Physical activity, nutrition and stress response in young adults born preterm – determinants of health and disease
The Helsinki Study of Very Low Birth Weight Adults

ACADEMIC DISSERTATION

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To my beloved husband Alek
Abstract

**Background:** Advancements in neonatal care during the past few decades are resulting in increasing numbers of adult survivors after preterm birth at very low birth weight (VLBW, ≤ 1500 g). VLBW is associated with risk factors of non-communicable diseases, including cardiovascular disease, osteoporosis and diabetes. The underlying mechanisms are unknown.

**Aims:** The mechanisms underlying the effects of preterm birth at VLBW on later health in healthy VLBW young adults were investigated, with a focus on 1) physical activity, 2) nutrition and 3) stress response.

**Subjects and Methods:** The participants were derived from a follow-up cohort study, the Helsinki Study of Very Low Birth Weight Adults. They were all born between 1978 and 1985 in the region of Uusimaa and treated and discharged alive from the only tertiary neonatal intensive care unit in the region. The controls, born at term, were group-matched for birth hospital, age and sex. From the original birth cohort, different subgroups have, as young adults, participated in the studies of this thesis. We evaluated physical activity by both self-report and objective measurement. The participants (94 VLBW and 101 controls) completed a validated 30-item, 12-month physical activity questionnaire, the modified Kuopio Ischaemic Heart Disease Risk Factor Study questionnaire, and the NEO-Personality Inventory. For objective measurement, a subsample of 57 VLBW and 47 control participants underwent wrist-worn accelerometer measurement. To assess dietary intake, 151 VLBW and 156 control participants completed a 3-day food record. For evaluation of stress response, 54 VLBW and 40 control participants underwent a standardized psychosocial stress test, the Trier Social Stress Test (TSST). In conjunction with TSST, we measured heart rate, salivary cortisol, plasma ACTH, cortisol, glucose, insulin, adrenalin and noradrenalin.

**Results:** 1) Based on self-report, healthy VLBW young adults undertake approximately 50% less conditioning leisure-time physical activity, with lower yearly frequency, total time, total volume and energy expenditure than controls born at term. Differences in personality shown to exist between VLBW and controls groups do not explain the association between VLBW and lower conditioning leisure-time physical activity. We were unable to confirm our finding of lower physical activity with wrist-worn accelerometer measurement. 2) Regarding dietary habits, VLBW young adults had a lower consumption of vegetables, fruits, berries and milk products. This was combined with a lower intake of calcium and vitamin D. 3) Regarding stress response, VLBW adults showed a lower hypothalamic-
p pituitary-adrenal axis response to stress than controls born at term. This was accompanied by a lower insulin response. No evidence of a higher sympathetic-adrenal-medullary system stress response was found. Furthermore, we observed a lower noradrenalin response to stress in VLBW women.

Conclusions: This study showed that VLBW young adults undergo less conditioning leisure-time physical activities and have unhealthier diets, both factors that negatively affect future health in this high-risk population. They may in part underlie the increased risk for chronic non-communicable diseases in VLBW individuals.

Contrary to our expectations, a lower hypothalamic-pituitary-adrenal axis response to stress was found in VLBW adults than in controls born at term. For the sympatho-adrenal-medullary stress response, the results were similar in VLBW and control groups, with a lower noradrenalin response to stress in VLBW women only. These findings reinforce the supposition that stress response is programmed early in life.

In sum, this study increased understanding of possible mechanisms linking preterm birth and adult risk of disease.

Keywords: very low birth weight, preterm, infant, neonate, newborn, adult, physical activity, accelerometer, actigraphy, diet, nutrition, food record, programming, hypothalamic-pituitary-adrenal axis, cortisol, Trier Social Stress Test, sympathetic-adrenal-medullary system, cortisol, adrenalin, noradrenalin, heart rate
Tiivistelmä

**Taustaa:** Viime vuosikymmenen kuluessa tapahtunut merkittävä kehitys vastasyntyneiden tehohoidossa on johtanut yhä epäkypsempänä syntyneiden keskosten eloonjäämiseen ja he saavuttavat myös aikuisiän. Pikkukakeskosilla (syntymäpaino ≤ 1500 g) on todettu lisääntyneitä riskitekijöitä aikuisiän pitkäaikaissairauksiin, mm. osteoporoosiin, diabetekseen ja sydän- ja verisuonisairauksiin. Syy-yhteys keskosuuden ja lisääntyneiden sairausriskien välillä on tuntematon.

**Tavoitteet:** Tämän väitöskirjan päätavoitteena oli selvittää taustamekanismeja pikkukeskosena syntymisen vaikutuksista aikuisiän terveyteen, keskittyen 1) liikuntaan, 2) ravitsemukseen ja 3) stressivasteeseen.


**Tulokset:** 1) Kyselylomakkeen perusteella pikkukeskosena syntyneet aikuisten harrastavat noin 50 % vähemmän kuntoliikuntaa; heillä oli vuositasona vähemmän liikuntakertoja, liikuntaan käytetty aika oli vähäisempiä, liikunnan kokonaisvolyymi oli pienempi ja liikunnan aiheuttama vuosittainen energiankulutus oli merkittävästi verrokkihmä pienempi. Aiemmin havaitut erilaiset peronallisuuspiirteet keskosilla ja verrokeilla eivät selittäneet todettuja eroja kuntoliikunnassa. Kyselylomakkeen perusteella todettuja eroja liikuntatutkimuksissa.

Päättelmät: Pikkukeskosena syntyneet nuoret aikuiset harrastavat vähemmän kuntoliikuntaa ja heillä on joiltakin osin epäteveellisemmat ruokailututottomukset verrokkeihin nähden. Nämä ovat molemmat tekijöitä jotka heikentävät terveyttä ja ovat näin ollen erityisen merkittäviä tässä suuren riskin ryhmässä. Lisäksi molemmat voivat osaltaan selittää lisääntyneitä pitkääikaissairauksien riskiä pikkukeskosilla.


Avainsanat: pikkukeskonen, ennenaikainen, vastasyntynty, aikuinen, liikunta, kiihtyvyysanturi, ruokavalio, ravitsemus, ruokapäiväkirja, ohjelmoituminen, hypotalamus-aivolisisäke-lisämunuaisakseli, stressi, Trier Social Stress Test-koe, sympaattinen hermosto, kortisol, adrenaliini, noradrenaliini, syke
**Sammandrag**

**Bakgrund:** Stora framsteg har gjorts inom neonatalvården under de senaste årtionden. Detta har lett till ett ökande antal överlevande unga vuxna bland dem som fötts för tidigt med mycket liten födelsevikt (≤ 1500 g). Av okänd orsak har för tidigt födda unga vuxna ökade riskfaktorer för kroniska sjukdomar, bl.a. hjärt- och kärlsjukdomar, osteoporos och diabetes.

**Mål:** Syftet med detta avhandlingsprojekt var att utreda mekanismer bakom sambandet mellan prematuritet och hälsa i vuxenåldern, med fokus på 1) fysisk aktivitet, 2) näring och 3) stressrespons.

**Deltagare och metoder:** Forskningsmaterialet består av en kohort unga vuxna födda som små prematurer (födelsevikt ≤ 1500 g) i Nyland under åren 1978-1985 (the Helsinki Study of Very Low Birth Weight Adults). Alla prematurer gavs neonatalvård på samma sjukhus. Som kontrollgrupp valdes personer av samma kön och ålder, födda på samma förlossningssjukhus efter fullgången graviditet. Från kohorten har undergrupper av unga vuxna deltagit i denna doktorsavhandlings olika delstudier. Vi mätte fysisk aktivitet med hjälp av frågeformulär samt objektivt med accelerometer. Deltagarna (94 för tidigt födda och 101 kontrollpersoner) fyllde i Kuopio Ischaemic Heart Disease-projektets standardiserade, detaljerade frågeformulär samt NEO-Personality Inventory-formuläret. Accelerometerregistrering (armbandsmodell) utfördes åt 57 för tidigt födda och 47 kontrollpersoner. Kostvanor undersöktes genom att deltagarna (151 prematurer och 156 kontrollpersoner) antecknade allt de åt och drack under 3 dygn. För att mäta stressrespons deltog 54 för tidigt födda och 40 kontrollpersoner i ett standardiserat stress test (Trier Social Stress Test, TSST). I samband med TSST registrerades pulsen och upprepade blod- och salivprov togs för ACTH-, kortisol-, glukos-, insulin-, adrenalin och noradrenalin-bestämningar.

**Resultat:** 1) Baserat på frågeformuläret konditionstränade prematurgruppen ungefär 50 % mindre: den årliga frekvensen, totaltiden, totalvolymen och energikonsumtionen för konditionsträning var klart lägre. Skillnader i personlighet, som tidigare konstaterats mellan för tidigt födda och individer födda efter fullgången graviditet, förklarar inte denna stora skillnad i fysisk aktivitet grupper emellan. Vi kunde inte påvisa dylika skillnader i fysisk aktivitet grupper emellan med accelerometer-registrering. 2) Unga vuxna som fötts för tidigt konsumerade klart mindre bär, frukt, grönsaker och mjölkprodukter. Deras dagliga kalcium och D-vitamin intag var märkbart mindre än kontrollgruppen. 3) De som fötts för tidigt visade en lägre hypotalamus-hypofys-binjure-axel respons efter psykosocial stress.

**Konklusion** För tidigt födda unga vuxna konditionstränar klart mindre och de har ohälsosammare kostvanor jämfört med individer födda efter fullgången graviditet. Dessa faktorer inverkar väsentligt på hälsa och välmående speciellt i denna högrisk-grupp. Dessa resultat kan delvis förklara den förhöjda risken för insjuknande i kroniska sjukdomar hos för tidigt födda individer.


Sammanfattningsvis har denna studie utökat kunskap kring eventuella mekanismer bakom sambandet mellan för tidig födsel och sjukdomsrisken i vuxen ålder.

**Nyckelord:** prematur, för tidigt född, nyfödd, vuxen, fysisk aktivitet, accelerometer, diet, kostvanor, näring, programmering, hypotalamus-hypofys-binjure-axel, Trier Social Stress Test, sympatiska nervsystemet, kortisol, adrenalin, noradrenalin, puls
Contents

Abstract .................................................................................................................. 7
Tiivistelmä ............................................................................................................ 9
Sammandrag ......................................................................................................... 11
List of original publications ................................................................. 15
Abbreviations .................................................................................................. 16
1 Introduction .................................................................................................. 17
2 Review of the literature .............................................................................. 18
   2.1 Preterm birth ......................................................................................... 18
      2.1.1 Definitions and epidemiology ....................................................... 18
      2.1.2 Aetiology and risk factors of preterm birth ............................... 19
      2.1.3 Neonatal and childhood outcomes of preterm birth ............... 21
      2.1.4 Adult outcomes of preterm birth .............................................. 23
   2.2 Physical activity ................................................................................... 25
      2.2.1 General recommendations .......................................................... 25
      2.2.2 Health implications .................................................................. 26
      2.2.3 Preterm birth, very low birth weight (VLBW) and later physical
          activity ......................................................................................... 26
      2.2.4 Measuring physical activity ........................................................ 28
   2.3 Diet and nutrition .................................................................................. 29
      2.3.1 General recommendations .......................................................... 29
      2.3.2 Preterm birth, VLBW and later nutrition .................................... 30
      2.3.3 Measuring dietary habits and nutrient intake ............................ 31
   2.4 Other lifestyle factors and VLBW ........................................................ 32
   2.5 Psychosocial stress .............................................................................. 33
      2.5.1 Stress response ........................................................................ 33
      2.5.2 Preterm birth and stress response ............................................... 35
      2.5.3 Measuring stress response .......................................................... 37
3 Aims of the study ......................................................................................... 40
4 Subjects and methods .................................................................................. 41
   4.1 Study population ............................................................................... 41
   4.2 Measures .............................................................................................. 41
      4.2.1 Background characteristics ....................................................... 41
      4.2.2 Assessment of physical activity based on self-report (Study I) ...... 43
         4.2.2.1 Adjustment for lean body mass ............................................ 44
         4.2.2.2 Adjustment for personality ................................................. 44
      4.2.3 Assessment of physical activity based on accelerometer
          measurements (Study II) ............................................................... 44
      4.2.4 Assessment of nutrition and diet (Study III) .............................. 45
List of original publications

This thesis is based on five original publications. In the text, they are referred to by their Roman numerals (I-V).


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Abbreviations

A  Adrenalin
ACTH  Adrenocorticotropic hormone
AGA  Appropriate for gestational age
AUCg  Area under the curve ground
BMI  Body mass index
BPD  Bronchopulmonary dysplasia
CI  Confidence interval
CP  Cerebral palsy
cpm  Counts per minute
CVD  Cardiovascular disease
DOHaD  Developmental origins of health and disease
E%  Percentage of total energy intake
EE  Energy expenditure
ELBW  Extremely low birth weight
HeSVA  Helsinki Study of Very Low Birth Weight Adults
HPAA  Hypothalamic-pituitary-adrenal axis
HR  Heart rate
IQ  intelligence quotient
KIHD  Kuopio Ischaemic Heart Disease Risk Factor Study - questionnaire
LTPA  Leisure-time physical activity
MET  Metabolic equivalents
NA  Noradrenalin
NCD  Non-communicable disease
NEO-PI  NEO-Personality Inventory
NICU  Neonatal intensive care unit
SAM  Sympathetic-adrenal-medullary
SD  Standard deviation
SES  Socio-economic status
SGA  Small for gestational age
TSST  Trier Social Stress Test
TSST-C  TSST for Children
VLBW  Very low birth weight
WHO  World Health Organization
1 Introduction

Preterm birth is relatively common. In 2011-2012, 5.6% of all children born in Finland were born preterm, by definition with a gestational age (GA) < 37 weeks (Vuori and Gissler, 2013). Of these preterm children, 1060 children or 0.8% of all newborns had a birth weight < 1500 g or a GA < 32 weeks (Vuori and Gissler, 2013). Of these children, 90.8% reached their first birthday (Vuori and Gissler, 2013). Thus, the number of survivors after preterm birth is considerable.

Since the late 1970s and early 1980s, when the participants of the studies included in this thesis were born, great advancements have been made in neonatal intensive care. However, preterm birth is similarly associated with pre- and postnatal adversities today, as it was approximately 30 years ago. Compared with the natural environment of the fetus, the mother’s womb, the preterm infant must continue to grow and develop in a markedly different environment, the neonatal intensive care unit (NICU) setting. Regardless of the many improvements in neonatal care, some similarities remain between the preterm-born of today and those born some decades ago. These include repeated stressful situations: painful treatments, administration of medicines and increased risk of infections, among others. Such circumstances may be assumed to similarly affect newborn infants undergoing intensive care, regardless of changes or advancements in care.

An increasing body of evidence shows that pre-and postnatal events affect health and disease later in life. As adults, people born at very low birth weight (VLBW, ≤ 1500 g) have, for instance, impaired glucose regulation (Hofman et al., 2004; Hovi et al., 2007), higher blood pressure (Doyle et al., 2003; Hack et al., 2005; de Jong et al., 2012; Parkinson et al., 2013; Kajantie and Hovi, 2014), lower bone mineral density (Hovi et al., 2009; Smith et al., 2011) and changes in lipid profile (Hovi et al., 2013; Parkinson et al., 2013) compared with controls born at term. Previous data also suggest that hypothalamic-pituitary-adrenal axis (HPAA) functioning and endocrine stress responses (Wüst et al., 2005; Jones et al., 2006; Buske-Kirschbaum et al., 2007; Grunau et al., 2007; Kajantie et al., 2007; Grunau et al., 2010; Kajantie and Räikkönen, 2010; Brummelte et al., 2011) as well as feeding preferences (Portella et al., 2012) may be affected by early life events. Physical activity and fitness in adolescence and adulthood also seems to be affected by preterm birth (Kajantie and Hovi, 2014). Some of the results of early life events may be reversed or attenuated by a healthy lifestyle, including adequate physical activity and good dietary habits. The focus of this thesis was to evaluate physical activity, nutrition and dietary habits, and stress response in a cohort of healthy VLBW young adults.
2 Review of the literature

2.1 Preterm birth

2.1.1 Definitions and epidemiology

Term birth refers to birth occurring between 37-42 weeks of gestation. The World Health Organization (WHO) defines preterm birth as birth before 37 completed weeks of gestation or 259 days since the first day of a woman’s last menstrual period (Howson et al., 2012), while post-term birth refers to > 42 completed weeks of gestation. Preterm birth can further be divided into extremely preterm (< 28 weeks), very preterm (28 - < 32 weeks) and moderate preterm (32 - < 37 weeks). Late preterm refers to birth at 34 - < 37 weeks of gestation. In most high-income countries there is a 50% chance for survival after birth at 24 weeks of gestation with neonatal intensive care, while in low-income settings 50% of the children born at even 32 weeks of gestation will not survive due to lack of adequate neonatal care (Howson et al., 2012).

Based on birth weight, the newborn can be classified into low birth weight (LBW < 2500 g), very low birth weight (VLBW < 1500 g) or extremely low birth weight (ELBW, <1000 g). For comparison, the mean birth weight of all children born in Finland in the year 2012 was 3498 g (Vuori and Gissler, 2013). Fetal growth according to expectation, based on population mean and gestational age, i.e. appropriate for gestational age (AGA), refers to birth weight within ± 2 standard deviations (SDs). Small for gestational age (SGA) refers to birth weight < -2 SDs of the population mean (Pihkala et al., 1989) and large for gestational age (LGA) to birth weight > 2 SDs. Alternatively, 10th and 90th percentiles may be used as cut-off points for SGA, AGA and LGA (Reeves and Bernstein, 2008).

Approximately 15 million preterm births occur yearly worldwide (Howson et al., 2012), more than 10% of all births. Of these 15 million infants, 1.1 million die of complications related to preterm birth (Howson et al., 2012). Preterm birth rates vary across the world, ranging from 5% to 18%. The highest preterm birth rates occur in the poorest countries (> 12%), with clearly lower rates (9%) in high-income countries (Howson et al., 2012). In this respect, the United States is an exception, with an 11.5% preterm birth rate in 2012. In Finland 5.6% of all children were born preterm in 2012, in total 3387 children (Vuori and Gissler, 2013). Based on WHO data, the global incidence of preterm birth is rising (Howson et al., 2012). Of the 65 countries with reliable data for the past 20 years, 14 countries have had stable rates of preterm birth, only 3 countries (Croatia, Ecuador and Estonia) have had a decrease in the rate of preterm birth and the majority of countries have shown
increased rates. Factors such as assisted reproduction and increasing maternal age account for only a minor portion in the rising numbers of preterm birth. These data are alarming. In addition to neonatal deaths, short- and long-term effects on the health and well-being of survivors and possible lifetime disability, the costs of prematurity are overwhelming.

