate to both BP and HR.

All signals were subsequently fed with electrode leads into a Biopac MP150 system (Santa Barbara, CA) using a general purpose amplifier module (DA100). Signals were digitally sampled at 1000 Hz, and calibrated according to the manufacturer’s instructions. Data recording was performed with Biopac AcqKnowledge 3.8.1 software (Santa Barbara, CA) and data reduction with WinCPRS® 1.160 software (Absolute Aliens, Turku, Finland).

3.4 Statistical analyses

Because mental stress measures for CV activity are more reproducible when responses to individual tasks are aggregated (Kamarck & Lovallo, 2003), we averaged all CV readings in studies I and III from 5-minute baseline, 10-minute task (speech and arithmetic) and 5-minute post-stress period. Besides these activity levels, we calculated
increments from the averaged baseline value to task and in Study IV to the post-stress period to obtain reactivity to and recovery from stress for BP, HR, PEP and HRV HF values. These values were then used as dependent variables to be predicted by prenatal indices such as size at birth and gestational age.

In Study II, cortisol and ACTH concentrations were log transformed to attain normality. We first analysed the responses of these hormones to the TSST by a linear mixed model with unstructured covariance structure. This was done to include all HPAA measures and not to lose information. Quadratic relationships were assessed by including a squared variable in the model and reactivity by including an interaction term with sampling time. In further analyses we used linear regression to demonstrate effect sizes of statistically significant associations with commonly used indicators of HPAA function during stress testing: baseline and post-stress peak concentrations, their relative increments (ratio of peak to baseline value), and time-weighted areas under the curve (AUC, calculated by the trapezoidal rule) as dependent variables. All analyses were adjusted for variables known to be associated with HPAA reactivity: sex, current age and BMI, time of day (dummy coded), and, except for analyses of sex differences, the use of oral estrogen therapy.

In Study III, we used multiple linear regression analyses to test whether body size at birth, and 2, 7, and 11 years, and growth (gain in height and BMI) between these ages predicted CV reactivity to psychological stress in late adulthood. The growth variables we used were residuals from linear regression models of standardized body size during each timepoint versus the corresponding body size during the previous timepoint. The resulting scores are referred to as “conditional growth” (Osmond et al., 2007), which avoids the statistical artifact of regression to the mean and problems with high correlations between successive measurements. We also constructed conditional growth scores within the larger sample (n=2003), and tested whether the scores of our sample (n=144) differ from the whole cohort, but no differences were found (all P-values > 0.2).

All statistical analyses were performed using SPSS 12.0 (SPSS Inc., Chicago, Illinois).
4 RESULTS

4.1 CV and HPAA responses to stress (Studies I – IV)

TSST induced robust CV responses to psychosocial stress. In both children and in adults, CV responses were mainly vascular, but in children there was also a clear cardiac sympathetic drive (measured with PEP) without an indication of significant stress-related changes in PNS (measured with HF HRV). In children, the average responses to TSST-C were 14.9 mmHg for SBP, 10 mmHg for DBP, 3.2 ms for PEP and 8.4 beats/second for HR. In adults, the average stress responses to TSST were 41.0 mmHg for SBP, 21.9 mmHg for DBP and 16.1 beats / min for HR.

In adults, there was also a robust response of saliva cortisol, serum cortisol and ACTH to psychosocial stress, which was indicated by significant main effects of time in mixed model analysis (all P-values < 0.0001). The average HPAA increment (the ratio of peak to baseline value) was 2.09 for salivary cortisol, 1.75 for plasma cortisol and 2.32 for plasma ACTH.

4.2 Markers of prenatal environment and CV stress reactivity in late adulthood (Study I)

The most robust early determinant of BP reactivity in adults was gestational age; however, with opposite relationships between the sexes (P for interaction ≤ 0.001). A one-week decrease in gestational age was associated with a 3.1 mmHg (95% CI, 0.4 to 5.9) and 1.2 mmHg (95% CI, -0.1 to 2.5) increase in systolic and diastolic BP reactivity in women, but with a 4.9 mmHg (95% CI, 1.9 to 8.0) and 2.3 mmHg (95% CI, 0.8 to 3.7) decrease in systolic and diastolic BP reactivity in men. The relationships were linear and graded as depicted in Figure 6. The interaction term “gestational age x sex” was statistically significant in the analyses of BP reactivity.

In women, smaller size at birth, including measures of length at birth, head circumference and PI failed to predict either BP or HR reactivity (all P-values>0.1, data not shown). In men, lower birth weight was significantly related to lower DBP reactivity (B=3.3; 95% CI, 0.1 to 6.6; P=0.04). However, this relationship disappeared after adjustment for gestational age (B=1.3; 95% CI, -2.0 to 4.7; P=0.4). No other
measure of size at birth was a significant predictor of CV reactivity in men.

![Figure 6](image)

**Figure 6.** Association between unadjusted systolic BP and diastolic BP reactivity in response to experimentally induced psychological stress and gestational age at birth in both men and women at age 60 to 70 years.

### 4.3 Markers of prenatal environment and HPAA stress reactivity in late adulthood (Study II)

It was then analysed whether the relationships between body size or gestational age at birth and the levels of cortisol and ACTH are different in men and women. Mixed-
model analyses showed no statistically significant interactions between the effects of sex and any of these variables on levels of cortisol or ACTH (P values for interactions > 0.2). The only statistically significant interaction on plasma cortisol responsiveness was found between the effects of sex and birth weight (P = 0.01) and sex and length at birth (P = 0.01). However, separate analyses in both sexes showed no statistically significant relationships between these measurements and plasma cortisol responsiveness (P values > 0.1).

Stress-related HPAA activity in adults was associated with birth weight. A linear relationship between low birth weight and low plasma ACTH emerged but there was no linear relationship with cortisol. There were, however, quadratic relationships between birth weight and salivary (P = 0.001) and plasma cortisol (P = 0.005) but not with plasma ACTH (P = 0.1). The lowest peak salivary cortisol concentrations were seen in the lowest third of birth weights (adjusted for gestational age and sex): 12.9 nmol/litre (95% confidence interval of mean 11.2–15.0), compared with 17.1 nmol/litre (14.8 – 19.8) in the middle and 14.1 nmol/litre (12.6 –15.7) in the highest third of birth weights. Corresponding figures for plasma cortisol were 418 nmol/litre (380–459), 498 nmol/litre (455–545), and 454 nmol/litre (428–482), and for plasma ACTH 8.17 pmol/litre (6.98 –9.57), 12.42 pmol/litre (10.64 –14.51), and 11.50 pmol/litre (10.06 – 13.14), respectively. Results for areas under the curve were similar and no non-linear relationships were found for gestational age or ponderal index.

These relationships are illustrated in Figure 7, which show salivary and plasma cortisol and plasma ACTH concentrations before and after the TSST according to thirds of birth weight adjusted for sex and gestational age (less than 3124 g; 3125–3496 g; more than 3497 g).
Figure 7. Salivary and plasma cortisol and plasma ACTH concentrations in groups according to thirds of birth weight adjusted for sex and gestational age. The concentrations are presented in geometric means, adjusted for sex, age, time of day, BMI, and the use of oral estrogen treatment. The bars represent 95% CIs.

Plasma ACTH concentrations were associated with birth weight (approaching statistical significance; 1 kg higher birth weight corresponded to 12.1% higher ACTH; 95% CI -1.5 to 27.5; P = 0.08) and length at birth (for each cm, 4.5% higher plasma ACTH; 95% CI 1.2– 8.0%; P = 0.008). These relationships were further illustrated by linear regression showing that a 1 kg higher birth weight was associated with 24.9% (95% CI 4.2–49.8%) higher peak ACTH and with 19.2% higher (95% CI 2.1–39.2%) ACTH AUC and that longer length at birth was also associated with higher baseline (P = 0.02) and peak (P = 0.002) ACTH and ACTH AUC (P = 0.002). No associations were seen with ponderal index (mixed model P > 0.7) or gestational age (P > 0.6) at birth, and birth data were not related to ACTH stress response (P > 0.2).