2.1.2 Aetiology and risk factors of preterm birth

A multitude of causes underlie preterm birth, many of them unknown. Commonly, preterm birth may be grouped into a) spontaneous preterm birth and b) provider-initiated preterm birth. Spontaneous onset of labour and prelabour premature rupture of membranes are included in the former, induction of labour or elective Caesarian section before 37 weeks of gestation in the latter. Spontaneous onset of labour occurs in approximately 45-50% of all preterm births, in 30% premature rupture of membranes occurs and 15-20% are provider-initiated (Menon, 2008).

Reasons or mechanisms behind preterm birth are mostly unknown. However, several risk factors, listed in Table 1, have been identified. Infection is associated with 30-40% of all preterm births (Goldenberg et al., 2008) and often more than one risk factor is present (Menon, 2008). This suggests aetologic heterogeneity in preterm birth. Ethnic and racial disparities that cannot fully be explained by differences in socio-economic status (SES) or maternal risk-taking behaviour do exist (Schaaf et al., 2013). There are marked differences between populations, for example, in the United States the preterm birth rates in Caucasians are clearly lower than those in African-Americans, 11.5 % versus 17.8 % (Menon, 2008). Severe allergic reactions can produce uterine cramping, and such allergic reactions with marked cytokine and antibody production have also been associated with preterm birth (Garfield et al., 2006).

Activation of four main pathways that lead to preterm birth have been identified:
1. stress activates maternal or fetal HPAA
2. infection provokes inflammation with subsequent cytokine and prostaglandin production
3. decidual haemorrhage
4. distension of the myometrium

How these pathways are activated is unclear. They overlap and interact and involve complex biochemical pathways with, for example, prostaglandins, metalloproteinases and cytokines. Pathological uterine distension caused by decidual haemorrhage and infection, which causes overwhelming inflammation, both trigger uterotonic activity. A contracting myometrium promotes cervical effacement and dilatation, leading to rupture of fetal membranes with onset of preterm labour and delivery (Menon, 2008).
Table 1. Known risk factors for preterm birth.

<table>
<thead>
<tr>
<th>Risk factors for preterm birth</th>
<th>Cervical anomalies</th>
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<tr>
<td>Infection</td>
<td>Fetal abnormalities</td>
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<td>Intrauterine infection</td>
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<tr>
<td>Extrauterine infection</td>
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<td><strong>Socio-economic status</strong></td>
<td>Low socio-economic status</td>
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<td><strong>Pregnancy related maternal conditions and maternal history</strong></td>
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<td>Previous preterm delivery</td>
<td>Social isolation</td>
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<td>Repeated second trimester abortion</td>
<td>Education</td>
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<td>In-vitro fertilization</td>
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<td>Multiple pregnancy</td>
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<td>Parity</td>
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<td>Maternal medical complications</td>
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<td>Malnutrition</td>
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<td>Gestational bleeding</td>
<td>Maternal weight gain</td>
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<td>Abnormal placentation</td>
<td>Smoking</td>
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<td>Low body mass index before conception</td>
<td>Alcohol abuse</td>
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<td>Age &lt; 17 years or &gt; 35 years</td>
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<td>Infertility</td>
<td>Drug abuse</td>
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<td>Heredity</td>
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<td>Ethnic and racial disparities</td>
<td>Sexual activities</td>
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<tr>
<td><strong>Stress</strong></td>
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<td>Abnormalities</td>
<td>Stressful life events</td>
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<td>Uterine anomalies</td>
<td>Psychosocial stress</td>
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<tr>
<td></td>
<td>Severe allergic reactions</td>
</tr>
</tbody>
</table>

Garfield et al. 2006; Goldenberg et al. 2008; Menon 2008; Schaaf et al. 2013
2.1.3 Neonatal and childhood outcomes of preterm birth

Prematurity is the leading cause of death in the newborn and the second leading cause of death in children aged under 5 years (Howson et al., 2012). With advancements in antenatal care, including prenatal corticosteroids, as well as postnatal care with, for example, surfactant administration and improved ventilation support systems, the numbers of extremely preterm infants surviving in high-income countries are growing. In countries with modern care available, most extremely and very preterm infants remain in hospital care close to term. As the focus of this thesis is on adult outcomes of VLBW, the neonatal and childhood outcomes will only be reflected on briefly, serving as an introduction to the adult outcomes of VLBW. The sequelae of preterm birth vary, and the morbidity is inversely related to gestational age (Moster et al., 2008; Saigal and Doyle, 2008).

After initial survival of preterm birth, respiratory distress syndrome, a patent ductus arteriosus, infection or pulmonary barotrauma are common problems in the early neonatal period. Tommiska et al. compared ELBW infants born in Finland during 1996-1997 (n = 529) and 1999-2000 (n = 511) and reported an increase in the incidence of respiratory distress syndrome and septicemia (75% vs. 83% and 23% vs. 31%) (Tommiska et al., 2007). However, no changes were seen in mortality rates between these time periods, and the survival rates with stillborn infants included were 40% and 44%, respectively (Tommiska et al., 2007).

Preterm-born babies are at risk for brain lesions (intraventricular haemorrhage, periventricular haemorrhagic infarction and periventricular leukomalacia) associated with adverse neurological outcomes (Ward and Beachy, 2003). In ELBW infants born in Finland, a rise in the overall incidence of intraventricular haemorrhage was seen between 1996-1997 and 1999-2000 (29% vs. 37%), while the rates of the most severe grades (3-4) remained similar (16% vs. 17%) (Tommiska et al., 2007). Hydrocephalus may develop after intraventricular haemorrhage, and to ensure adequate cerebral fluid reabsorption a shunt may be required. In ELBW infants, 1-2% of those admitted to the NICU required a shunt before reaching the age of 40 weeks of gestation (Tommiska et al., 2007).

As for bowel complications, necrotizing enterocolitis is more common in infants born preterm. In ELBW infants, the incidence of necrotizing enterocolitis with bowel perforation was reported to be 4-8% (Tommiska et al., 2007).

Prolonged mechanical ventilation and oxygen supplementation may cause damage to the lungs and eyes. Bronchopulmonary dysplasia (BPD) and retinopathy of prematurity are complications that may develop somewhat later during NICU care. In one study including 279 VLBW and 210 controls born during 1991-1992, retinopathy of prematurity of any severity was reported in 51% of VLBW children, and 13% of VLBW versus 4% of full-term children wore glasses at 7 years of age.
(Cooke et al., 2004). In that study, the VLBW children were more likely than the controls to have strabismus, reduced stereopsis and poor visual acuity (Cooke et al., 2004).

Serious health problems, such as cerebral palsy (CP), intellectual impairment, cognitive problems, developmental delay, short bowel syndrome, growth reduction, chronic lung disease, and impairment of motor development, vision and hearing may follow the acute complications (Ward and Beachy, 2003). In a large cohort of people born in Norway between 1967 and 1983, the prevalence of having CP was 9.1% for those born between 23 and 27 weeks of gestation and 0.1% for those born full-term (Moster et al., 2008), while in ELBW infants born in the late 1990s CP rates of 11-14% have been reported (Tommiska et al., 2007).

At the time of discharge from hospital, suboptimal growth is common in VLBW infants. This delay in growth often continues in early childhood. A recent study comprising 181 VLBW children at age 5 years showed that in AGA infants, good weight gain and growth of head circumference between birth and 2 years was associated with better cognitive outcome at 5 years of age (Leppänen et al., 2014). In SGA infants, the significant period for head circumference growth regarding cognitive outcome was at term age (Leppänen et al., 2014).

As the above examples illustrate, there is a marked risk of serious health problems in individuals born preterm. These preterm-born infants may face a multitude of potential health problems with far-reaching effects, extending beyond the neonatal period and throughout life. They thus require follow-up and specialized care. Despite the increased survival rates due to improved neonatal care, there is not a simultaneous increase in disability rates. On the contrary, morbidity rates in VLBW survivors first decreased and then plateaued in the 1990s (Horbar et al., 2002; Darlow et al., 2003; Fanaroff et al., 2007).

As for childhood, the level of immaturity at birth as well as the amount of complications developed during NICU care will be reflected in growth and development during infancy through school age and adolescence (Saigal and Doyle, 2008). Interestingly, VLBW has been shown to be associated with advanced pubertal growth spurt compared with controls (Wehkalampi et al., 2011). This may reflect advanced pubertal maturation in VLBW children. This is of importance since advanced puberty and early maturation as such increase the risk of developing type 2 diabetes (Lakshman et al., 2008) and high blood pressure (Remsberg et al., 2005) later in life. Within the limits of this thesis, other effects of preterm birth on childhood and adolescence will be discussed in the following sections (entitled physical activity, diet and nutrition, stress response).
2.1.4 Adult outcomes of preterm birth

Implications of preterm birth extend throughout the lifespan of the individual. The Developmental Origins of Health and Disease (DOHaD) theory suggests that conditions at a specific sensitive period in early pre- or postnatal life may program the functioning of cells, tissues and organs, altering their function throughout life (Bateson et al., 2004; Gluckman et al., 2008). Preterm birth and low birth weight mirror early life conditions that markedly differ from early life conditions in individuals born at term with normal birth weight. An increasing body of evidence suggests that adults who were born preterm have increased risk factors for later cardiometabolic disease (Kajantie and Hovi, 2014). Regarding disease outcomes, current data mostly describe increases in risk factors in young adult survivors of preterm birth (in their twenties and thirties), and chronic non-communicable diseases (NCDs), such as type 2 diabetes, stroke and osteoporosis, typically manifest later in life.

Several neonatal centres have established follow-up cohorts of former preterm-born infants for investigating their later health. As for increased risk factors for NCDs in preterm-born adults, reports on lower bone density (Hovi et al., 2009; Smith et al., 2011), negative effects on glucose and insulin metabolism (Hofman et al., 2004; Lawlor et al., 2006; Hovi et al., 2007; Rotteveel et al., 2008; Kaijser et al., 2009; Kajantie et al., 2010; Pilgaard et al., 2010; Crump et al., 2011; Smith et al., 2011), higher blood pressure (de Jong et al., 2012; Parkinson et al., 2013) and an atherogenic lipid profile (Hovi et al., 2013; Parkinson et al., 2013) have been published. In addition to lower bone density, adults born preterm are shorter than their term-born counterparts (Roberts and Cheong, 2014). In a recent systematic review and meta-analysis on markers of metabolic syndrome by Parkinson et al. (2013), no differences were found in preterm and term-born adults regarding body mass index (BMI), waist-hip ratio, percentage fat mass, flow-mediated intima-media thickness, fasting glucose and insulin profiles. However, the authors reported higher plasma low-density lipoproteins in young adults born preterm (Parkinson et al., 2013). Also in our Helsinki Study of Very Low Birth Weight Adults (HeSVA) cohort, a more atherogenic lipid profile, with higher concentrations of triglycerides in very-low-density and high-density lipoprotein subclasses, was found in the VLBW adults (Hovi et al., 2013). Furthermore, in the same review, preterm birth was associated with higher blood pressure, especially in women (Parkinson et al., 2013). Similar findings of higher systolic blood pressure in preterm-born or VLBW individuals were reported in another systematic review and meta-analysis focusing entirely on blood pressure (de Jong et al., 2012). Modestly higher blood pressure levels present already in early adulthood increase the risk of developing hypertension and its sequelae later in life. A possible additional risk factor for hypertension is elevated arterial stiffness, which has been reported in 11-year-old
children born before 26 weeks of gestation (McEniery et al., 2011). The above-described differences between adults born preterm and controls born at term may represent a greater risk for atherosclerosis and cardiovascular diseases (CVDs) in later adulthood.

When preterm birth occurs, many developmental stages that normally occur in utero during the last trimester have to take place during hospitalization, in a NICU environment. For example, normally, nephrogenesis in humans occurs during 9-36 weeks of gestation and new nephrons are not formed after birth, with the exception of extremely preterm-born infants. In one study, smaller kidney size and impaired renal function were found in very preterm SGA participants compared with term-born controls (Keijzer-Veen et al., 2007). VLBW and prematurity may also predispose to secondary focal segmental glomerulosclerosis (Hodgin et al., 2009). Also cardiac development seems to be affected by preterm birth. Birth is associated with a change in cardiomyocyte phenotype from the fetal hyperplastic form to the neonatal hypertrophic form as the cardiomyocytes are exposed to the change from a low-resistance fetal blood circulation to the high-resistance arterial system that normally occurs after birth (Gessner et al., 1965). When this shift in blood circulation occurs in the preterm infant, the cardiomyocytes are still immature and this has been associated with significantly higher left ventricular mass in adulthood (Lewandowski et al., 2013). The more premature the birth, the greater the increase in left ventricular mass in the 102 25-year-old adults born preterm compared with term-born controls (Lewandowski et al., 2013). This finding of greater left ventricular mass in preterm-born adults was independent of the higher blood pressure also reported in the same preterm-born group. Increased left ventricular mass is a known risk factor for cardiovascular morbidity and mortality (Lorell and Carabello, 2000).

Preterm birth is associated with chronic respiratory morbidity in infancy (Been et al., 2014; Greenough, 2013). Long-term respiratory consequences seem to last, as evidenced by subtle lung function abnormalities and diminished lung function in former preterms at 19 years of age (Vrijlandt et al., 2006). The development of immune system responses and immunologic pathways are likely affected by preterm birth. This is supported by the finding of a significantly lower incidence of atopy in young VLBW adults, defined as a positive skin prick test reaction, than in controls (Siltanen et al., 2011).

Preterm birth, especially when combined with SGA, is a risk factor for a range of psychiatric disorders, including depression, non-affective psychosis, bipolar affective disorder and eating disorders (Räikkönen et al., 2008; Nosarti et al., 2012). Differences in personality traits have been reported. The VLBW subjects seem more conscientious and agreeable and show less neuroticism than controls (Pesonen et al., 2008). VLBW adults also show more inhibition, internalizing behaviour problems
and risk avoidance (Hack et al., 2002; Hille et al., 2008; Pesonen et al., 2008; Schmidt et al., 2008; Schmidt et al., 2010). For instance, VLBW adults report less smoking, less alcohol and drug use, have lower pregnancy rates and engage in less criminal activities as young adults (Hack et al., 2002; Hille et al., 2008). They also seem to have more difficulties in establishing social contacts (Hille et al., 2008), perhaps caused by more prominent internalizing behaviour. Some outcomes may be different in subgroups of VLBW individuals. For instance, in one study, VLBW adults born at AGA were shown to be at reduced risk for some psychiatric disorders, including depression (Räikkönen et al., 2008).

At 8 years of age, VLBW children showed higher rates of neurosensory impairment, e.g. CP, shunt-dependent hydrocephalus, blindness or deafness, and subnormal intelligence quotient (IQ) compared with normal birth weight children (Hack et al., 2009). Many of these findings persist into young adulthood, as shown in a cohort of 242 20-year-old VLBW survivors born between 1977 and 1979, which is approximately the same time period that the participants of our studies were born. Fewer VLBW adults graduated from high school, and they had lower mean IQ (87 vs. 92) and academic achievement scores than controls (Hack et al., 2002). Furthermore, the rates of neurosensory impairments were higher (10% vs. < 1%), and VLBW men were less likely to continue post-secondary studies (Hack et al., 2002). Among survivors of preterm birth without medical disabilities, gestational age at birth was associated with attained educational level, income, receiving social security benefits and establishment of a family, but not with criminal activity or rates of unemployment (Moster et al., 2008). In a meta-analysis on neurobehavioural outcomes, moderate to severe deficits in academic achievement, attention problems, internalizing behavioural problems and poor executive function were found to strongly correlate with the degree of immaturity at birth and to persist into adulthood in former preterm or VLBW individuals (Aarnoudse-Moens et al., 2009).

2.2 Physical activity

2.2.1 General recommendations

Regular physical activity is associated with the reduction of many chronic diseases, including coronary heart disease, hypertension, stroke, metabolic syndrome, breast and colon cancer, type 2 diabetes, osteoporosis, and depression, as well as all-cause mortality (Physical Activity Guidelines Advisory Committee, 2008; Warburton et al., 2010; World Health Organization, 2010). Guidelines on physical activity for adults aged 18-64 years recommend at least 150 minutes of moderate-intensity aerobic physical activity per week (Physical Activity Guidelines Advisory Committee, 2008; World Health Organization, 2010). Alternatively, at least 75 minutes of weekly vigorous-intensity aerobic physical activity is recommended to improve
cardiorespiratory fitness and bone health and to reduce the risk of NCDs and depression (Physical Activity Guidelines Advisory Committee, 2008; World Health Organization, 2010). The aerobic activity should last at least 10 minutes each time in order to achieve health benefits. Guideline recommendations are similar for adults aged 65 years and above. For children aged 5-17 years, the aim is at least 60 minutes of moderate to vigorous-intensity physical activity every day to improve cardiorespiratory and muscular fitness, bone health, and cardiovascular and metabolic health biomarkers and to reduce symptoms of depression and anxiety (World Health Organization, 2010).

2.2.2 Health implications
Physical inactivity is identified as the 4\textsuperscript{th} leading risk factor for global mortality, accounting for 5.5\% of deaths globally (World Health Organization, 2009). Only high blood pressure (12.8\% of deaths globally), tobacco use (8.7\%) and high blood glucose (5.8\%) precede physical inactivity as risk factors (World Health Organization, 2009). Overweight and obesity come next, accounting for 4.8\% of global mortality (World Health Organization, 2009). Adults tend to spend considerable time daily in sedentary behaviour, and increasing evidence shows time spent sedentary to be an important, independent risk factor for health (Rhodes et al., 2012). In a large review including 109 papers, sedentary behaviour (divided into e.g. computer use, TV viewing, sitting, socializing) and its correlates were evaluated, and several socio-demographic and health factors were linked to sedentary behaviour in addition to the simple absence of physical activity (Rhodes et al., 2012). The impact of physical inactivity has even been characterized similarly to that of smoking as being related to risk for NCDs (Lee et al., 2012). For example, in the Finnish population, physical inactivity has been calculated to alone contribute to 6.3\% of all coronary heart disease, 7.8\% of type 2 diabetes, 9.1\% of breast cancer, 11.2\% of colon cancer and 10.1\% of all-cause mortality (Lee et al., 2012).