4.4 Markers of childhood growth and CV stress reactivity in late adulthood (Study III)

Before investigating the relationships to childhood growth, we investigated relationships to absolute measures of height and BMI. Height at 2, 7 or 11 years or in adulthood did not predict BP or HR reactivity in late adulthood (all P-values > 0.1). Figure 8 shows the relationship between BMI at different ages in childhood and adult BP reactivity. This association became stronger with increasing age, reaching statistical significance with SBP reactivity at approximately 9 years.
Figure 8. Standardized regression coefficients (solid lines) and 95% confidence limits (dashed lines) for both systolic and diastolic BP reactivity adjusted with current age and sex, according to annual body mass index (BMI) from birth to 11 years and at the time of the Trier Social Stress Test. Ages from 3 to 5 are not included, due to infrequent measurements within the children during this period. Standardized regression coefficients (y-axis) are interpreted as the standard deviation (SD) change of BP reactivity for one SD change in BMI at each age.

We then found that several of the actual childhood growth scores were related to BP reactivity to psychosocial stress in late adulthood. In both women and men, gain in body mass index (BMI; kg/m²) between 7-11 years was related to BP reactivity to TSST. For each 1-SD more rapid gain in BMI from 7 to 11 years, SBP reactivity increased by 3.8 mmHg and DBP reactivity by 1.4 mmHg.

By contrast, effects of height gain were dissimilar between sexes (Figure 9). In men, one SDS increase in conditional infant (0-2 years) height gain was associated with a 2.4 mmHg (95% CI, 0.3 to 4.4; P = 0.02) increase, but in women with a 2.9 mmHg (95% CI, 0.4 to 5.3, P = 0.02) decrease in DBP reactivity. In addition, slower height gain during 2-7 years was associated with higher SBP reactivity only in men, so that one SDS increase in height gain during 2-7 years in men was associated with a decrease of 6.9 mmHg (95% CI, 1.2 to 12.7; P = 0.02) in SBP reactivity. Adjusting for adult body size, body size at birth, or childhood socio-economic status did not change the results.
We first investigated associations to baseline CV scores. Among girls, a one SD lower birth length SD score was related to 2.7 mmHg (95% CI, 0.7 to 4.6; P=0.008) lower baseline SBP and 2.2 mmHg (95% CI, 0.7 to 3.6; P=0.004) lower baseline DBP, whereas there was no association between ponderal index and baseline BP (P-values>0.7). Among boys, no significant associations between birth length SD score and baseline SBP/DBP were found (both P-values>0.4), while a one kg/ cm³ lower ponderal index was associated with a 1.0 mmHg higher (95% CI, 0.0 to 1.9; P=0.05) baseline SBP. P-values for interaction ‘birth length SD*sex’ was 0.04 for baseline SBP, 0.03 for baseline DBP, and for interaction ‘ponderal index*sex’ it was 0.2 for baseline SBP.

Next, we examined associations to BP reactivity. Among girls, a one SD lower length at birth was related to increases of 1.7 mmHg (95% CI, 0.1 to 3.3; P=0.04) and 1.0 mmHg (95% CI, -0.1 to 2.2; P=0.06) in SBP and DBP reactivity, respectively, while
ponderal index at birth was not associated with BP reactivity (P-values>0.5). Among girls, a one SD lower length at birth was related to increases of 1.7 mmHg (95% CI, 0.1 to 3.3; P=0.04) and 1.0 mmHg (95% CI, -0.1 to 2.2; P=0.06) in SBP and DBP reactivity, respectively, while ponderal index at birth was not associated with BP reactivity (P-values>0.5). Among boys, no significant associations between birth length SD score and SBP/DBP reactivity were found (P-values>0.8), whereas a one kg/cm³ lower reading in the ponderal index was associated with a 1.1 mmHg lower SBP reactivity (95% CI, 0.4 to 1.8; P=0.002) and 0.7 mmHg lower DBP reactivity (95% CI 0.2 to 1.1; P=0.008) reactivity, respectively. Relationships between BP reactivity and birth weight SD score were linear and graded as depicted in Figure 10.
Figure 10. Relationships of birth weight SD score to systolic and diastolic BP reactivity to psychosocial stress in both girls and boys aged 8. BP responses are adjusted with age, current height/BMI, maternal tobacco/alcohol/liquorice use and socioeconomic status.