2.2.3 Preterm birth, very low birth weight (VLBW) and later physical activity
Survivors of preterm birth are at risk for developing long-term pulmonary sequelae, especially after BPD. Former preterm-born tend to have more bronchial obstruction and lower diffusion capacity, leading to diminished lung function in young adulthood (Vrijlandt et al., 2006). In a recent review, preterm birth was associated with a 1.7-fold (95\% CI: 1.57-1.87) increased risk of childhood wheezing disorders (Been et al., 2014). Evidence suggests that lung function in infants born very prematurely may even deteriorate over the first year of life (Greenough, 2013). Even mild impairment in lung function in infancy, childhood and adulthood may have a
negative effect on physical activity. Subtle abnormalities that persist into adulthood may be of importance with aging, especially in smokers.

Motor problems are frequently seen after preterm birth. In a large meta-analysis of 9653 children aged 0-15 years, VLBW and birth at ≤ 32 weeks of gestation were associated with significant motor impairment that persisted from infancy through childhood and into late adolescence (de Kieviet et al., 2009). The different types of motor impairment reported included balance skills, ball skills, manual dexterity and gross motor development (de Kieviet et al., 2009). For comparison, in 9009 healthy 14-year-olds born at ≥ 36 weeks of gestation, earlier infant motor development was associated with higher frequency of participation in leisure-time physical activity (LTPA) and participation in a larger number of different types of sports (Ridgway et al., 2009). In 54 ELBW 12-year-olds, a significant fitness deficit was shown relative to 55 controls (Burns et al., 2009). In that study, motor coordination was the most powerful predictor of physical fitness as measured by maximal oxygen uptake (Burns et al., 2009). Complications of preterm birth at VLBW also include visual impairments; for example, poor visual acuity and strabismus are more frequent in VLBW adolescents than in controls (Evensen et al., 2009). Such visual impairments have been shown to influence definite and borderline motor problems, balance and manual dexterity in VLBW adolescents (Evensen et al., 2009). Poor motor coordination (Rogers et al., 2005), impaired lung function (Vrijlandt et al., 2006), visual impairment (Evensen et al., 2009), motor impairment (de Kieviet et al., 2009) combined with lower physical self-confidence (Hack et al., 2007) and exercise capacity (Rogers et al., 2005) and lower perceived physical ability (Saigal et al., 2007) are all factors that may lead to undertaking less physical activity in former preterm adolescents and young adults.

Previous studies, based on a relatively small number of questionnaire items, suggest that adolescents or young adults born severely preterm participate less in sports (Rogers et al., 2005; Saigal et al., 2007; Hille et al., 2008) and undertake less LTPA (Rogers et al., 2005; Kajantie et al., 2010) than their term-born peers. They also perceive their physical abilities as poorer in young adulthood (Hack et al., 2007). ELBW individuals have weaker hand grip strength, lower scores for physical self-efficacy, lower perceived physical ability and lower physical self-confidence, all factors affecting the willingness to engage in physical activity (Saigal et al., 2007). A limitation of these studies is, however, that they are based on self-report. Only in one study has accelerometry been used to objectively measure physical activity in 31 11-year-olds born before 25 weeks of gestation and 30 controls born at term (Welsh et al., 2010). This study used hip-worn accelerometers, and similarly to Study II, the authors found no difference in physical activity between extremely preterm-born and control groups. However, in the same study, the preterm group reported more breathing difficulties and found physical activity to be more difficult than controls (p
for difference 0.01) (Welsh et al., 2010). They also showed reduced peak oxygen consumption and alternations in ventilatory adaptations during peak exercise as measured by cycle ergometer and spirometry (Welsh et al., 2010).

A large meta-analysis including Nordic cohorts with birth weights ranging from 1.26 kg to 5.25 kg found that adolescents and adults at the extreme ends of the birth weight spectrum were the least physically active. The lower end of the distribution is likely to represent preterm-born subjects.

### 2.2.4 Measuring physical activity

Methods for measuring physical activity can simply be divided into a) self-report and b) objective measurement.

Self-report methods on physical activity are cost-effective and participant-friendly. Furthermore, a large sample size can be handled. Detailed, prospective data on daily physical activity can be gathered using a physical activity diary or record. In the physical activity record, all bouts of activity during the day are reported. Physical activity logs are used to capture time spent in different activity categories; in this type of self-report, also sedentary activities (such as inactive periods and sitting) are reported. Specific physical activity questionnaires are widely used in research and vary in detail (Strath et al., 2013). Recall questionnaires typically contain 5-15 items, while quantitative history questionnaires may contain 15-75 items. The data may be obtained by either interview or a record maintained by the participant. Using a compendium of physical activities, data acquired from both questionnaires and diaries can be transferred into metabolic equivalents (METs) (Ainsworth et al., 1993; Ainsworth et al., 2000; Ainsworth et al. 2011) for evaluation of energy expenditure (EE) from physical activity. For children and adolescents, a separate compendium for calculating EE has been published (Ridley et al., 2008). One MET equals the ratio of metabolic rate during exercise to metabolic rate at rest and corresponds to an EE of about 1 kcal/kg/hour. For classification of physical activities by intensity, the following cut-off points using METs are recommended: moderate-intensity activity 3.0 to 5.9 METs and vigorous intensity ≥ 6 METs (Physical Activity Guidelines Advisory Committee, 2008). Thus, the recommended 150 minutes of moderate-intensity aerobic physical activity per week for adults (Physical Activity Guidelines Advisory Committee, 2008; World Health Organization, 2010) equals 450-885 MET-minutes weekly (150 minutes *3 METs, 150 minutes * 5.9 METs).

Among the objective methods assessing physical activity, the doubly labelled water method (Lifson et al., 1955) is regarded as the gold standard for evaluating total EE. This method is not suitable for large or epidemiologic studies as it is expensive, time-consuming, burdensome on the participant and does not provide qualitative data. In brief, the participant is to drink a known dose of water enriched
with $^2$H and $^{18}$O. Repeated samples of blood, saliva or urine are collected during the next 5-14 days for calculating the elimination rates of the isotopes to estimate CO$_2$ production. The $^2$H is lost by the body only as water, while the $^{18}$O is lost as both water and CO$_2$. Thus, the difference between the turnovers of these isotopes provides a measure of CO$_2$ production.

The most commonly used objective measure of physical activity is accelerometry. Depending on its location, the accelerometer measures acceleration and movement of the body or its segments. It is usually placed on the wrist, hip, thigh or ankle. The accelerometer can be used for relatively long time periods, typically 3-28 days. It is easy to wear and a multitude of validation studies have been done for separate models (Strath et al., 2013). Another type of motion sensor is the pedometer, which is usually belt-worn. The pedometer measures steps and it is used to estimate the distance walked over a specific time period.

Other objective measures of assessing physical activity are indirect calorimetry performed in a laboratory setting, direct observation by a trained observer (more often used in children) and heart rate monitoring. One of the weaknesses of heart rate monitoring is that it is affected by several factors besides physical activity, e.g. medications, caffeine and emotions. Sometimes also combinations of the above-described methods are used for a more exact evaluation of physical activity. Heart rate monitoring, for example, may be combined with accelerometry to differentiate active and inactive periods and different intensity levels of physical activity.

All of the forementioned methods for measuring physical activity have their strengths and limitations. Many of these are related to cost-effectiveness, data processing, participant burden, measurable time period, type of activity investigated and possible need for a laboratory setting.

### 2.3 Diet and nutrition

#### 2.3.1 General recommendations

An unhealthy diet is a major contributing factor to many NCDs such as type 2 diabetes and CVD. In high-income countries (defined by WHO as gross national income per capita US$ ≥ 10 066 or 7344 €), a low intake of fruits and vegetables was ranked as the 7th leading risk factor for mortality, accounting for 2.5% of deaths globally (World Health Organization, 2009). Compared with omnivorous diets, consumption of vegetarian diets is associated with lower blood pressure; in adults, 5 mmHg lower mean systolic and 2-7 mmHg lower mean diastolic blood pressure have been reported (Yokoyama et al., 2014). Based on a recent meta-analysis, even small actions count; Briggs et al. (2013) calculated that daily consumption of an apple weighing 100 g would reduce cardiac-related deaths almost equally efficiently to daily simvastatin (40 mg) on a population level.
Slight variations in recommended daily nutritional intakes exist countrywise. The Finnish nutrition recommendations are based on the Nordic nutrition recommendations (Nordic Council of Ministers, 2014) and the new, updated Finnish recommendations have been published in 2014 (National Nutrition Council, 2014). One specific difference between the recommendations is noteworthy; the recommended daily salt intake for Finns is 5 g/day, while the Nordic recommendation is 6 g/day. The new recommended Finnish macro- and micronutrient intakes for adults aged 18-64 years are shown in detail in Table 6. In brief, the recommended percentages of total energy intake (E%) of daily macronutrient intake is as follows: carbohydrates 45-60%, protein 10-20% and fat 25-40%. Of carbohydrates, the intake of fibres should be at least 25-35 g/day and the E% of sucrose < 10%. The quality of fat is important; the recommendation is that saturated and transfatty acids comprise < 10 E%. Children and adults aged 65 years and above have separate nutrition recommendations (National Nutrition Council, 2014).

2.3.2 Preterm birth, VLBW and later nutrition

As already pointed out in the previous sections, people born preterm have increased risk factors for many NCDs. Food and nutrient intakes are also associated with NCDs, e.g. hypertension (salt), type 2 diabetes (excess energy intake) and osteoporosis (calcium and vitamin D). Although dietary habits and nutrient intake are closely related to NCDs, previous data on VLBW subjects’ food and nutrient intake are scarce. VLBW subjects often experience adverse environmental conditions, such as inadequate nutrition and growth, during both prenatal and early postnatal life. Such conditions predict dietary habits later in life (Lussana et al., 2008; Barbieri et al., 2009; Portella et al., 2012). For example, severe maternal undernutrition during the fetal period has been linked to preference for fatty food in later life (Lussana et al., 2008). Poor fetal growth has been found to correlate with altered hedonic response to sweet taste in preterm SGA infants at birth (Ayres et al., 2012). At 3 years of age, girls born SGA were more responsive towards a sweet reward and the impulsivity predicted fat preference and BMI at 4 years of age (Silveira et al., 2012). Also in young women, birth with SGA has been associated with higher carbohydrate intake compared with AGA women (Barbieri et al., 2009).

In young children born at term, AGA children with lower birth weight had higher fat intake, especially in boys (Stafford and Lucas, 1998; Shultis et al., 2005). In a study with 1797 term-born Finnish adults aged 56-70 years, daily intake of fruits and berries increased with birth weight: + 83 g per 1 kg higher birth weight (Perälä et al., 2012). In addition, a lower birth weight was also associated with higher E% of daily fat and lower E% of daily carbohydrate intake (Perälä et al., 2012). In that study, a validated food-frequency questionnaire was used for assessing dietary intake.
Early prenatal and postnatal flavour experiences may explain differences in food choices or food preferences. This seems related to fetal growth or size at birth. In a study of infants aged approximately 6 months, maternal diet during pregnancy affected postnatal preference for the same diet (Mennella et al., 2001). This is likely the way culture-specific flavour preferences are initiated in early life (Mennella et al., 2001). Furthermore, in another study, birth weight was inversely associated with both salty taste acceptance and salt intake in children at 2 months as well as at 3-4 years of age (Stein et al., 2006). In this study, only participants with a birth weight > 2500 g were included. This is of note, as salt intake is directly related to blood pressure (Chobanian and Hill, 2000; Kaplan, 2000), and at least in one study those born with a low birth weight were especially sensitive to the blood pressure-raising effect of salt as elderly adults (Perälä et al., 2011).

2.3.3 Measuring dietary habits and nutrient intake

The most commonly used methods for evaluating dietary intake are based on self-report. The weighed food record (or diary) is considered to be the most precise self-report method (Livingstone et al., 1990). All foods and drinks consumed are weighed by the participant, who then records this information. This method does not rely on an individual’s memory as everything consumed is recorded at the time of consumption. The weighed food record is more labour-intensive for the participant than the estimated food record (or diary), which is also a prospective dietary assessment tool. Similarly, the participant records everything eaten and drunk at the time of consumption. The amount of food or drink consumed is estimated based on photographs, household measures or unit sizes (e.g. one slice of bread). Dietary habits vary over the week and a 7-day diary takes this into account. Also foods consumed only once or twice weekly may be underestimated or overestimated with shorter evaluation periods. However, for practical reasons, shorter measurement periods are also used, as was the case in Study III.

For large, epidemiologic studies, dietary recall may be the method of choice. This retrospective method of dietary assessment is mostly used to gather information on food and drink consumption only over the previous day or a 24-hour period, as it relies on memory. Detailed information is gathered by interview, often by telephone.

Also widely used in epidemiologic studies is the food frequency questionnaire. The food frequency questionnaire is based on a list of food items and assesses the frequency of use over a specific time. Frequency categories ranging from “never” or “less than once monthly” to “6+ per day” are used. The aim is to assess habitual diet. Thus, foods commonly consumed in the study population, major sources of specific nutrients or foods that contribute to variability in intake between the study participants, are of interest. The food frequency questionnaires can be self-administered or interviewer-administered. For this type of questionnaire, bias for
overestimating foods perceived as healthy and underestimating unhealthy foods is common. Data support that measurement error with food frequency questionnaires is greater than with 7-day estimated food records (Bingham et al., 1997; Day et al., 2001).

The dietary checklist, observation, diet history (i.e. a structured interview enquiring about dietary habits during a past time period) and duplicate diets are methods seldom used in epidemiologic studies. The dietary checklist is a combination of an estimated food record and a food frequency questionnaire. The participant receives a list of foods to report or check, and also reports portion sizes at the time of consumption. The duplicate method refers to retaining duplicate portions of everything consumed during the day. These are weighed and later chemically analysed.

Many dietary surveys report lower than expected intakes of energy and nutrients. This may to some extent be explained by inaccurate estimates of consumed foods. The participant may also consciously or subconsciously make changes in normal dietary habits during the follow-up period (Livingstone et al., 1990). Also underreporting may occur, consciously or subconsciously (Livingstone et al., 1990).

Objective methods for evaluation of dietary intake are expensive and burdensome for the participant. Typically, nutritional biomarkers are measured from blood or urine to evaluate nutrient intakes (Arab and Akbar, 2002; Bingham, 2002). Doubly labelled water (measures EE), urinary potassium (intake of e.g. vegetables and fruits) and urinary nitrogen (protein intake) are regarded as gold standards for objective measurement of nutrient intake. Plasma carotenoids and vitamin C correspond to nutrient intake, although these measures do not reflect total nutrient intake. In addition, sodium, phytoestrogens, polyphenols and aflatoxin can be used as proxies for measuring intake. The above-mentioned biomarker-based objective measurements are mostly used for validation studies on dietary self-report methods (Bingham, 2002).

2.4 Other lifestyle factors and VLBW

Lifestyle factors are closely linked to health and disease. Knowledge on lifestyle factors in the increased-risk VLBW population is especially important, as many of these factors are modifiable and therefore possible targets for interventions. According to the latest WHO report (World Health Organization, 2009), the top 10 leading risk factors causing death in high-income countries are as follows: tobacco use (17.9%), high blood pressure (16.8%), overweight and obesity (8.4%), physical inactivity (7.7%), high blood glucose (7.0%), high cholesterol (5.8%), low fruit and vegetable intake (2.5%), urban outdoor air pollution (2.5%), alcohol use (1.6%) and occupational risks (1.1%). Of these risk factors, physical inactivity and poor dietary habits are central themes of this thesis, both of which are associated with high blood
Pressure, overweight, obesity and elevated glucose levels. Dietary habits are more closely associated with cholesterol levels and food choices.

Previous studies show differences in lifestyle between young VLBW and control adults (Kajantie and Hovi, 2014). As for tobacco, alcohol and drug use, the parents of young VLBW adults have reported lower rates of use than controls (Hack et al., 2002). In two other studies, VLBW participants smoked less cannabis and consumed less alcohol than normal birth weight controls (Cooke, 2004; Strang-Karlsson et al., 2008b). In addition, Hille et al. (2008) reported lower use of alcohol and drugs in VLBW adults, while in a slightly older study similar use of drugs and alcohol was seen in VLBW and control adults (Bjerager et al., 1995). Regarding tobacco use, the results are mixed. In some studies, VLBW subjects report less smoking (Hille et al., 2008; Strang-Karlsson et al., 2008b), whereas other studies show no difference in smoking between VLBW and control groups (Cooke, 2004; Hack et al., 2002).

Of other lifestyle factors, sleep duration of less than 6 hours daily is associated with weight gain (Xiao et al., 2013), and both the amount and quality of sleep are associated with cardiometabolic risk factors (Merikanto et al., 2013). Based on accelerometer measurement, VLBW adults have similar amounts and quality of sleep as term-born controls (Strang-Karlsson et al., 2008a). Furthermore, night owl behaviour is related to an increased risk for type 2 diabetes and higher blood pressure (Merikanto et al., 2013). Thus, the finding of a trend towards early bird behaviour in VLBW adults, based on both questionnaire (Strang-Karlsson et al., 2010) and accelerometer measurement (Strang-Karlsson et al., 2008a), may be protective.

2.5 Psychosocial stress

2.5.1 Stress response

Two interrelated pathways constitute the main stress response mechanisms in humans: 1) the HPAA and 2) the sympathetic-adrenal-medullary (SAM) system (Figure 1). In response to stress, the hypothalamus releases corticotropin-releasing hormone, which stimulates the pituitary to release adrenocorticotropic hormone (ACTH). ACTH in turn stimulates the adrenal glands. Thus, the HPAA is activated and cortisol, the end-product, is released from the adrenal cortex. Simultaneously, perceived stress activates the hypothalamus to stimulate the sympathetic nervous system, which then stimulates the adrenal medulla to release two end-products: adrenalin (A) and noradrenalin (NA). These two stress response pathways are important determinants of health and disease. The intensity of the stress responses varies between individuals and altered stress response is linked to several adverse outcomes. A hyperactive HPAA increases the risk of type 2 diabetes (McEwen, 1998), CVD (McEwen, 1998), depression (Björntorp, 1996) and metabolic...
syndrome with its components (Chrousos, 2000). Furthermore, a hyporesponsive HPAA has been linked to several conditions, including fibromyalgia, post-traumatic stress disorder, burnout and depression (Fries et al., 2005). Regarding autonomic stress response and blood pressure reactivity, evidence shows that high cardiovascular reactivity to stress predicts later development of hypertension (Treiber et al., 2003; Matthews et al., 2004; Chida and Steptoe, 2010; ), carotid atherosclerosis (Treiber et al., 2003; Matthews et al., 2006;) and increased left ventricular mass (Treiber et al., 2003). In a meta-analysis including 36 trials, the association between greater stress reactivity and poor cardiovascular risk status (including a myocardic ischaemic event, hypertension and elevated systolic or diastolic blood pressure) was clearer in men, in populations aged under 18 years and in follow-ups ≥ 3 years (Chida and Steptoe, 2010).