After this, we examined associations with BP recovery scores. Among girls, a one SD lower length at birth SD score was related to a 1.3 mmHg (95% CI, 0.3 to 2.4; P=0.01) lower DBP recovery score, while ponderal index in girls had no significant effects (P-values>0.6 for SBP/DBP recovery). Again, among boys there were no effects for length at birth (P-values>0.1), whereas a one kg/cm³ lower ponderal index was associated with a 0.8 mmHg (95% CI, 0.2 to 1.4; P=0.01) and 0.5 mmHg (95% CI, 0.0 to 0.9; P=0.05) lower SBP and DBP recovery score, respectively. (P-values for interactions ‘birth length SD*sex’ and ‘ponderal index*sex’<0.05).

Birth weight SD score was associated with none of the CO values among either girls or boys. Neither was it associated with TPR among girls, while among boys, a one SD lower birth weight was related to an 87.7 dynes/sec/cm⁵ (95% CI, 3.2 to 172.2; P=0.04) higher baseline TPR and 4.1 % (95% CI, 0 to 8.1; P=0.03) lower TPR reactivity to stress (P-value for interaction ‘birth weight SD*sex’=0.06 for both baseline TPR and TPR reactivity). The baseline TPR result in boys became statistically significant only after controlling for current height or BMI, while the association with TPR reactivity was not affected by current body size. The result on reactivity remained similar also when further controlling for the baseline TPR value. Among boys, a one kg/cm³ lower ponderal index was associated with 2.0 % (95% CI, 0.0 to 3.9; P=0.03) lower TPR reactivity (P>0.9 in girls) (P-value for interaction ’ponderal index*sex’=0.003).
5 DISCUSSION

The present study investigated in children and in adults whether physiological stress reactivity is associated with markers of growth of prenatal or postnatal period until 11 years of age. The main results confirmed several of our hypotheses. We found that size at birth was associated with late adulthood HPAA activity during psychosocial stress, and gain in BMI during years 7-11 was associated with CV stress responses in late adulthood. We also found that size at birth in children and gestational age and early postnatal (0-2 years and 2-7 years) gains in height in adults were associated with CV stress responses. These results were, however, sex-specific. Given that heightened CV stress responses and increased HPAA activity are markers of CV disease vulnerability, our results may partly explain the associations between early growth and later CV disease.

The value of this thesis is dependent upon several aspects. First, we applied a wide variety of different physiological markers to describe cardiac, vascular and endocrine reactions to stress. Second, our stress test is well validated and offers the most robust and reliable CV and HPAA responses. Third, we applied TSST to both children and late middle aged adults, age groups which are rarely used in this field. Fourth, we were able to link not only prenatal but also postnatal markers of growth to CV stress responses in late adulthood. These aspects enable a more comprehensive perspective on the health effects of the early environment.

Previous studies in this field have nevertheless shown some discrepant results and our studies are no exceptions. Sex- and age -specificity of the associations between early growth and later physiological stress reactivity still remain largely unexplained and warrant further investigation into underlying mechanisms. In addition, birth weight and gestational age are only proxies to prenatal environment and we are unaware what are the exact factors and critical windows in the course of fetal development that may have long-lasting effects on human health late into adulthood.
5.1 Markers of prenatal growth and CV reactivity to stress in childhood and in late adulthood

Similar to others (Jones et al., 2008; Ward et al., 2004), we found profound sex differences in prenatal and early postnatal programming of CV responses to stress in childhood and in adulthood. It is well documented that there are great sex differences in BP dynamics and its control mechanisms (Convertino, 1998; K. A. Matthews, Woodall, & Stoney, 1990; Shoemaker, Hogeman, Khan, Kimmerly, & Sinoway, 2001). Interestingly, animal studies have shown that estrogen and testosterone have opposing effects on postnatal BP only when there has been nutritional deprivation during the fetal period (Ojeda et al., 2007; Ojeda, Grigore, Robertson, & Alexander, 2007). Due to these sex differences in studies of prenatal CV programming, we will discuss the results of Studies I and IV separately in men and women.