Later HPAA function is affected by pre- and postnatal events. Examples from animal studies show that prenatal events may program the HPAA; maternal stress during pregnancy (Weinstock, 2001; Welberg and Seckl, 2001), exposure to synthetic glucocorticoids (Matthews, 2000; Liu et al., 2001) and nutrient restriction (Hoet and Hanson, 1999; Lesage et al., 2002) all seem to affect HPAA functioning in offspring. Likewise, maternal undernutrition is a stressor for the human fetus. Based on animal studies on the effects of reduced nutrition in pregnancy on HPAA function of offspring (Hoet and Hanson, 1999; Lesage et al., 2002), it has been speculated that also in humans, maternal stress and undernutrition during pregnancy might lead to fetal programming of later HPAA function. In animal models maternal or fetal undernutrition affects the development and responses of the HPAA, blunted responses in utero swich to enhanced responses postnatially (Hoet and Hanson, 1999). The mechanisms behind these changes are unknown.

After birth, neonatal handling (Meaney et al., 2000), maternal behaviour (Meaney, 2001), exposure to synthetic glucocorticoids (Bakker et al., 2001) and infection (Nilsson et al., 2002) have effects on future HPAA functioning.
Physical activity, nutrition and stress response in young adults born preterm – determinants of health and disease

Review of the literature

2.5.2 Preterm birth and stress response

The DOHaD theory implies that early life events affect later health and disease through programming; this also seems to be true for stress responses (Kajantie and Räikkönen, 2010). It has been postulated that a hyporeactive HPAA might develop after prolonged periods of stress (Hellhammer and Wade, 1993). Prolonged stress with constant activation of the HPAA leads to long periods of elevated cortisol levels. The prolonged elevation of cortisol levels in turn lead to suppression of the HPAA through negative feedback. Pre- and postnatal stress in the VLBW neonate would thus link preterm birth with later stress response. Therefore, all types of stressful events that fetuses and preterm neonates undergo may be risk factors adversely affecting future HPAA functioning. This is supported by previously published data suggesting that fetal growth, gestational age and birth weight influence lifelong functioning of both HPAA and SAM stress response (Wüst et al., 2005; Jones et al., 2006; Buske-Kirschbaum et al., 2007; Grunau et al., 2007; Johansson et al., 2007; Kajantie et al., 2007; Grunau et al., 2010; Kajantie and Räikkönen, 2010; Brummelte et al., 2011). Neonatal intensive care after preterm birth is one example of such stress (Carbajal et al., 2008). In addition to postnatal stress, also prenatal stress may affect later HPAA function, as was shown in a study of 12 adult men and 48 women whose mothers were exposed to severe stress in the

Figure 1. Two main pathways of stress response in humans: the sympathetic-adrenal-medullary system and the hypothalamic-pituitary-adrenal axis.
form of a major life event during pregnancy. These young adults showed higher cortisol responses to the Trier Social Stress Test (TSST) than controls (Entringer et al., 2009).

More specifically, also the different types of treatment given during neonatal intensive care may alter later stress response. For example, dexamethasone was widely used to treat or prevent chronic lung disease of prematurity in the 1990s. In a study comparing children born before 32 weeks of gestation, cortisol, NA, and cardiovascular responses to Trier Social Stress Test for Children (TSST-C) at school age were all lower in those children exposed to dexamethasone treatment than in children receiving hydrocortisone treatment or in former preterm children who did not receive any corticosteroid treatment (Karemaker et al., 2008a; Karemaker et al., 2008b).

As for HPAA response to stress, previous studies have indicated lower cortisol responses in infants born preterm. For example, immunization, a stressor to the infant, provoked lower cortisol responses in 4-month-old infants born preterm (divided into subgroups according to GA: 24-28 weeks and 29-32 weeks) than in full-term infants (Grunau et al., 2010). This lower cortisol response to stress in the preterm infants was statistically significant only in boys. Grunau et al. (2007) also reported lower salivary cortisol levels in extremely preterm infants at 3 months of corrected age. In these same infants, at 8 and 18 months of corrected age the authors reported a shifting to higher cortisol levels, perhaps indicative of long-term effects of prematurity on HPAA (Grunau et al., 2007). Also among 8- to 12-year-old children born at any degree of prematurity, the cortisol response to psychosocial stress was attenuated, but not statistically significantly, in those born preterm (Buske-Kirschbaum et al., 2007). In that study, the TSST-C was used as a stressor and the participants comprised 18 preterm children and 18 same-sex friends.

Recently published data showed lower hair cortisol levels in 83 healthy children born ≤ 32 of weeks gestation compared with 45 term-born children at age 7 years (p = 0.018) (Grunau et al., 2013). Hair cortisol represents a measure of chronic HPAA activity, and also this finding suggests persisting effects of early HPAA programming.

Mechanically ventilated neonates often undergo procedures and treatments causing both pain and stress (Carbajal et al., 2008). In a follow-up study of 5-year-old children born at 24-42 weeks of gestation who were mechanically ventilated as neonates, higher cortisol levels were measured across the day than in full-term control children (Joke de Graaf et al., 2014). This finding supports the early-life programming concept of the HPAA, as production of cortisol follows a diurnal rhythm, with the highest concentrations occurring in the morning (Sherman et al., 1985). This diurnal rhythm is an important index of HPAA regulation (Rosmalen et
Physical activity, nutrition and stress response in young adults born preterm – determinants of health and disease

Review of the literature

al., 2005), and it is established during the first year of life (Tollenaar et al., 2010), in some infants even at 2 months of age (de Weerth et al., 2003).

As for birth weight, the association with HPAA stress response has been studied previously (Kajantie and Räikkönen, 2010). Lower birth weight was associated with greater salivary cortisol response in 7- to 9-year-old boys (Jones et al., 2006) as well as young, healthy male twins (Wüst et al., 2005). In the twin study, a trend for higher cortisol responses was seen in participants born at an earlier GA. Contrary to those two studies, in 60- to 70-year-old adults TSST provoked lower cortisol and ACTH response in those born with a lower birth weight, mostly after term pregnancy (Kajantie et al., 2007). However, data on HPAA stress reactivity in adults born preterm are scarce, and the results have been mixed (Kajantie and Räikkönen, 2010).

Some data on SAM response to stress in preterm children have been published. For example, after immunization, heart rate (HR) responses were similar in 4-month-old infants born at GA 24-28 weeks, at GA 29-32 weeks and at term (Grunau et al., 2010). Furthermore, in 9- to 10-year-old children, both preterm birth (n=39) and fetal growth restriction (n=29) were associated with increased SAM activity, as indicated by urinary catecholamine and HR responses after a mathematical mental stress (Johansson et al., 2007). After TSST-C, HR responses to stress in 8- to 12-year-old children were similar in former preterm infants and controls infants (Buske-Kirschbaum et al., 2007).

Previously reported from our HeSVA cohort, diastolic blood pressure responses to psychosocial stress were higher in young adult VLBW participants (Pyhälä et al., 2009). Also slightly higher resting HR was found in the HeSVA cohort VLBW participants in conjunction with a clinic visit (Hovi et al., 2007). Previously published data on SAM response to stress in adults born preterm are scarce.

2.5.3 Measuring stress response

Stress response tests can be divided into a) psychosocial stressors and b) physiological stressors. The psychosocial stressors include mental arithmetics, mirror drawing or other cognitive tasks and public speaking (Dickerson and Kemeny, 2004). Of the different psychosocial stressors, the TSST has been reported to most consistently stimulate the HPAA (Kirschbaum et al., 1993). This test measures response to moderate psychosocial stress in a laboratory setting. It includes a 5-minute anticipation period and a 10-minute test period (Kirschbaum et al., 1993). During the test the participant delivers an unprepared speech and performs mental arithmetic tasks in front of an evaluation committee (Evaluation Committee, Figure 2). A modified version of the test has been developed specifically for children, the TSST-C (Buske-Kirschbaum et al., 1997). Key factors of the TSST, as well as other psychosocial stressors, are the participant’s feelings of uncontrollability and social-
evaluative threat or judgement (Dickerson and Kemeny, 2004). This stimulates the participant to undergo strong feelings of discomfort and stress and triggers the release of ACTH, cortisol, A and NA.

Figure 2. The TSST evaluation committee at work.

The cold pressor test, exercise testing and nutritional challenge (e.g. intake of standardized meals) are examples of physiological stressors (Kudielka et al., 2009). The cold pressor test is performed by having the participant’s hand immersed in cold water (0-5°C) for 1-6 minutes. This procedure provokes a vascular sympathetic response with increased peripheral resistance. As a result, elevations in blood pressure (Greene et al., 1965; Victor et al., 1987) and changes in HR (Mourot et al., 2009) are observed. Another type of physiological stressor, intense physical exercise, elicits significant cortisol responses, and in contrast to psychological stressors, no strong habituation effect is seen in exercise-induced cortisol responses (Kudielka et al., 2009). Cortisol also increases after meals, and the level of cortisol response varies with the time of day, with higher rises in lunchtime than in evening responses (Brandenberger et al., 1982; Follenius et al., 1982; Quigley and Yen, 1979).

A variety of pharmacological stimulants, such as vasopressin, synthetic ACTH or corticotropin-releasing hormone, are also used to stimulate HPAA stress response (Kudielka et al., 2009). Such pharmacological challenges measure HPAA response at different levels of the HPAA system, and they are dose-dependent in assessing, for example, adrenal cortex sensitivity (low dose of synthetic ACTH) or capacity (high dose of synthetic ACTH) (Kudielka et al., 2009).

Exposure to the different types of stressors results in different physiological responses. As a result of habituation, the stress response also tends to attenuate after
repeated exposure to the same psychosocial stressor (Dickerson and Kemeny, 2004; Kudielka et al., 2009). Furthermore a multitude of factors, including age, gender, menstrual cycle phase, medications (e.g. hormonal contraception and hormone replacement therapy), pregnancy, lactation, breast-feeding, nicotine, coffee, alcohol, dietary energy supply, time of testing, early life stress experiences and genetic and personality factors, affects especially cortisol responses to stress (Kudielka et al., 2009).
3 Aims of the study

The general aim of this study was to evaluate mechanisms underlying the link between preterm birth and later health, focusing on stress response and lifestyle, more specifically physical activity, dietary habits and nutrition. The general hypothesis was that differences between former preterm and term-born adults exist, and these may in part explain the increased risk factors for chronic non-communicable diseases in former preterm, very low birth weight adults.

Specific aims were as follows:

1. To investigate whether preterm birth at very low birth weight affects physical activity in young adulthood (Studies I and II). Special attention was directed to conditioning leisure-time physical activity.
2. To explore dietary habits and nutrition intake in young adults born preterm at very low birth weight (Study III).
3. To determine whether very low birth weight is associated with changes in hypothalamic-pituitary-adrenal axis (Study IV) and sympathetic-adrenal-medullary system (Study V) responses to psychosocial stress in young adulthood.
Subjects and methods

4.1 Study population
All participants of the studies were derived from the HeSVA, a follow-up, case-control cohort (Figure 3). During 1978-1985 a total of 474 VLBW infants were admitted to the NICU of Children’s Hospital, Helsinki University Central Hospital. All tertiary neonatal care in the province of Uusimaa in southern Finland is centralized to this NICU. Of the 474 VLBW infants admitted to the NICU, 71% (335) survived. They were discharged from the hospital and followed up during infancy and childhood (Järvenpää and Granström, 1987).

These VLBW subjects were traced using data provided by the Population Register Centre of Finland. For each VLBW subject, a control was selected based on hospital records. From the same birth hospital in which the VLBW participant was born, the next person who was born full-term, singleton, not SGA and of the same sex as the VLBW participant was chosen as a control. During 2004-2005 those 255 VLBW and 314 control subjects living in the greater Helsinki area (within 110 km of the study clinic) were invited to participate in a clinical study. Of those invited, 166 VLBW (65%) and 172 controls (55%) chose to participate (Study III). A follow-up study was carried out during 2007-2008. To the follow-up, we invited participants of the first visit, excluding 25 individuals for the following reasons: developmental delay (n =1), earlier refusal of future contact (n =4), living abroad (n =11), being untraceable (n= 2) and being ineligible for the glucose metabolism studies included in the follow-up visit (n= 7; pregnancy, medication, type 1 diabetes). Thus, 159 VLBW and 154 control subjects were invited. Of these, 113 VLBW (71%) and 105 controls (68%) chose to participate (Studies I, II, IV, V).

The clinical study visits were carried out in collaboration with the Children’s Hospital, Helsinki University Central Hospital, the National Institute for Health and Welfare, and the Institute of Behavioural Sciences, University of Helsinki.

4.2 Measures

4.2.1 Background characteristics
Maternal and perinatal data were collected from maternal welfare clinics, hospital records and well-baby clinic records. During the clinical study visits the participants completed questionnaires covering medical history, current illnesses, use of medications and smoking habits. Information regarding schooling and family socio-economic status was gathered by self-report. In Studies I-V, the highest parental education of either parent is used as a proxy of childhood socio-economic status.
**Figure 3.** Flow chart of the Helsinki Study of Very Low Birth Weight cohort. Subgroups of the original cohort participated in Studies I-V.
4.2.2 Assessment of physical activity based on self-report (Study I)

In the two studies on physical activity, we assessed physical activity by both self-report (Study I) and objective measurement (Study II). In Study I, we used the modified Kuopio Ischaemic Heart Disease Risk Factor Study (KIHD) questionnaire for assessing physical activity habits. The KIHD questionnaire has been shown to be reproducible and valid in several different populations (De Backer et al., 1981; Jacobs et al., 1993; Lakka and Salonen, 1992; Lakka and Salonen, 1993). This questionnaire includes a 30-item list of different physical activity types, and it collects data on the previous 12-month period. The participant could also add physical activity types not included in the 30-item list. The participant was to report monthly frequency and duration of each physical activity during the previous 12 months. The self-reported monthly data were then transformed into units of times/year (frequency), and the duration of each physical activity session was summed and transformed into units of minutes/year (total time). The participant was also asked to report the intensity of each physical activity on a scale from 0-3 (0 = light, 1 = moderate, 2 = strenuous and 3 = very strenuous). These self-rated physical activity intensities were transformed into METs by use of standardized activity-specific tables (Ainsworth et al., 1993; Ainsworth et al., 2000). By definition, a MET equals the ratio of metabolic rate during exercise to metabolic rate at rest. Roughly, 1 MET corresponds to an EE of approximately 1 kcal/kg/hour. This is approximately equivalent to the energy cost of sitting quietly. We then used the MET values to calculate the total volume of physical activity (METh/year) as follows: MET x hours of physical activity / year. Yearly EE (kcal/year) was calculated as total time of physical activity (min/year) x MET (kcal/kg/min/year) x weight (kg).

The KIHD questionnaire further divides physical activity into commuting to work (walking and cycling), conditioning LTPA and non-conditioning LTPA. For conditioning LTPA, 20 different types of sports participation, e.g. running, swimming and skiing, are included in the questionnaire. For non-conditioning LTPA, 8 activities other than sports participation requiring physical efforts, e.g. shoveling snow, gardening and household chores, are included. Based on MET values, physical activity was additionally categorized into vigorous physical activity if MET ≥ 5. We separately looked at vigorous conditioning LTPA, vigorous non-conditioning LTPA and vigorous commuting activity.

The KIHD questionnaire was completed by the participants during the second clinical visit in 2007-2008. Of the 113 VLBW and 105 control study visit participants, 12 and 3, respectively, did not complete the KIHD questionnaire. Of the 101 VLBW and 102 control participants with data available, 7 and 1 participant, respectively, were excluded due to CP, developmental delay, hearing deficit,
blindness or another condition affecting mobility. Thus, 94 VLBW and 101 controls were included in the analyses of Study I.

4.2.2.1 Adjustment for lean body mass
We had information on lean body mass (total body mass – fat and bone mass) in a subset of the participants of Study I (91 VLBW and 88 control participants). During the first clinical study visit, in 2004-2005, these subjects had their body composition measured by dual-energy x-ray absorptiometry (DXA, Discovery A, Hologic, Hologic Inc., Bedford, MA, USA). The DXA scan required a separate visit, and not all study participants were willing to undergo DXA. This information on lean body mass was used in additional analyses as body composition is an important covariate in analyses of physical activity.

4.2.2.2 Adjustment for personality
Individual personality traits are linked to physical activity. In the analyses of Study I, we utilized information on personality traits of the participants assessed at the first clinical study visit in 2004-2005. At that time, the participants completed the NEO-Personality Inventory (Costa and McCrae, 1985). This is a 180-item inventory based on the Big Five taxonomy. The Big Five is the most commonly used classification of personality traits (agreeableness, conscientiousness, extraversion, neuroticism and openness to experience). The 180 items are rated on a 5-point scale (0 = very untrue, 4 = very true). Data on personality traits were available for 90 VLBW and 98 control participants.

4.2.3 Assessment of physical activity based on accelerometer measurements (Study II)
To objectively assess physical activity, we used a wrist-worn accelerometer, the Actiwatch AW4 model (Cambridge Neurotechnology Ltd., UK). The AW4 registers body movements as minute-by-minute activity counts (cpm, counts per minute) and is a validated tool for measuring physical activity in free living subjects (Heil et al., 2009).

The participants were instructed to wear the accelerometer on the non-dominant wrist for at least three days. It was to be removed only when showering, bathing or swimming. Simultaneously with the accelerometer recording, the participants kept a sleep log for reporting bedtimes and awakening times. They also registered getting up and bedtimes on the accelerometer by pressing a button. We used 1-min epochs in the scoring and analysed data between 8:00 and 24:00, excluding times in bed and times not wearing the accelerometer. Analysis started upon getting up and ended at bedtime. To be included in the analyses, we required a minimum of 600 min/day of wearing the accelerometer and ≥ 3 days of recording. We further separately analysed
Subjects and methods

4.2.4 Assessment of nutrition and diet (Study III)

To assess dietary intake we used the 3-day food record. Among the various self-report methods for estimating dietary intake, the 3-day food record is considered one of the most reliable (Prentice et al., 2011). During the clinical study visit a study nurse instructed the participants on completion of the food record. The participants were instructed to report everything they ate and drank during 3 consecutive days. This 3-day period was to include 2 workdays and 1 day off. The participants used a picture booklet of portion sizes for estimating the amounts of food consumed. Estimating portion size with the aid of a picture booklet gives more accurate estimations of the amounts of food consumed (Ovaskainen et al., 2008). At the time of returning the food record, a trained nutritionist interviewed the participant to ensure completeness of the 3-day food record.

From the 3-day food record, information regarding all intakes of foods and drinks was collected. Using a dietary analysis program based on the FINELI database (Finnish Food Composition Database) (Ovaskainen et al., 1996), mean daily energy intake, amounts of foods consumed and macronutrient and micronutrient intakes were calculated. The FINELI database was developed at the National Public Health Institute, and it includes 987 food items and 1622 composite dishes.

Of the 338 individuals who participated in the first clinical study during 2004-2005, 155 VLBW and 156 controls completed the food record data. Of these, 4 VLBW participants were excluded from the analyses due to incomplete food record data. Thus, Study III included 151 VLBW and 156 control participants.
4.2.5 Psychosocial stress responses (Studies IV and V)

To assess stress response, we used a standardized stressor, the TSST. The TSST measures response to moderate psychosocial stress in a laboratory setting (Kirschbaum et al., 1993). The test includes a 5-min anticipation period and a 10-min test period. During the test the participant delivers an unprepared speech to apply for a job and performs arithmetic tasks in front of a two-person evaluation committee (Figure 2). The arithmetic task starts with calculating 2023-17-17-17… and, if needed, the difficulty of the task is modified according to the mathematic abilities of the participant. To maximize the unpleasantness of the situation, the committee minimizes all verbal and non-verbal communication with the participant.

The TSST was performed between 10:45 and 16:10, and in the analyses we adjusted for the time of day (dummy-coded based on when the TSST began: 10:50, 12:05 or 13:20). The participants were to refrain from eating and drinking 2 h before the test. An intravenous line was inserted 45 min prior to the beginning of the TSST for collection of blood samples. Blood was drawn and salivary samples were collected at baseline (15-30 min before the test) and at 0, 10, 20, 30, 45, 60 and 90 min after the TSST (Figure 4). HPAA and SAM stress response was evaluated by repeated biomarker measurements. Plasma and salivary cortisol were measured at all eight time-points. Plasma ACTH was measured from the four first time-points, as it returns faster to pre-stress levels. Plasma insulin and glucose were measured at baseline, 0, 20 and 90 min, while A and NA samples were collected at baseline, 0, 10 and 90 min. All samples were immediately frozen to -20 °C and transferred once a week to -70 °C for storage until the time of analysis.

Plasma cortisol concentrations were determined by ELISA (ImmunoBiological Laboratories, Hamburg, Germany) and salivary cortisol concentrations by competitive solid-phase, time-resolved fluorescence immunoassay with fluorometric endpoint detection (DELFIA, Wallac, Turku, Finland). ACTH was determined by chemiluminescence immunofluorometric assay (Nichols Institute Diagnostics, San Clemente, CA, USA). Cortisol and ACTH measurements were assayed in duplicate at the University of Trier, Germany. Plasma insulin concentrations were determined by Immunotech Insulin(e) IRMA kit (Beckman Coulter Inc., Prague, Czech Republic). Glucose concentrations were determined by an enzymatic hexokinase method (Gluco-quant®, Roche Diagnostics, Tokyo, Japan). Plasma A and NA concentrations were determined by high-performance liquid chromatography (HPLC, ChromSystems diagnostics by HPLC, München, Germany).
Subjects and methods

Figure 4. The TSST was performed between 10:45 and 16:10 applying the above schedule.

In addition to the above-described biomarker measurements, we also measured HR response to stress in conjunction with the TSST. A continuous beat-to-beat monitoring of HR during baseline and task was conducted by ECG. We averaged all HR readings, as mental stress measures for cardiovascular activity are more reproducible when responses to individual tasks are aggregated (Kamarck and Lovallo, 2003). In line with a previous report on blood pressure response to TSST in the same cohort of participants (Pyhälä et al., 2009), mean HR was reported 1) during the 5-min baseline, 2) during the 10-min task period (speech and arithmetic) and 3) as HR reactivity (task response, i.e. task average minus baseline average). The recording of HR data was performed with Biopac AcqKnowledge 3.8.1 software (Santa Barbara, CA, USA).

The TSST was performed on a subset of the original HeSVA cohort. A random sample among the participants of the first clinical visit in 2004-2005 was invited to the TSST in 2005. From the randomization process, we excluded subjects who 1) were unable to stand or to manage without an assistant, 2) used glucocorticoids or 3) had a nightshift during the previous week. A total of 54 VLBW (28 women, 52%) and 40 controls (23 women, 56%) attended the TSST and were included in the analyses of Study IV. Of these TSST participants, 50 VLBW (28 women, 56%) and 39 controls (22 women, 56%) had adequate blood samples for also analysing A and NA responses to stress and were thus included in the analyses of Study V.
4.3 Statistical analyses

Statistical analyses were conducted with SPSS for Windows versions 17, 19 or 21 (SPSS Inc., Chicago, IL, USA) and R 2.8.1 (R Foundation for Statistical Computing, Vienna, Austria).

In all studies, descriptive characteristics between VLBW and control groups were compared with independent samples t-test (continuous variables) and \( \chi^2 \)-test (categorical variables). In all analyses, a p-value < 0.05 was considered significant. We explored interactions between gender and birth status by entering an interaction term (sex*VLBW/control) into the statistical models. If no significant interaction was found, the results were presented with men and women combined.

In the self-report-based study on physical activity (Study I), all outcome variables were log-transformed \( \left[ 10 \log(\text{variable}+1) \right] \) to attain normality. We used multiple linear regression to compare yearly frequency, total time, total volume and EE of conditioning, non-conditioning commuting and vigorous physical activity (MET ≥ 5). Adjustment was made for common confounders (age, sex, BMI, daily smoking, highest parental education). In further analyses, adjustment for personality based on the mean scores of the NEO-Personality Inventory was performed. In the subgroup with data available, we reran all analyses after replacing BMI with body composition (lean body mass, measured by DEXA). The results are presented as mean differences (%) and 95% confidence intervals (CIs) between VLBW and control groups. In addition, the influence of each personality trait on conditioning LTPA was analysed by incorporating each trait one at a time into the linear regression model. The influence of each personality trait is presented as a correlation coefficient.

In the physical activity study based on accelerometer measurement (Study II), a linear regression model adjusted for common confounders (age, sex, season, BMI, smoking, SES) was used to compare physical activity between VLBW and control groups. Season was dummy-coded as follows: December-February, March-May, June-August and September-November. The results are presented as mean differences in activity cpm registered by the accelerometer, with 95% CI between VLBW and control participants. We also compared differences in the intensity of physical activity after dividing physical activity into sedentary time (< 1.5 METs, < 320 cpm), moderate physical activity (3-6 METs, 1048 -1624 cpm), vigorous physical activity (> 6 METs, > 1624 cpm) and moderate-to-vigorous physical activity (MVPA, ≥ 3 METs, ≥ 1048 cpm). These cut-off points are based on a validation study in 8- to 10-year-old children as to date such validation studies have not been conducted in adults (Ekblom et al., 2012).

In the study on dietary habits and nutrition (Study III), a linear regression model was used to compare differences in daily food and nutrient intakes. For easier
interpretation, the results are presented as mean daily food and nutrient intakes in VLBW and control groups.

In Studies IV and V, all biomarker concentrations were log-transformed to attain normality. A mixed-effects model was used to analyse the biomarker responses to stress. We also used a linear regression model to compare differences between VLBW and control groups in commonly used indicators of stress response, i.e. baseline, peak, relative increment (peak after stress / baseline value) and areas under the curve ground (AUCg), calculated as described elsewhere (Kajantie et al., 2007). Age, sex, BMI, hormonal contraception, time of day (dummy-coded based on time when TSST began: 10:50, 12:05 or 13:20) and highest parental education were adjusted for in all analyses. In addition, we further adjusted for menstrual cycle phase. We divided the women with data available on menstrual cycle phase into two groups (cycle phase days 1-8 and days ≥9). Only the women not using hormonal contraception were included in the two groups. In addition to examining gender interactions (sex*VLBW/control group), we assessed interactions by including an interaction term with sampling time (time*VLBW/control group) and (sex*time*VLBW/control group).

4.4 Ethics
This study was performed according to the Declaration of Helsinki guidelines. The study protocol was approved by the Ethics Committee of the Helsinki and Uusimaa Hospital District. Written informed consent was obtained from each participant.
5 Results

5.1 Description of study participants
Different subgroups from the HeSVA cohort participated in the five studies included in this thesis. For comparison, characteristics of the different subgroups in Studies I-V are presented in Table 2. As adults, the VLBW participants were shorter and had lower lean body mass than controls. Daily smoking was more common among controls.

A summary of the main results is shown in Table 3.
Table 2. Descriptive characteristics of the subgroups participating in Studies I-V.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Study I VLBW (n = 94)</th>
<th>Study I Term (n = 101)</th>
<th>Study II VLBW (n = 57)</th>
<th>Study II Term (n = 47)</th>
<th>Study III VLBW (n = 151)</th>
<th>Study III Term (n = 156)</th>
<th>Study IV-V VLBW (n = 54)</th>
<th>Study IV-V Term (n = 40)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Birth</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gestational age, mean (SD), weeks</td>
<td>29.5 (2.3)</td>
<td>40.1 (1.1)</td>
<td>29.3 (2.5)</td>
<td>40.1 (1.1)</td>
<td>29.2 (2.3)</td>
<td>40.1 (1.2)</td>
<td>29.4 (2.3)</td>
<td>40.2 (1.1)</td>
</tr>
<tr>
<td>Birth weight, mean (SD), grams</td>
<td>1157 (208.7)</td>
<td>3608 (492.0)</td>
<td>1116 (215.5)</td>
<td>3648 (499.0)</td>
<td>1111 (221)</td>
<td>3595 (472)</td>
<td>1103 (212.4)</td>
<td>3639 (455.6)</td>
</tr>
<tr>
<td>Birth weight SDS, mean (SD)</td>
<td>-1.3 (1.5)</td>
<td>0.1 (1.1)</td>
<td>-1.4 (1.6)</td>
<td>0.2 (1.1)</td>
<td>-1.4 (1.5)</td>
<td>0.1 (1.0)</td>
<td>-1.5 (1.5)</td>
<td>0.1 (1.0)</td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>57 (60.6)</td>
<td>59 (58.4)</td>
<td>35 (61.4)</td>
<td>32 (68.16)</td>
<td>60 (39.7)</td>
<td>60 (38.5)</td>
<td>26 (48.1)</td>
<td>17 (42.5)</td>
</tr>
<tr>
<td>Men, n (%)</td>
<td>37 (39.4)</td>
<td>42 (41.6)</td>
<td>22 (38.6)</td>
<td>15 (31.9)</td>
<td>54 (35.8)</td>
<td>0</td>
<td>23 (42.6)</td>
<td>0</td>
</tr>
<tr>
<td>SGA b, n (%)</td>
<td>35 (37.2)</td>
<td>0</td>
<td>21 (36.8)</td>
<td>0</td>
<td>12 (21.2)</td>
<td>11 (7.1)</td>
<td>12 (22.2)</td>
<td>4 (10.0)</td>
</tr>
<tr>
<td>Preeclampsia, n (%)</td>
<td>24 (25.5)</td>
<td>9 (8.9)</td>
<td>10 (18.2)</td>
<td>3 (6.5)</td>
<td>5 (3.3)</td>
<td>0</td>
<td>5 (1.9)</td>
<td>0</td>
</tr>
<tr>
<td>Twin, n (%)</td>
<td>14 (14.9)</td>
<td>0</td>
<td>6 (10.9)</td>
<td>0</td>
<td>21 (13.9)</td>
<td>0</td>
<td>7 (13.0)</td>
<td>0</td>
</tr>
<tr>
<td>Triplet, n (%)</td>
<td>2 (2.1)</td>
<td>0</td>
<td>2 (3.6)</td>
<td>0</td>
<td>5 (3.3)</td>
<td>0</td>
<td>1 (1.9)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Current</strong></td>
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<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Age, mean (SD), years</td>
<td>24.9 (2.1)</td>
<td>25.1 (2.2)</td>
<td>24.6 (2.0)</td>
<td>24.9 (2.2)</td>
<td>22.4 (2.1)</td>
<td>22.5 (2.2)</td>
<td>23.1 (2.2)</td>
<td>23.5 (2.0)</td>
</tr>
<tr>
<td>Height, mean (SD), cm</td>
<td>163.0 (7.4)</td>
<td>166.4 (6.2)</td>
<td>163.9 (7.2)</td>
<td>166.5 (6.5)</td>
<td>162.0 (7.6)</td>
<td>167.4 (6.6)</td>
<td>161.5 (6.9)</td>
<td>165.7 (6.7)</td>
</tr>
<tr>
<td>Women</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>176.2 (7.2)</td>
<td>180.8 (6.1)</td>
<td>173.7 (6.7)</td>
<td>180.9 (5.0)</td>
<td>174.1 (8.1)</td>
<td>180.6 (6.4)</td>
<td>174.3 (8.2)</td>
<td>180.2 (4.9)</td>
</tr>
<tr>
<td>Men</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

Footnotes are on the page following Table 2.
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Study I VLBW (n = 94)</th>
<th>Term (n =101)</th>
<th>Study IIa VLBW (n =57)</th>
<th>Term (n =47 )</th>
<th>Study III VLBW (n =151)</th>
<th>Term (n =156)</th>
<th>Study IV-V VLBW (n =54)</th>
<th>Term (n =40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body mass index, mean (SD), kg/m²</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>21.8 (3.7)</td>
<td>22.9 (4.3)</td>
<td>22.7 (4.5)</td>
<td>23.9 (5.5)</td>
<td>22.2 (4.0)</td>
<td>22.8 (3.8)</td>
<td>21.7 (3.3)</td>
<td>23.7 (4.6)</td>
</tr>
<tr>
<td>Men</td>
<td>22.4 (3.5)</td>
<td>23.0 (2.9)</td>
<td>22.8 (4.0)</td>
<td>24.2 (3.2)</td>
<td>21.9 (3.7)</td>
<td>23.5 (3.2)</td>
<td>22.3 (4.2)</td>
<td>23.9 (3.1)</td>
</tr>
<tr>
<td>Daily smoking, n (%)</td>
<td>15 (16.0)</td>
<td>31 (30.7)</td>
<td>7 (12.3)</td>
<td>12 (25.5)</td>
<td>31 (20.8)</td>
<td>46 (29.5)</td>
<td>19 (35.2)</td>
<td>10 (25.0)</td>
</tr>
<tr>
<td>Parental education, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elementary</td>
<td>8 (8.5)</td>
<td>5 (5.0)</td>
<td>5 (8.8)</td>
<td>3 (6.4)</td>
<td>15 (10.1)</td>
<td>11 (7.1)</td>
<td>5 (9.3)</td>
<td>3 (7.5)</td>
</tr>
<tr>
<td>High school</td>
<td>21 (22.3)</td>
<td>19 (18.8)</td>
<td>17 (29.8)</td>
<td>9 (19.1)</td>
<td>30 (20.3)</td>
<td>28 (18.1)</td>
<td>14 (25.9)</td>
<td>4 (10.0)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>32 (34.0)</td>
<td>33 (32.7)</td>
<td>14 (24.6)</td>
<td>15 (31.9)</td>
<td>62 (41.9)</td>
<td>51 (32.9)</td>
<td>19 (35.2)</td>
<td>15 (37.5)</td>
</tr>
<tr>
<td>University</td>
<td>33 (35.1)</td>
<td>44 (43.6)</td>
<td>21 (36.8)</td>
<td>20 (42.6)</td>
<td>41 (27.7)</td>
<td>65 (41.9)</td>
<td>16 (29.6)</td>
<td>18 (45.0)</td>
</tr>
</tbody>
</table>

a Of the participants in Study I 50 VLBW (53%) and 46 controls (46%) also participated in Study II.
b small for gestational age, birth weight < -2SD
Table 3. Summary of the main results for Studies I-V.

<table>
<thead>
<tr>
<th>Study</th>
<th>VLBW / Term (n)</th>
<th>Main outcome</th>
<th>Method</th>
<th>Main results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study I</td>
<td>94 / 101</td>
<td>Physical activity</td>
<td>Questionnaire (Kuopio Ischemic Heart Disease Risk Factor Study Questionnaire)</td>
<td>Markedly lower yearly frequency, total time, total volume and energy expenditure of conditioning leisure-time physical activity in VLBW adults.</td>
</tr>
<tr>
<td>Study II</td>
<td>57 / 47</td>
<td>Physical activity</td>
<td>Accelerometer (Actiwatch AW4)</td>
<td>No statistically significant difference in physical activity between VLBW and control groups.</td>
</tr>
<tr>
<td>Study III</td>
<td>151 / 156</td>
<td>Diet and nutrition</td>
<td>3-day food record</td>
<td>Lower consumption of milk products, vegetables, fruits and berries in VLBW adults, accompanied by a lower intake of calcium and vitamin D.</td>
</tr>
<tr>
<td>Study IV</td>
<td>54 / 40</td>
<td>Psychosocial stress response</td>
<td>Trier Social Stress Test</td>
<td>Overall lower plasma cortisol reactivity and lower cortisol peak after stress in VLBW adults</td>
</tr>
<tr>
<td>Study V</td>
<td>50 / 39</td>
<td>Psychosocial stress response</td>
<td>Trier Social Stress Test</td>
<td>Overall adrenalin, noradrenalin and heart rate responses to stress were not significantly different between VLBW and control adults. For VLBW-women, noradrenalin reactivity after stress was lower.</td>
</tr>
</tbody>
</table>
5.2 Conditioning leisure-time physical activity is lower in VLBW adults (Study I)

Based on the modified KIHD questionnaire, we evaluated yearly frequency, total time, total volume and EE of conditioning LTPA, non-conditioning LTPA, vigorous physical activity and commuting physical activity. All dimensions of conditioning LTPA were lower in VLBW participants (Table 4). For non-conditioning LTPA, vigorous physical activity or commuting physical activity, this difference was not statistically significant in the fully adjusted model (Table 4). Further adjusting for personality traits slightly increased the difference in yearly frequency [-48.1% (95% CI: -64.8, -23.6)], total time [-60.5% (95% CI: -77.7, -30.2)], total volume [-54.9% (95% CI: -71.6, -28.4)] and EE [-68.4% (95% CI: -84.0, -37.2)] of conditioning LTPA.

No significant difference in physical activity was present between those 19 VLBW participants with a history of BPD and the remaining 75 VLBW participants without BPD. Furthermore, all results remained similar after we re-analysed the data after excluding those 16 VLBW and 6 control participants with a history of asthma.