5.1.1 Females

We found in 7-9 year old girls who were born light or short that BP was low during the baseline prior stress test but showed a strong increase and stayed high during recovery period 20 minutes after the stress had ended. Previous studies in adult women concur with these findings of small size at birth and heightened BP reactivity to stress (Painter et al., 2006; Ward et al., 2004). In addition, low birth weight girls in our study were under high cardiac sympathetic activity at the time of stress, which is consistent with the rapid rise of BP.

In women aged 60-70, it was not low birth weight but low gestational age that was associated with higher BP and HR reactivity to psychosocial stress. It may be that the effects of birth weight are age-dependent; a study in younger individuals born full-term and a study in younger individuals born with a very low-birth weight did not find the association with gestational age (Pyhala et al., 2009; Ward et al., 2004). It has been demonstrated that BP dynamics are altered with increasing age (Barnett et al., 1999; Reckelhoff, 2001; Uchino et al., 1999) and it might be that the early life events for which gestational age serves as a marker, appear later in adulthood. Our findings may therefore indicate an alternative pathway from low gestational age to CV disease through heightened CV activity. This is plausible given that both low gestational age
and heightened CV activity are associated with adverse CV health outcomes later in life. In addition, gestational age might be linked with maternal plasma CRH levels (McLean et al., 1995), which moderate the sympathetic innervation and cardiac noradrenergic and sympathetic processes with effects lasting until adulthood.

Generally, our results in females add to previous literature that women with a low birth weight or short length at birth might develop high BP and CV diseases due to heightened BP reactivity to stress and heightened cardiac sympathetic activity and due to the inability of BP to quickly stabilize back to baseline after stress has ended. Then again, if born early, there may be a risk of heightened CV activity and on account of that a risk of CV disease later in adulthood (Koupil, Leon, & Lithell et al., 2005; Osmond et al., 2007).

5.1.2 Males

In contrast to girls, low birth weight boys aged 7-9 had a high baseline BP prior stress test and generally low cardiac sympathetic activity, but only after adjusting with current body size. It was shown that the highest baseline BP was seen in boys who had a low birth weight but rapidly put on weight during childhood. Similar to our findings, Mirzeai et al. (Mirzaei, Taylor, Morrell, & Leeder, 2007) noticed that in boys, but not in girls, the negative association between birth weight and BP is significant only after adjusting with current body size. Independent of current size, we found that boys had a low TPR reactivity to stress and a rapid recovery of both BP and cardiac sympathetic activity 20 minutes after stress had ended. This may protect the individual from developing CV disease.

There were no significant associations between size at birth and PNS activity, reactivity or recovery in boys. However, speech tasks involve irregular breathing patterns, which may complicate the interpretation of HRV indices (Beda, Jandre, Phillips, Giannella-Neto, & Simpson, 2007). Breathing should therefore be controlled in future investigations.

We found that low birth weight boys exhibiting higher baseline BP together with lower BP stress reactivity might be the results of their generally low cardiac sympathetic activity we found. Jones et al. (Jones et al., 2008) also witnessed a negative association between birth weight and baseline CV activity in 7-9 year old boys when
current BMI was adjusted. It may be that cardiac sympathetic activity works as a buffer for changes in BP.

In contrast to our results with 7-9 year old boys, we found in men aged 60-70 that it was again not size at birth but gestational age which was positively associated with CV reactivity to stress. There is no ready explanation for this, but similar to the results for women, it may be that the early life events for which gestational age serves as a marker appear later in adulthood and that the phenomenon is highly age-dependent. While an inverse association between gestational age and resting BP in men has been described in young military conscripts (Johansson et al., 2005; Leon et al., 2000) the sparse data available about middle-aged men have shown discrepant results (Martyn et al., 1995; Mi et al., 2000; Siewert-Delle & Ljungman, 1998).

These results add to the complex nature of prenatal programming of CV stress activity in males. However, the strong sex differences regarding peripheral resistance in the older study sample in Study I might also be explained by hormonal interference. Testosterone is suggested to upregulate neuropeptide Y (Zukowska-Grojec, 1995), which is a potent vasoconstrictor, and testosterone has been shown to enhance the contractile effects of endothelin-1 in porcine coronary artery rings, an effect which is attenuated by estrogen (Teoh, Quan, Leung, & Man, 2000). However, the differences in sex hormones are probably somewhat small and the peripheral interference of these hormones are unlikely to fully explain the sex differences. Such an effect would, however, be of significant potential clinical relevance as it is suggested that especially among hypertensive patients the BP responses to stress are driven peripherally rather than centrally (Dimsdale, Ziegler, Mills, Delehanty, & Berry, 1990), and among the elderly hypertension is characterized by increased vascular resistance and reduced cardiac output (Sowers & Lester, 2000). This underlying cause to sex-specific programming remains however speculative.

5.2 Markers of prenatal growth and late adulthood HPAA reactivity to stress

We found in individuals in their late adulthood that size at birth was associated with HPAA activity during baseline, stress and recovery such that the highest overall cortisol
and ACTH concentrations were seen in individuals whose birth weight was in the middle third and lowest concentrations in individuals with low birth weight.

Although apparently counterintuitive, low birth weight has previously been associated with low HPAA activity in late adulthood. Ward et al. (Ward, Syddall, Wood, Chrousos, & Phillips, 2004) compared bottom and top birth weight quartiles and noticed that there were lower ACTH and cortisol responses to a dexamethasone (synthetic glucocorticoid) test in the low birth weight group. Studies with psychosocial stressors have found a negative association between birth weight and HPAA activity in male twins (Wust et al., 2005) and in 7-9-year-old boys (Jones et al., 2006).

Unlike in our studies of CV activity (studies I, III & IV), we did not find any significant sex effects on our HPAA study. This is similar to what has previously been suggested (Reynolds et al., 2005). Additionally, it was birth weight that predicted HPAA responses and gestational age that predicted CV activity. It has to be noted that although producing a unified stress response, the connections between CV and HPAA are complicated. For example, glucocorticoids inhibit sympathetic nervous system activity (Lenders, Golczynska, & Goldstein, 1995), increase the sensitivity of the myocardium to β-adrenergic stimulation (Szemeredi, Bagdy, Kopin, & Goldstein, 1989) and effect the baroreflex control of heart rate (Scheuer & Bechtold, 2002), but in certain situations glucocorticoids activate SNS and decrease beta-adrenergic stimulation (Seckl & Meaney, 2004). Therefore, it might be that programming of both CV and HPAA stress responses have their own separate and unique pathways.

### 5.3 Markers of childhood growth and late adulthood CV reactivity to stress

In Study III, we found that childhood growth trajectory predicts BP and HR reactivity to psychological stress in late adulthood. A rapid gain in BMI between 7 and 11 years of age predicted heightened BP reactivity, which is in line with previous findings concerning disease outcomes. It has also shown that growth during infancy has a modest association (Law et al., 2002), whereas increase in BMI later in childhood has a stronger association with the resting level of BP later in adulthood (Cole, 2004; Falkner,
Epidemiological studies in the Helsinki Birth Cohort have revealed distinct childhood growth patterns associated with adult diagnosis of CHD (J. G. Eriksson et al., 1999) and type 2 diabetes (J. G. Eriksson et al., 2006), and a strong predictor in both of these studies is rapid gain in BMI before 11 years of age. This was also found for people aged 60-70 with a diagnosis of hypertension (J. G. Eriksson et al., 2007). In this study, the risk of hypertension depended on the rate of growth rather than the body size attained at any particular age. Interestingly, this was true only for people with a more severe hypertension. People with no previous diagnosis of hypertension but who had a systolic blood pressure of \( \geq 140 \) mmHg or a diastolic blood pressure of \( \geq 90 \) mmHg on a visit to clinic during the study had a persisting small body size until 11 years of age. Our results resemble more with the growth profile for people with a more severe hypertension and also reinforce the suggestions that, besides actual size, the rate of growth during childhood may have independent health effects.