We evaluated the effects of personality on physical activity by incorporating personality scores one by one into the linear regression model. Extraversion and agreeableness had a positive correlation and neuroticism a negative correlation with all dimensions of conditioning LTPA (yearly frequency, total time, total volume and EE). Openness to experience had a positive correlation and extraversion a negative correlation with commuting physical activity. The five personality traits did not have any significant correlations with non-conditioning LTPA. Furthermore, conscientiousness was not correlated with any measured type of physical activity. A significant interaction was found between extraversion and birth status on total volume and EE of conditioning LTPA. No other interactions were found between personality traits and birth status on conditioning LTPA.

Of the VLBW participants, 35 (37%) were born SGA and 59 (63%) AGA. We reran all analyses comparing the SGA (Pihkala et al., 1989) and AGA VLBW participants. No significant differences in physical activity emerged.

Guidelines on physical activity for adults recommend at least 150 min/week of moderate PA (Physical Activity Guidelines Advisory Committee, 2008; World Health Organization, 2010). This criteria was fulfilled by 55.3% of VLBW and 57.4% of control participants (p = 0.77 and p = 0.73, adjusted, unpublished results).
Table 4. Mean difference (%) and 95% CI between VLBW (n = 94) and control (n = 101) participants.

<table>
<thead>
<tr>
<th>Activity</th>
<th>Frequency (times/year)</th>
<th>Total time (min/year)</th>
<th>Total volume (METh/year&lt;sup&gt;a&lt;/sup&gt;)</th>
<th>Energy expenditure (kcal/year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conditioning leisure-time physical activity</td>
<td>-38.5 (-58.9, -7.7)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>-47.4 (-71.2, -4.1)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>-44.3 (-65.8, -9.2)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>-55.9 (-78.6, -9.4)&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Non-conditioning leisure-time physical activity</td>
<td>-4.5 (-34.5, 39.6)</td>
<td>-4.3 (-49.2, 79.9)</td>
<td>-8.4 (-41.3, 43.2)</td>
<td>-12.1 (-57.0, 79.9)</td>
</tr>
<tr>
<td>Commuting physical activity</td>
<td>6.2 (-48.7, 119.8)</td>
<td>16.9 (-60.5, 246.7)</td>
<td>6.7 (-56.6, 162.4)</td>
<td>14.3 (-68.2, 314.0)</td>
</tr>
<tr>
<td>Vigorous physical activity&lt;sup&gt;b&lt;/sup&gt;</td>
<td>-34.7 (-58.0, 1.9)</td>
<td>-8.8 (-21.3, 5.7)</td>
<td>-9.2 (-21.7, 5.4)</td>
<td>-55.3 (-80.1, 0.5)</td>
</tr>
</tbody>
</table>

<sup>a</sup> MET x hours of physical activity / year (MET = metabolic equivalents; ratio of metabolic rate during exercise and estimated metabolic rate at rest; 1 MET corresponds to energy expenditure of approximately 1 kcal/ kg x hour)

<sup>b</sup> physical activity with MET ≥ 5

<sup>c</sup> p < 0.05

Predicted by linear regression and adjusted for age, sex, body mass index, daily smoking of the participant and highest education of either parent.
5.3 Lack of difference in physical activity by objective measurement in VLBW adults and controls (Study II)

Both VLBW and control participants spent the majority of the day in sedentary activity (521 min/day vs. 508 min/day, p for difference 0.6). Time spent in sedentary or moderate activity was not significantly different between VLBW and control groups (Table 5). Neither did daily MVPA significantly differ between groups (37 min vs. 45 min, p = 0.4). The VLBW participants undertook slightly less vigorous physical activity [-5.8 min/day (95% CI: -13.1, 1.5)] and MVPA [-8.3 min/day (95% CI: -25.7, 9.1)], although these differences did not attain statistical significance.

As expected, daily physical activity varied with season. During wintertime both groups were least active. Daily total physical activity was not significantly different between VLBW and control participants [-18.9 cpm (95% CI: -77.3, 39.5)] after adjustment for age, sex, season, BMI, daily smoking and highest parental education (Table 5). No significant difference between groups was seen in physical activity when analysed separately for weekdays [-15.5 cpm (95% CI: -76.8, 45.9)] and weekends [-40.4 cpm (95% CI: -109.3, 28.6)] (Table 5).

5.4 Unhealthier dietary intake in VLBW adults (Study III)

We found lower intakes of all milk products, low-fat (≤2%) dairy products and vegetables, fruits and berries in VLBW adults than in controls. High-fat (> 2%) dairy product intake and intake of pasta, potatoes and rice were not significantly different in the fully adjusted model. Consumption of meat, fish, fat spreads, sugared beverages, bread, cereals, sugar and sweets was similar in both groups. Detailed information on food intake is shown in Table II, Study II (Kaseva et al., 2013).

The macro- and micronutrient intakes of participants are shown in detail in Table 6. For comparison, the new 2014 Finnish nutrition recommendations are also provided (National Nutrition Council, 2014). In brief, no significant differences were seen in carbohydrate, protein or fat intakes between VLBW and control participants. VLBW participants showed lower intakes of calcium, vitamin D, vitamin C, zinc, iodide and magnesium. The acquisition of polyunsaturated fatty acids was higher in VLBW participants, while the daily intake of cholesterol was lower in VLBW participants [189 mg (74) vs. 227 mg (105), p = 0.002]. The daily cholesterol dose recommended by the Finnish Heart Association is ≤ 300 mg, while the National Nutrition Council no longer provides daily recommendations on intake of cholesterol. In both VLBW and control participants, intakes of carbohydrates, protein and fat were within recommended daily levels (National Nutrition Council, 2014). Daily intakes of sucrose, saturated and transfatty acids and salt were higher than recommended, while the intakes of fiber, magnesium, vitamin D and folate were lower than recommended in both groups (National Nutrition Council, 2014).
The daily intake of polysaturated fatty acids was slightly lower than recommended in controls only.

Of the VLBW participants, 54 (36%) were born SGA (Pihkala et al., 1989). In line with our previous studies, we reran all analyses comparing the SGA and AGA VLBW participants. The daily intake of cholesterol was higher in SGA participants [204 (80) mg vs. 180 (70) mg, p = 0.03]. No other significant differences in macro- or micronutrient intake emerged.

**Table 5.** Daily physical activity presented as mean differences (95% CI) between VLBW and control participants. Predicted by linear regression and adjusted for covariates in models 1 and 2.

<table>
<thead>
<tr>
<th>Physical activity</th>
<th>Model 1</th>
<th></th>
<th>Model 2</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily physical activity, mean cpm</td>
<td>-16.5 (-77.5, 44.5)</td>
<td>Model 1: adjusted for age, sex and season</td>
<td>-18.9 (-77.3, 39.5)</td>
<td>Model 2: adjusted for age, sex, season, body mass index, daily smoking of the participant and highest education of either parent.</td>
</tr>
<tr>
<td>Daily physical activity on weekdays only, mean cpm</td>
<td>-15.4 (-79.3, 48.6)</td>
<td>Model 1: adjusted for age, sex and season</td>
<td>-15.5 (-76.8, 45.9)</td>
<td>Model 2: adjusted for age, sex, season, body mass index, daily smoking of the participant and highest education of either parent.</td>
</tr>
<tr>
<td>Daily physical activity on weekends only, mean cpm</td>
<td>-31.8 (-98.5, 34.9)</td>
<td>Model 1: adjusted for age, sex and season</td>
<td>-40.4 (-109.3, 28.6)</td>
<td>Model 2: adjusted for age, sex, season, body mass index, daily smoking of the participant and highest education of either parent.</td>
</tr>
<tr>
<td>Sedentary time, min/day</td>
<td>16.4 (-39.4, 72.2)</td>
<td>Model 1: adjusted for age, sex and season</td>
<td>14.1 (-40.4, 68.5)</td>
<td>Model 2: adjusted for age, sex, season, body mass index, daily smoking of the participant and highest education of either parent.</td>
</tr>
<tr>
<td>Moderate physical activity, min/day</td>
<td>-1.6 (-13.5, 10.4)</td>
<td>Model 1: adjusted for age, sex and season</td>
<td>-2.5 (-14.6, 9.6)</td>
<td>Model 2: adjusted for age, sex, season, body mass index, daily smoking of the participant and highest education of either parent.</td>
</tr>
<tr>
<td>Moderate-to-vigorous physical activity, min/day</td>
<td>-6.9 (-24.2, 10.4)</td>
<td>Model 1: adjusted for age, sex and season</td>
<td>-8.3 (-25.7, 9.1)</td>
<td>Model 2: adjusted for age, sex, season, body mass index, daily smoking of the participant and highest education of either parent.</td>
</tr>
<tr>
<td>Vigorous physical activity, min/day</td>
<td>-5.3 (-12.6, 2.0)</td>
<td>Model 1: adjusted for age, sex and season</td>
<td>-5.8 (-13.1, 1.5)</td>
<td>Model 2: adjusted for age, sex, season, body mass index, daily smoking of the participant and highest education of either parent.</td>
</tr>
</tbody>
</table>
Table 6. Daily nutrient intake in preterm-born VLBW young adults and term-born controls. Recommended daily values for the adult Finnish population are also shown.

<table>
<thead>
<tr>
<th></th>
<th>VLBW (n = 151)</th>
<th>Term (n = 156)</th>
<th>Recommended daily intake (^a)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total energy, kcal</td>
<td>1800 (563)</td>
<td>1994 (613)</td>
<td>—</td>
<td>0.2</td>
</tr>
<tr>
<td>Alcohol, E%</td>
<td>3.0 (6.5)</td>
<td>3.2 (4.9)</td>
<td>(\leq 5)</td>
<td>0.6</td>
</tr>
<tr>
<td>Macronutrients</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbohydrates, E%</td>
<td>46.3 (7.4)</td>
<td>47.2 (8.4)</td>
<td>45-60</td>
<td>0.3</td>
</tr>
<tr>
<td>Fiber, g</td>
<td>14.6 (8.1)</td>
<td>16.3 (7.1)</td>
<td>25-35</td>
<td>0.3</td>
</tr>
<tr>
<td>Fiber, g/1000kcal</td>
<td>8.4 (4.4)</td>
<td>8.7 (4.1)</td>
<td>12.6</td>
<td>0.3</td>
</tr>
<tr>
<td>Protein, E%</td>
<td>16.1 (3.8)</td>
<td>16.2 (3.9)</td>
<td>10-20</td>
<td>0.2</td>
</tr>
<tr>
<td>Fat, E%</td>
<td>34.7 (7.0)</td>
<td>33.4 (7.1)</td>
<td>25-40</td>
<td>0.2</td>
</tr>
<tr>
<td>Saturated and transfatty acids, E%</td>
<td>13.4 (3.9)</td>
<td>13.6 (4.0)</td>
<td>(\leq 10)</td>
<td>0.8</td>
</tr>
<tr>
<td>Monounsaturated fatty acids, E%</td>
<td>11.7 (2.9)</td>
<td>11.1 (2.8)</td>
<td>10-20</td>
<td>0.1</td>
</tr>
<tr>
<td>Polyunsaturated fatty acids, E%</td>
<td>5.3 (1.8)</td>
<td>4.8 (1.6)</td>
<td>5-10</td>
<td><strong>0.04</strong></td>
</tr>
<tr>
<td>Essential fatty acids, E%</td>
<td>4.3 (1.5)</td>
<td>4.0 (1.5)</td>
<td>(\geq 3)</td>
<td><strong>0.01</strong></td>
</tr>
<tr>
<td>(\alpha)-Linolenic fatty acid (FA 18:3 n-3), E%</td>
<td>0.9 (.4)</td>
<td>0.8 (.3)</td>
<td>0.5</td>
<td><strong>0.007</strong></td>
</tr>
<tr>
<td>Micronutrients</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium, mg</td>
<td>858 (389)</td>
<td>1080 (514)</td>
<td>800 / 900 (^b)</td>
<td><strong>&lt;0.001</strong></td>
</tr>
<tr>
<td>Salt (NaCl), g</td>
<td>6.2 (2.2)</td>
<td>6.9 (2.5)</td>
<td>(&lt; 5)</td>
<td>0.2</td>
</tr>
<tr>
<td>Iron, mg</td>
<td>9.8 (3.4)</td>
<td>11.1 (5.2)</td>
<td>9 / 15 (^c)</td>
<td>0.2</td>
</tr>
<tr>
<td>Zinc, mg</td>
<td>9.6 (3.1)</td>
<td>10.9 (4.9)</td>
<td>9/7</td>
<td><strong>0.02</strong></td>
</tr>
<tr>
<td>Iodide, (\mu)g</td>
<td>195 (71)</td>
<td>228 (98)</td>
<td>150</td>
<td><strong>0.004</strong></td>
</tr>
<tr>
<td>Magnesium, mg</td>
<td>278 (100)</td>
<td>315 (103)</td>
<td>350 / 280 (^c)</td>
<td><strong>0.02</strong></td>
</tr>
<tr>
<td>Vitamin D, (\mu)g</td>
<td>3.7 (2.6)</td>
<td>4.4 (3.6)</td>
<td>10</td>
<td><strong>0.02</strong></td>
</tr>
<tr>
<td>Vitamin A, (\mu)g</td>
<td>771 (986)</td>
<td>726 (368)</td>
<td>900 / 700 (^c)</td>
<td>0.3</td>
</tr>
<tr>
<td>Vitamin C, mg</td>
<td>76 (66)</td>
<td>88 (62)</td>
<td>75</td>
<td><strong>0.04</strong></td>
</tr>
<tr>
<td>Thiamin, mg</td>
<td>1.0 (.5)</td>
<td>1.2 (.6)</td>
<td>1.4/1.1 (^c)</td>
<td>0.08</td>
</tr>
<tr>
<td>Folate, (\mu)g</td>
<td>189 (87)</td>
<td>211 (74)</td>
<td>300 / 400 (^c)</td>
<td>0.09</td>
</tr>
</tbody>
</table>

Footnotes are on the page following Table 6.
P-values for the difference in means obtained by linear regression and adjusted for age, sex, body mass index, height, living at parental home, daily smoking and highest parental education

a Finnish nutrition recommendations for ages 18-30 years (National Nutrition Council, 2014)
b ages 21-30 years / 18-20 years
c men / women

5.5 Blunted hypothalamic-pituitary-adrenal axis and insulin response to stress in VLBW adults (Study IV)

As we found no gender differences between the effects of preterm birth at VLBW on stress response measured as changes in cortisol, ACTH, glucose and insulin concentrations, these results are reported with men and women combined (p for interaction sex*birth status > 0.3 and time* sex*birth status > 0.4). Overall, ACTH and cortisol reactivities to TSST were lower in VLBW participants; this result was statistically significant for plasma cortisol only (Table 7). Similarly, no significant differences were found in overall glucose or insulin reactivity to TSST. Results of the mixed effects model are shown in Table 7.

<table>
<thead>
<tr>
<th></th>
<th>Mean difference (95% CI)</th>
<th>P for difference</th>
<th>P for interaction time*birth status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma ACTH</td>
<td>-24.2 % (-43.8 to 2.4)</td>
<td>0.07</td>
<td>0.5</td>
</tr>
<tr>
<td>Plasma cortisol</td>
<td>-17.2 % (-28.9 to -3.5)</td>
<td><strong>0.02</strong></td>
<td><strong>0.02</strong></td>
</tr>
<tr>
<td>Salivary cortisol</td>
<td>-15.0 % (95% CI; -33.4 to 8.4)</td>
<td>0.2</td>
<td><strong>0.04</strong></td>
</tr>
<tr>
<td>Plasma glucose</td>
<td>-2.8 % (-6.2 to 0.8)</td>
<td>0.1</td>
<td>0.9</td>
</tr>
<tr>
<td>Plasma insulin</td>
<td>-6.8 % (-28.5 to 21.5)</td>
<td>0.6</td>
<td>0.2</td>
</tr>
<tr>
<td>Plasma adrenalin</td>
<td>-3.0 % (-15.7 to 9.6)</td>
<td>0.6</td>
<td>0.07</td>
</tr>
<tr>
<td>Plasma noradrenalin</td>
<td>-19.1 % (-42.5 to 4.4)</td>
<td>0.1</td>
<td>0.4</td>
</tr>
</tbody>
</table>

Table 7. Mixed model results are presented as mean differences (95% CI). The analyses are adjusted for age, sex, BMI, hormonal contraception use, menstrual cycle phase, time of day and highest parental education.
Baseline concentrations, peak after stress, increments and AUCg of the measured biomarkers are shown in Table 8. In line with the lower overall plasma cortisol reactivity to TSST in VLBW participants, also the cortisol peak after stress was lower in the VLBW group (Table 8). Furthermore, the VLBW participants had on average a lower increase in plasma and salivary cortisol (p for time*birth status 0.02 and 0.04, respectively).

Of the VLBW participants, 23 (43%) were born SGA (Pihkala et al., 1989). With a mixed model, the responses to TSST in all overall concentrations (cortisol, ACTH, glucose and insulin) were similar in SGA and AGA participants. Glucose and insulin responsiveness after TSST was higher in the SGA participants (p for the interaction time*SGA status < 0.001 for glucose and 0.01 for insulin).
## Results

Physical activity, nutrition and stress response in young adults born preterm – determinants of health and disease

### Table 8. ACTH, cortisol, glucose, insulin, A and NA concentrations of participants.

<table>
<thead>
<tr>
<th></th>
<th>VLBW</th>
<th>Term</th>
<th>P c</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline concentrations</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACTH, pmol/l</td>
<td>3.5 (1.8)</td>
<td>3.6 (2.5)</td>
<td>.6</td>
</tr>
<tr>
<td>Plasma cortisol, nmol/l</td>
<td>325.3 (1.4)</td>
<td>302.3 (1.8)</td>
<td>.5</td>
</tr>
<tr>
<td>Salivary cortisol, nmol/l</td>
<td>7.0 (1.7)</td>
<td>6.1 (2.0)</td>
<td>1.0</td>
</tr>
<tr>
<td>Insulin, mU/l</td>
<td>6.8 (2.1)</td>
<td>7.3 (2.1)</td>
<td>.7</td>
</tr>
<tr>
<td>Glucose, mmol/l</td>
<td>4.6 (1.1)</td>
<td>4.7 (1.1)</td>
<td>.3</td>
</tr>
<tr>
<td>Adrenalin, pmol/l</td>
<td>25.6 (1.4)</td>
<td>24.9 (1.4)</td>
<td>.7</td>
</tr>
<tr>
<td>Noradrenalin, pmol/l</td>
<td>178.1 (1.6)</td>
<td>180.4 (1.5)</td>
<td>.6</td>
</tr>
<tr>
<td><strong>Peak after stress</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACTH, pmol/l</td>
<td>8.5 (2.7)</td>
<td>11.3 (2.7)</td>
<td>.3</td>
</tr>
<tr>
<td>Plasma cortisol, nmol/l</td>
<td>471.3 (1.5)</td>
<td>509.4 (1.5)</td>
<td>.03</td>
</tr>
<tr>
<td>Salivary cortisol, nmol/l</td>
<td>12.7 (1.9)</td>
<td>13.7 (2.0)</td>
<td>.3</td>
</tr>
<tr>
<td>Insulin, mU/l</td>
<td>9.7 (1.9)</td>
<td>11.5 (1.9)</td>
<td>.6</td>
</tr>
<tr>
<td>Glucose, mmol/l</td>
<td>5.0 (1.1)</td>
<td>5.1 (1.1)</td>
<td>.2</td>
</tr>
<tr>
<td>Adrenalin, pmol/l</td>
<td>40.9 (1.8)</td>
<td>40.9 (1.6)</td>
<td>.2</td>
</tr>
<tr>
<td>Noradrenalin, pmol/l</td>
<td>461.3 (1.6)</td>
<td>494.5 (1.5)</td>
<td>.09</td>
</tr>
<tr>
<td><strong>Increments</strong> d</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACTH</td>
<td>2.5 (1.9)</td>
<td>3.1 (2.6)</td>
<td>.5</td>
</tr>
<tr>
<td>Plasma cortisol</td>
<td>1.4 (1.4)</td>
<td>1.7 (1.5)</td>
<td>.1</td>
</tr>
<tr>
<td>Salivary cortisol</td>
<td>1.7 (1.9)</td>
<td>2.3 (2.2)</td>
<td>.2</td>
</tr>
<tr>
<td>Insulin</td>
<td>1.3 (1.7)</td>
<td>1.5 (1.5)</td>
<td>.08</td>
</tr>
<tr>
<td>Glucose</td>
<td>1.1 (1.1)</td>
<td>1.1 (1.1)</td>
<td>.3</td>
</tr>
<tr>
<td>Adrenalin</td>
<td>1.6 (1.6)</td>
<td>1.6 (1.6)</td>
<td>.3</td>
</tr>
<tr>
<td>Noradrenalin</td>
<td>2.7 (1.4)</td>
<td>2.8 (1.4)</td>
<td>.2</td>
</tr>
<tr>
<td><strong>Time-weighted area under curve</strong> e</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACTH</td>
<td>5.9 (1.9)</td>
<td>7.8 (2.2)</td>
<td>.2</td>
</tr>
<tr>
<td>Plasma cortisol</td>
<td>349.4 (1.4)</td>
<td>352.8 (1.6)</td>
<td>.2</td>
</tr>
<tr>
<td>Salivary cortisol</td>
<td>7.5 (1.6)</td>
<td>8.4 (1.9)</td>
<td>.1</td>
</tr>
<tr>
<td>Insulin</td>
<td>9.7 (2.0)</td>
<td>12.0 (2.3)</td>
<td>.6</td>
</tr>
<tr>
<td>Glucose</td>
<td>6.3 (1.1)</td>
<td>6.6 (1.1)</td>
<td>.3</td>
</tr>
<tr>
<td>Adrenalin</td>
<td>30.1 (1.5)</td>
<td>28.3 (1.4)</td>
<td>.4</td>
</tr>
<tr>
<td>Noradrenalin</td>
<td>328.1 (1.5)</td>
<td>365.0 (1.4)</td>
<td>.2</td>
</tr>
</tbody>
</table>

a Geometric mean, denotes the n\textsuperscript{th} root of the product of n individual values
b Geometric standard deviation, denotes the relative increase in a variable corresponding to one standard deviation unit change in the logarithm of the variable
c All analyses are adjusted for age, sex, BMI, hormonal contraception, menstrual cycle phase, time of day and highest parental education
d Log (peak after stress/baseline value)
e Area under the curve with respect to ground (above zero)
5.6 Similar or lower sympathetic-adrenal-medullary system response to stress in VLBW adults (Study V)

Overall A [-3.0% (-15.7 to 9.6)] and NA [-19.1% (-42.5 to 4.4)] reactivity to TSST did not significantly differ between VLBW and control participants (Table 7). In line with Section 5.5, which presents results of Study IV, these results are shown after additionally adjusting for menstrual cycle phase (unpublished results). The effects of preterm birth at VLBW on A and NA stress response were similar in both sexes. P-values for interaction terms for A were as follows: sex*birth status 0.36 and time*sex*birth status 0.41, and for NA 0.48 and 0.92, respectively. We reran all analyses for men and women separately, and the results remained unchanged regarding A. For women, we found a significantly lower overall NA reactivity to TSST [-27.7% (-52.2 to -3.1)]. Among men, this difference was not statistically significant [-15.1% (-38.9 to 8.8)].

Baseline concentrations, peak after stress, increments and AUCg of A and NA with men and women combined are shown in Table 8 (unpublished results). In Table 2 of Study V (Kaseva et al., 2014), the results are presented separately for men and women.

We found no differences in HR at baseline [1.8 beats/min (-7.3 to 10.8)], during the task [1.6 beats (-11.7 to 14.8)] or in HR task reactivity [0.4 beats/min (-10.1 to 10.8)] between VLBW and control women. Similarly, the mean difference in HR at baseline [2.6 beats/min (-7.6 to 12.8)], during the task [9.9 beats/min (-4.2 to 24)] and in HR task reactivity [7.3 beats/min (-2.6 to 16.9)] was not significantly different in VLBW and control men. The mean values for HR at baseline, during the task and in HR task reactivity are shown in Table 9.

We also compared those 22 VLBW participants (44%) born SGA (Pihkala et al., 1989) with the remaining 28 AGA VLBW participants. With a mixed model, the overall concentrations for A and NA were similar in SGA and AGA VLBW participants. Also baseline, peak after stress, increment and AUCg for A and NA were similar.
Results

Table 9. Changes in heart rate provoked by the Trier Social Stress Test in study participants.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>VLBW</th>
<th>Term</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 22)</td>
<td>(n = 17)</td>
<td></td>
</tr>
<tr>
<td>Heart rate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline d</td>
<td>83.9 (15.3)</td>
<td>77.9 (9.4)</td>
<td>0.61</td>
</tr>
<tr>
<td>Task e</td>
<td>101.0 (18.1)</td>
<td>92.0 (15.6)</td>
<td>0.16</td>
</tr>
<tr>
<td>Reactivity f</td>
<td>17.2 (12.0)</td>
<td>14.1 (11.6)</td>
<td>0.13</td>
</tr>
<tr>
<td>WOMEN, mean b (SD c)</td>
<td>(n=28)</td>
<td>(n= 22)</td>
<td></td>
</tr>
<tr>
<td>Heart rate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline d</td>
<td>85.1 (12.3)</td>
<td>82.9 (14.3)</td>
<td>0.70</td>
</tr>
<tr>
<td>Task e</td>
<td>109.1 (19.1)</td>
<td>106.9 (20.9)</td>
<td>0.81</td>
</tr>
<tr>
<td>Reactivity f</td>
<td>24.7 (15.2)</td>
<td>24.0 (16.7)</td>
<td>0.94</td>
</tr>
</tbody>
</table>

* P for linear regression model, analyses are adjusted for age, BMI, time of day and highest parental education in men, the same covariates plus hormonal contraception in women
  
  b Geometric mean, denotes the n\textsuperscript{th} root of the product of n individual values
  
  c Geometric standard deviation, denotes the relative increase in a variable corresponding to one standard deviation unit change in the logarithm of the variable
  
  d Mean heart rate during a 5-min baseline measurement
  
  e Mean heart rate during a 10-min task period
  
  f Mean heart rate during task minus mean heart rate at baseline

**5.7 Non-participant analysis**

We performed non-participant analyses separately for all studies included in this thesis (I-V), as different subgroups of the original HeSVA cohort participated in these five studies.

For Study I, we compared the adult characteristics of the participants (94 VLBW and 101 controls) with those 72 VLBW and 71 controls who were invited and chose not to participate or met an exclusion criterion. They had all participated in the first clinical examination in 2004-2005 (Figure 3), and data on adult measurements were therefore available. We found no differences in height, BMI or SES, as indicated by highest parental education (all p-values ≥ 0.1). We further compared perinatal characteristics between the participants of Study I and the remaining original cohort with data available (161 VLBW and 213 controls). No significant differences were found regarding gestational age, birth weight, sex, pre-eclampsia or multiple pregnancy (all p-values ≥ 0.1).
In line with the non-participant analyses performed in Study I, we compared the adult characteristics of the participants of Study II (57 VLBW and 47 controls) with those 109 VLBW and 125 controls who were invited and chose not to participate. Since all of them participated in the first clinical examination in 2004-2005 (Figure 3), data on adult measurements were available. We found no differences in height, BMI or SES (all p-values ≥ 0.2). Daily smoking was more common in non-participant VLBW subjects (28% vs. 12%, p = 0.02). In the controls, no difference in daily smoking was seen (34% vs. 27%, p = 0.4). We further compared perinatal characteristics between the participants of Study II and the remaining original cohort with data available (198 VLBW and 267 controls). No significant differences were found regarding gestational age, birth weight, or the incidence of SGA (Pihkala et al., 1989), pre-eclampsia or multiple pregnancy (all p-values ≥ 0.4). In both VLBW and control groups, there were more men among the non-participants (VLBW 48% vs. 35%, p for difference 0.1 and controls 49% vs. 29%, p = 0.02); this finding was significant for controls only.

We compared perinatal characteristics of the participants of Study III (151 VLBW and 156 controls) with the remaining original cohort subjects who were invited to the first clinical examination in 2004-2005 (Figure 3) and were without food record data (104 VLBW and 158 controls). We separately compared VLBW and control participants and found no differences in gestational age, birth weight, type of birth, incidence of pre-eclampsia or multiple pregnancy between the participants of Study III and those who were not included in this study (all p-values ≥ 0.1). In both VLBW and control groups, there were more men among the non-participants (VLBW 54% vs. 40%, p for difference 0.03 and controls 52% vs. 45%, p = 0.01). Furthermore, maternal smoking was more common among VLBW non-participants (32% vs. 17%, p = 0.004).

In Studies IV and V, perinatal and current descriptive characteristics were compared between the participants of the TSST (54 VLBW and 40 controls) and the group from which they were recruited (Figure 3), i.e. the remaining cohort subjects who had previously participated in the clinical examination (112 VLBW and 132 controls). VLBW and control groups were separately compared, and we found no differences in gestational age, birth weight, sex, incidence of pre-eclampsia, multiple pregnancy or SGA (Pihkala et al., 1989) between the participants of Studies IV and V and the group from which they were recruited (all p-values ≥ 0.1). Age, daily smoking, hormonal contraception use, parental education, adult height and BMI were also similar between the participants of Studies IV and V and the group from which they were recruited (all p-values ≥ 0.1).
6 Discussion

Preterm birth at VLBW is associated with increased risk factors for adulthood NCDs; impaired glucose and insulin metabolism (Hofman et al., 2004; Lawlor et al., 2006; Hovi et al., 2007; Rotteveel et al., 2008; Kajser et al., 2009; Kajantie et al., 2010; Pilgaard et al., 2010; Crump et al., 2011; Smith et al., 2011), higher blood pressure (de Jong et al., 2012; Parkinson et al., 2013), an atherogenic lipid profile (Hovi et al., 2013; Parkinson et al., 2013) and lower bone density (Hovi et al., 2009; Smith et al., 2011) have been reported. These are all factors that may be modified by lifestyle. In Studies I, II and III, we focused on physical activity and dietary habits of young VLBW adults.

Individual differences in stress response are to some extent programmed during the fetal period and early childhood. Studies IV and V assessed psychosocial stress responses in VLBW adults.

6.1 Physical activity

The most important finding of questionnaire-based Study I was the markedly lower conditioning LTPA in young adults born at VLBW relative to the term-born controls. Based on the detailed, validated KIHD questionnaire, we found that the healthy VLBW adults showed 48% lower yearly frequency, 61% lower total time, 55% lower total volume and 68% lower EE of conditioning LTPA. This was not explained by age, sex, BMI, daily smoking, socio-economic status or personality traits. No significant differences in non-conditioning LTPA or commuting physical activity were observed. Despite clear differences in conditioning LTPA in Study I, we were unable to confirm the finding of lower physical activity in a subgroup of VLBW adults by accelerometer measurement in Study II.

Guidelines on physical activity for adults recommend at least 150 minutes weekly of moderate intensity physical activity (Physical Activity Guidelines Advisory Committee, 2008; World Health Organization, 2010). This recommendation was met by 55% of VLBW and 57% of control participants (unadjusted p for difference = 0.8 and adjusted p = 0.7, unpublished results). For comparison, approximately half of the general adult population in Finland meets this recommendation (Husu et al., 2011). The participants of Study I were healthy young adults, and thus, a slightly higher physical activity level than in the general adult population is not surprising.

Earlier studies, by us and others, using self-report methods consistently show lower sports participation and LTPA in young VLBW adults (Vrijlandt et al., 2006; Hack et al., 2007; Kajantie et al., 2010). Also ELBW adolescents have reported lower
physical activity, muscle strength and flexibility (Rogers et al., 2005). In line with these findings, young ELBW adults reported lower physical efficacy, self-perceived physical ability and physical self-confidence than controls (Saigal et al., 2007). Objective measurement of physical activity has not previously been performed in VLBW adults. Only one study in extremely preterm children has used accelerometry for objective evaluation of physical activity. This was done in 11-year-old children using hip-worn accelerometers, and, as in Study II, no difference was found in physical activity between the 31 former extremely preterm-born subjects and the 30 controls (Welsh et al., 2010). Measuring physical activity and sedentary behaviour is complex, and self-report probably captures different aspects of overall physical activity than accelerometry during a relatively short period of measurement.

Personality traits are linked to physical activity. Differences in personality offer one potential explanation for the lower conditioning LTPA in VLBW adults. Conscientiousness and extraversion are personality traits associated with higher levels of physical activity, while neuroticism is related to lower levels of physical activity (Rhodes and Smith, 2006). Based on earlier published data, VLBW individuals are more conscientious, agreeable and show less neuroticism and openness to experience than their peers born at term (Pesonen et al., 2008). Also in ELBW adults, higher shyness, behavioural inhibition and socialization (a measure of prosocial behaviour) and lower sociability and emotional well-being have been reported (Schmidt et al., 2008). However, these differences in personality traits did not explain the lower conditioning LTPA in VLBW adults that we found in Study I.

Other factors possibly accounting for the lower conditioning LTPA in VLBW adults may include visual impairment (Evensen et al., 2009), impaired lung function (Vrijlandt et al., 2006), poor motor coordination (Rogers et al., 2005), lower muscle strength (Keller et al., 2000; Rogers et al., 2005), lower physical self-confidence (Hack et al., 2007), lower exercise capacity (Rogers et al., 2005) and lower perceived physical ability (Saigal et al., 2007), all reported from childhood onwards in the former preterm-born. However, the participants of Studies I and II were all healthy VLBW adults. It is therefore not likely that impairment in functioning would explain the lower conditioning LTPA that we reported in Study I.

Adults born preterm have in some studies shown lower BMI (Hack et al., 2003; Hovi et al., 2007) and been found to be shorter (Roberts and Cheong, 2014) and have lower lean body mass (Weiler et al., 2002; Hovi et al., 2007) than controls. Such differences in body composition may lead to or reflect the lower physical activity levels reported in preterm-born subjects. This was also seen in Study I. When we adjusted for lean body mass instead of BMI in the subgroup with data available, the differences in frequency, total time, total volume and EE of conditioning LTPA were attenuated.
Specific dietary and lifestyle factors, e.g. low physical activity, alcohol use, smoking, watching television and sleep (< 6 h or > 8 h), are all factors independently associated with long-term weight gain. In non-obese populations, gradual weight gain tends to accumulate over time; in a large study including 120877 men and women in the United States, the rate was approximately 0.36 kg/year (Mozaffarian et al., 2011). Even moderate weight gain increases the risk of NCDs, e.g. type 2 diabetes (Chan et al., 1994; Colditz et al., 1995) and CVD (Willett et al., 1995). Small lifestyle changes have an impact; reducing daily energy intake by 2-3% or walking an extra 10-15 minutes daily could offset weight gain in approximately 90% of the population (Zhai et al., 2008). Commonly, weight gain results from a relatively small energy imbalance or gap; 46-72 kcal/day in children (Plachta-Danielzik et al., 2008) and 45-100 kcal/day in adults (Zhai et al., 2008).

6.2 Diet and nutrition

We observed that young adults born preterm at VLBW consume markedly less milk products, vegetables, fruits and berries than their term-born counterparts. Lower daily intakes of vitamin D and calcium were also seen. Lower consumption of vegetables, fruits and berries reflects an unhealthy diet and poses a risk factor for CVD (Joshipura et al., 1999; Dauchet et al., 2009; Mirmiran et al., 2009). The observed differences in dietary habits may to some extent underlie the VLBW adults’ increased risk factors for NCDs, including CVD, type 2 diabetes and osteoporosis.

Dietary quality, i.e. the types of foods and beverages consumed, influences dietary quantity, which affects total calorie intake. Food fat content, energy density and added sugars are factors to be emphasized when evaluating food and nutrient intake. Energy intakes of fat, carbohydrates and protein were similar in VLBW and control groups. High intake of protein, especially animal protein, is associated with an elevated risk for type 2 diabetes (van Nielen et al., 2014). Thus, maintaining protein intake at recommended levels is important in a high-risk population such as VLBW adults. The total daily energy intake was slightly lower in VLBW adults. After adjusting for body size (BMI and height), daily energy intake was similar to that of controls. Naturally food consumption reflects body size, and those born preterm at VLBW tend to be smaller (Roberts and Cheong, 2014).

The difference in daily consumption of vegetables, fruits and berries was 58 g/day, corresponding to 0.3 SDs. The daily recommendation of 500 g/day was not reached by the VLBW or control participants (183 g vs. 241 g, p = 0.002). However, this may be of greater importance to the VLBW participants, as they have higher levels of other risk factors for NCDs. A low consumption of vegetables and fruits is an important, modifiable risk factor of CVD (Joshipura et al., 1999; Dauchet et al., 2009; Mirmiran et al., 2009). This is emphasized by the WHO ranking low
consumption of fruits and vegetables as the 7th leading risk factor for mortality (World Health Organization, 2009).