While people who gain BMI rapidly in childhood are more likely to be obese in adult life, our results were not explained by BMI in adulthood. Changes in body composition are however one possibility. BMI gain during late childhood reflects increase in body fat content and central adiposity rather than increase in lean body mass (Sachdev et al., 2005; Yliharsila et al., 2007). The latter is associated with increased BP response to stress (Barnes, Treiber, Davis, Kelley, & Strong, 1998; Goldbacher, Matthews, & Salomon, 2005), and obesity is characterized by increased sympathetic activity and overall autonomic imbalance (Riva et al., 2001). However, further studies are needed in order to clarify whether changes in body composition during childhood growth have long-term effects to CV reactivity.

We also found that the effects of early postnatal height gain were dissimilar between the sexes. Evidence from the Whitehall II studies suggest that shorter leg length in adulthood, a proxy for slow growth in height and low socioeconomic status during childhood before puberty, is associated with a gradual rise in BP with age and several other CHD risk factors (Ferrie, Langenberg, Shipley, & Marmot, 2006; Langenberg, Hardy, Breeze, Kuh, & Wadsworth, 2005). Specific evidence for the role of slow growth in height and adult disease came from a Helsinki Birth Cohort Study showing that high BP in people with no previous diagnosis of hypertension is predicted by slow
growth in height during the first years of life (J. G. Eriksson et al., 2007). Our results with slow height gain between birth and 2 years in women and slow height gain between 2 and 7 in men leading to heightened BP reactivity to psychosocial stress in adult age concur with these findings.

5.4 Methodological considerations

A recent study suggested that to achieve the highest laboratory to life generalizability different types of public speaking tasks should be used, the responses of which are then aggregated (Kamarck, Debski, & Manuck, 2000). Although a highly ecologically valid experiment among stress tests, the generalizability of TSST to real life environment is moderate at best. There are numerous ways to measure stress in the laboratory environment, and there is constant debate whether such measurements are ecologically valid. There are multiple mental and physical challenges in our daily lives, and each of them has their own unique spectrum of physiological responses. TSST produces high responses of cortisol, moderately high sympathetic response and a high BP response that is more vascular than cardiac. Other stress tests and real life measurements with ambulatory devices are needed to both confirm and expand these findings. We also measured only parts of HPAA, CV system and ANS activity. It would therefore be interesting to measure more comprehensively both systems, their interactions to one another, or even the responses of other systems to psychosocial stress such as immune and central nervous system.

Additionally, size at birth is only a summary measure of prenatal adaptations. Babies born small may have achieved their genetic growth potential and are in the lower tail of the birth weight distribution, whereas other babies with similar weight at birth may have experienced a prenatal nutritional deficit, which has slowed their growth, and later on experience catch-up growth to gain their genetic growth potential. Therefore, further studies with improved surveillance and markers of prenatal environment are needed. Finally, since prenatal stress may also contribute to our findings, future studies should investigate with sophisticated statistical models what exactly underlies with the associations between prenatal growth and later stress reactivity to psychosocial stress.
5.5 Conclusions

In summary, these studies provide support for the hypothesis that CV reactivity to and recovery from stress may be determined in utero and during the early postnatal period. We suggest that in similar studies both the gender of the subjects and the peripheral and central components should be investigated separately. Second, it may also be that both hyper- and hypocortisolism is programmed during the fetal period. Third, our result highlights the role of gestational age at birth as a potential marker of intrauterine conditions in birth cohort studies.

Overall, these results reinforce previous suggestions that intrauterine programming of BP, sympathetic, and HPAA activity may be important contributors to the link between fetal and early growth and adult CV disease.
6 REFERENCES


56


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