Data are lacking on dietary habits and nutrient intake in VLBW adults, while associations between birth size and food intake in term-born children and adults have been reported. In line with our results, term-born adults, aged 56 to 70 years, showed higher daily intake of fruits and berries with increasing birth weight (83 g per 1 kg higher birth weight) (Perälä et al., 2012). Those adults with smaller birth size also had higher intake of fat and lower intake of carbohydrates, sucrose, fructose and fibre (Perälä et al., 2012). Also in young children born at term, an inverse association between fat intake and birth weight has been described (Stafford and Lucas, 1998; Shultis et al., 2005). These data suggest that intrauterine growth may modify food intake later in life.

We also observed lower daily intake of milk products in VLBW participants. In the Finnish diet, milk products are a central source of vitamin D and calcium. Accordingly, the VLBW participants had significantly lower intake of both vitamin D and calcium than controls. Both protective and predisposing associations have been reported regarding the impact of dairy product use on the risks for CVD (Larsson et al., 2009; Goldbohm et al., 2011; Phelan and Kerins, 2011; Soedamah-Muthu et al., 2011; Sonestedt et al., 2011; Astrup, 2014). In a recent review, consumption of dairy products had a beneficial effect on dyslipidaemia, insulin resistance, blood pressure and body fat (Astrup, 2014). The consumption of high-fat (> 2%) dairy products, expected to be more harmful for health, was not significantly different between VLBW and control groups, while intake of low-fat (≤ 2%) dairy products was lower in VLBW adults. Previously, lower bone mineral density, a risk factor for osteoporosis, has been reported in the HeSVA cohort’s VLBW participants (Hovi et al., 2009). This finding of lower bone mineral density may to some extent be explained by the lower intake of calcium and vitamin D relative to the controls. Low levels of vitamin D are also associated with increased risk for diabetes (Forouhi et al., 2012), as is preterm birth (Hofman et al., 2004; Lawlor et al., 2006; Hovi et al., 2007; Rotteveel et al., 2008; Kaijser et al., 2009; Kajantie et al., 2010; Pilgaard et al., 2010; Crump et al., 2011; Smith et al., 2011). Furthermore, low intake of calcium is associated with higher blood pressure at least in children (Gillman et al., 1992; Gillman et al., 1995).

In previous studies of VLBW adults, one of the most consistent findings is high blood pressure (Irving et al., 2000; Doyle et al., 2003; Hacket et al., 2005; Pyhälä et al., 2009; Hovi et al., 2010; Norman, 2010; de Jong et al., 2012; Parkinson et al., 2013). High salt intake is directly related to higher blood pressure in infants (Pomeranz et al., 2002), children (Simons-Morton and Obarzanek, 1997) and adults (Chobanian and Hill, 2000; Kaplan, 2000). Furthermore, high blood pressure is a known risk factor for cardiovascular complications such as stroke and coronary heart disease
(Campbell et al., 2011). Thus, our finding of similar salt intake in VLBW and control groups when adjusting for body size (BMI and height) is especially important, as already young VLBW adults tend have higher blood pressure than term-born controls (de Jong et al., 2012; Parkinson et al., 2013). The effects of dietary intake may also be different in individuals born at low birth weight. For example, Perälä et al. (2011) found that individuals born at a low birth weight were more sensitive to the blood pressure-raising effect of salt as elderly adults.

Compared with controls, the VLBW group had a higher intake of essential fatty acids, including α-linoleic fatty acid. However, seafood intake, which is a central source of omega-3 polyunsaturated fatty acids and vitamins, was similar in both groups, as was intake of other fatty acids. The intake of fibre was lower than recommended in both VLBW and control groups. Obtaining a satisfactory dietary intake may be more important to VLBW individuals since they are at greater risk for NCDs.

A possible explanation for the differences in dietary habits and nutrient intake between VLBW and control groups may be found in the eating difficulties that VLBW individuals often experience in early infancy and childhood (Samara et al., 2010). Evidence also suggests that inadequate nutrition pre- or postnatally may program individual food preferences later in life. Epidemiological data shows that exposure to the Dutch famine in 1944-1945 during early pregnancy (defined as first 16 weeks of gestation) is associated with a preference for fatty foods in the offspring later in life (Lussana et al., 2008). It is likely that during postnatal care in 1978-1985, when the participants of the HeSVA cohort were born, NICU care offered inadequate nutrition. In addition to early programming of food preferences (Lussana et al., 2008; Barbieri et al., 2009; Portella et al., 2012), differences in oral motor abilities, socio-economic factors and family eating habits may play a role in later dietary habits (Portella et al., 2012). The effects of early under-nutrition on adult diet could also in part be mediated through psychological functioning; early childhood under-nutrition predicts depressive symptoms (Galler et al., 2010), anxiety and lower self-esteem (Walker et al., 2007), all of which could be related to an unhealthy diet. Another possible explanation for our findings is that low birth weight may affect appetite. Parents might also feed their infants more to compensate for the low birth weight.

Other possible mechanisms behind food choices or food preferences include prenatal and early postnatal flavour experiences. Maternal diet during pregnancy has been shown to affect the infant’s postnatal preference for the same diet (Mennella et al., 2001). Culture-specific flavour preferences are likely initiated this way in early life (Mennella et al., 2001). Furthermore, both salty taste acceptance and salt intake have been demonstrated to be inversely associated with birth weight in small
children (Stein et al., 2006). That study included only participants with a birth weight > 2500 g.

6.3 Stress response
We measured HPAA (Study IV) and SAM (Study V) responses to psychosocial stress and, contrary to our hypothesis, found that healthy VLBW adults had lower HPAA response after stress. This was followed by a lower insulin response. Also contrary to our hypothesis, we found no evidence of higher SAM response to psychosocial stress in VLBW adults. In VLBW women, the rise in NA was lower than in controls. The results were not explained by age, sex (Study IV), BMI, hormonal contraception, menstrual cycle phase, timing of TSST or childhood socio-economic status.

Both animal (Weinstock, 2001; Welberg and Seckl, 2001) and human studies (Kajantie and Räikkönen, 2010) give us reason to believe that stressful events pre- and postnatally influence later stress response. Preterm birth at VLBW is likely to involve both pre- and postnatal stress. The mechanisms involved in programming of stress response are not well understood. Our finding of lower HPAA response to stress in young VLBW adults supports the concept of programming of the HPAA. The lack of difference in HPAA response after TSST between AGA and SGA VLBW subgroups indicates that our finding of lower HPAA response was caused by immaturity rather than intrauterine growth retardation. Although HPAA stress response after TSST in VLBW adults has not been studied previously, data on preterm children have been published. In line with our results, a study of 18 children aged 8-12 years with any degree of prematurity and 18 term-born controls showed attenuated salivary cortisol responses to TSST-C (Buske-Kirschbaum et al., 2007). This finding did not, however, reach statistical significance, possibly due to the small sample size. Also in 4-month-old preterm infants, a lower cortisol response to immunization than in term-born controls has been reported (Grunau et al., 2010). Based on these data, preterm birth can be speculated to be associated with blunted HPAA response to stress. Data on lower salivary cortisol levels in extremely preterm infants at 3 months of corrected age compared with term infants have also been published (Grunau et al., 2007). In that study, a shift to higher cortisol levels in the former preterm children was seen at 8 and 18 months.

Somewhat different results on the effects of birth weight and HPAA response to TSST have been reported after term pregnancy relative to preterm birth (Kajantie and Räikkönen, 2010). Lower birth weight has been found to be associated with higher salivary cortisol response after TSST in both 7- to 9-year-old boys (Jones et al., 2006) and young adult male twins (Wüst et al., 2005). In line with our results, TSST provoked lower cortisol and ACTH responses in adults aged 60-70 years who were born with lower birth weight, mostly after term birth (Kajantie et al., 2007).
These mixed results of the effects of birth weight on HPAA function may to some extent be explained by a variety of mechanisms causing low birth weight.

In addition to the blunted HPAA response to stress in VLBW adults, we found that insulin concentrations increased 1.3-fold in VLBW participants, while the increase in the term group was 1.5-fold. This in contrast to the insulin response after a 75-g oral glucose load, which was higher in the VLBW participants: 6.1-fold versus 5.1-fold in controls (Hovi et al., 2007). A lower rise in insulin after stress may be a potential protective factor. There is a dearth of knowledge about the effects of psychosocial stress on glucose and insulin responses in individuals born preterm. Thus, the finding of a blunted insulin response to stress in former preterm individuals is new.

Early life predictors of the SAM stress response in later life have been investigated previously (Kajantie and Räikkönen, 2010). After immunization, 4-month-old preterm-born and term-born infants showed similar HR responses (Grunau et al., 2010). This is in line with our results in Study V in which HR responses to TSST did not differ between VLBW and control groups. Also consistent with our results, HR responses after TSST-C in 8- to 12-year-old children were found to be similar in preterm and control groups (Buske-Kirschbaum et al., 2007). In contrast to our findings, higher urinary catecholamines and higher HR at both rest and after mental stress were seen in former preterm children at 9-10 years of age (Johansson et al., 2007). This may be due to methodological differences, as in that study a single morning urine sample was collected for evaluation of catecholamines the day after the stress test. The analysis of one urinary sample provides a summary measure of stress response, while we used repeated measurements at the time of performing the TSST. Repeated measurements at the time of undergoing stress can be assumed to yield more precise data in terms of acute stress response, as other incidents occurring later the same day will not affect these measurements.

It is noteworthy that data on the effects of preterm birth on SAM stress response in VLBW adults is scarce. Provoked by TSST, the same VLBW participants, in who we found similar A and HR responses and lower NA after stress in the VLBW women (Study V), Pyhälä et al. (2009) reported higher diastolic blood pressure responses than controls. A higher blood pressure response to stress, not seen in HR, A or NA levels, may in part be explained by differences in arterial stiffness, endothelial function or renal function. Also somewhat higher HR was seen in the HeSVA cohort VLBW participants in conjunction with a clinic visit (Hovi et al., 2007). This may be due to different mechanisms underlying HR and catecholamine stress responses. The circulating A and NA levels reflect release from both the adrenal medulla and noradrenergic nerve terminals, while HR reacts to sympathetic and parasympathetic nervous system activity. The finding of lower NA after stress
in VLBW women could be a protective characteristic for CVD in this high-risk population (Parkinson et al., 2013). SAM overactivity is associated with hypertension (Julius, 1996), and increased HR predicts cardiovascular mortality (Palatini et al., 2006).

Abnormal stress responses, mediated by both the HPAA and SAM pathways, are also associated with increased risk for NCDs, including type 2 diabetes (McEwen, 1998), CVD (McEwen, 1998), depression (Bjorntorp, 1996), metabolic syndrome (Chrousos, 2000), hypertension (Treiber et al., 2003; Matthews et al., 2004; Chida and Steptoe, 2010) and carotid atherosclerosis (Treiber et al., 2003; Matthews et al., 2006). It is not known whether these changes in stress response can be modified later in life.

6.4 Strengths and limitations

An important strength of the study population (the HeSVA cohort) is the age-, sex- and birth hospital-matched control participants. The study sample is relatively small, but still comparable to or larger than previous studies with related outcomes on physical activity (Keller et al., 2000; Rogers et al., 2005; Vrijlandt et al., 2006; Saigal et al., 2007; Welsh et al., 2010) and stress response (Wüst et al., 2005; Jones et al., 2006; Buske-Kirschbaum et al., 2007; Johansson et al., 2007; Brummelte et al., 2011). The sample size in Study II on dietary habits can be considered relatively large, as well. We were also able to adjust for the most important confounding factors in the five different studies of this thesis. One limitation of the HeSVA cohort is that the participants were born in the late 1970s and 1980s. The current treatment of prematurely born infants differs from when the HeSVA participants received neonatal intensive care. Today, we have more to offer, which hopefully will lead to a healthier next generation of VLBW individuals. Thus, all of the results in this thesis may not be directly applied to the present.

Subgroups of the original cohort were used in Studies I-V. It is possible that these subgroups are not representative of the original cohort. This is unlikely since non-participant analyses showed only slight differences between participants and non-participants in Studies II and III. There were more men among the non-participants in both VLBW and control groups in Studies II and III. Daily smoking was more common among the non-participant VLBW subjects in Study II. Maternal smoking during pregnancy was more common among VLBW non-participants in Study III. No significant differences regarding perinatal or current characteristics were found in non-participant analyses for Studies I, IV and V.

Data on physical activity (Study I) and dietary habits (Study III) were gathered by self-report. A limitation of all data obtained by self-report is potential bias arising from underreporting or overreporting. Questionnaires concerning physical activity have been found to be fairly reliable and not all types of physical activity can be
measured by objective measurement. The reproducibility and validity of the detailed KIHD questionnaire (Study I) have been confirmed in different populations in Finland (Lakka and Salonen, 1992; Lakka and Salonen, 1993), Belgium (De Backer et al., 1981) and the United States (Jacobs et al., 1993). Using one of the most reliable self-report methods for estimating dietary intake, the prospective 3-day food record, is a major strength (Prentice et al., 2011) of Study III. In addition, the 3-day food record was combined with use of a picture booklet for estimating portion sizes, as this improves the accuracy of self-reported food intake (Ovaskainen et al., 2008).

People tend to underestimate their food intake and this was probably also the case in Study III, as overall energy intake was somewhat low in both VLBW and control groups. Also of importance, the intake of rarely consumed food items, such as fish, might be overestimated or underestimated when only a 3-day period is assessed. Another weakness of the 3-day food record is the difficulty in gathering reliable information on micronutrient intake.

Former preterm-born individuals may also respond differently to questionnaires than those born at term. Preterm-born individuals show a tendency to give more false answers to appear more socially acceptable (Allin et al., 2006). However, regarding physical activity as well as dietary habits, the VLBW group showed findings that may be perceived as less acceptable outcomes, i.e. they were less physically active and their diets were unhealthier.

Furthermore, as the aim of this thesis was to explore the effects of preterm birth on healthy VLBW individuals, the full extent of physical inactivity in all individuals born at VLBW may be underestimated since having an impairment affecting physical activity was an exclusion criterion in Studies I and II.

In Study II, accelerometer measurement was used to objectively measure physical activity and sedentary behaviour. For this, the wrist-worn Actiwatch AW4 model (Cambridge Neurotechnology Ltd., UK), validated for measuring physical activity in free-living people (Heil et al., 2009), was used. However, there are some limitations in the use of accelerometers for measuring physical activity. The accelerometer must be removed when showering, swimming or bathing, and the wrist-worn model is not well suited for all types of physical activity, e.g. cycling is not captured reliably by this model. However, participant compliance is important and the wrist-worn accelerometer is easier to wear than the hip-worn models. Comparable data can be obtained by both models (Heil et al., 2009). All participants were asked to wear the accelerometer on the non-dominant wrist continuously and to record the bedtimes and awakening times by both pressing an event marker and simultaneously recording this in a sleep log. For inclusion in the analyses, a minimum of 600 min/day of wearing the accelerometer and at least 3 days of recording were required. A 3-day record of physical activity is relatively short, and this may lead to overestimating or underestimating an individual’s physical activity.
Furthermore, for evaluating the intensity of physical activity, we had to use cut-off points validated for 8- to 10-year-old children (Ekblom et al., 2012) since no validation studies have been done in adults. Children tend to be more physically active than adults, and therefore, using cut-off points validated for children is suboptimal. Also of note is that we did not assess cardiorespiratory fitness in any of the studies. Lower cardiorespiratory fitness would be expected with lower physical activity levels. A further limitation of Study II is the relatively small sample size. In sum, measuring physical activity as well as sedentary behaviour is complex, and regardless of the above limitations, a major strength of Study II is the use of an objective measure.

A major strength of Studies IV and V, regarding HPAA and SAM stress response, is the use of a standardized stressor, the TSST (Kirschbaum et al., 1993). We used a wide range of measurements, including repeated salivary and blood samples for the different biomarkers and recording of HR. We were also able to adjust for important confounders, including menstrual cycle phase, use of hormonal contraception and time of day when the TSST was performed. The participants underwent TSST between 10:45 and 16:10; for this time interval, the responses to TSST are regarded as comparable (Kudielka et al., 2004). A limitation of these two studies evaluating stress response is the small sample size, which may diminish the possibilities of finding associations in subgroups, i.e. when evaluating men and women separately. This should be noted when interpreting the lack of sex interactions in HPAA/ cortisol response to stress, as well as the lower NA response in VLBW women. Sex differences have previously been reported in several HPAA stress response studies (Kajantie and Phillips, 2006). The TSST is a labour-intensive test and our group sizes are similar or larger than in previous studies in the field (Wüst et al., 2005; Jones et al., 2006; Buske-Kirschbaum et al., 2007; Johansson et al., 2007; Brummelte et al., 2011). Preterm birth is caused by a variety of factors, with varying impacts on adult HPAA or SAM stress response. Of the VLBW participants in Studies IV and V, some were born SGA (43% in Study IV, 44% in Study V) from pre-eclamptic (IV: 22%, V: 26%) or multiple pregnancy (IV: 15%, V: 16%). This reflects the reality of the VLBW population and may limit the extent to which these data can be generalized to all individuals born preterm. However, in previous studies the cardiovascular outcomes of VLBW infants have been quite similar regardless of maternal pregnancy conditions (Kajantie and Hovi, 2014). This suggests that the programming of cardiovascular outcomes may occur after birth. The time spent in neonatal intensive care, with the painful and stressful treatments neonates routinely undergo (Carbajal et al., 2008), could represent a time period when programming of the stress response occurs. Lifetime stressful experiences and current perceived stress are factors affecting stress response that we were unable to control for in Studies IV and V.
6.5 Implications for future research

The finding of lower conditioning LTPA in VLBW adults, based on self-report, offers a potential mechanism linking preterm birth and increased risk factors for chronic NCDs later in life. This finding was not confirmed in a subgroup of VLBW participants with objective measurement (accelerometry). To date, no other studies have objectively assessed physical activity in VLBW adults. Thus, larger studies using objective measurement are warranted to confirm this hypothesis. Also evaluation of cardiorespiratory fitness in VLBW adults, not only studies focusing on behaviour, would give additional information on individual risk for NCDs.

Our finding of unhealthier dietary habits in a specific risk group, VLBW adults, is important. However, the 3-day food record is suboptimal for gathering detailed data on, for example, micronutrient, salt and vitamin intake. To obtain more reliable data, studies using objective measurement of nutrient intake should be conducted.

The blunted HPAA response to stress in VLBW adults in a laboratory setting strengthens the association between early life events and programming of later stress response. Of relevance would be additional information on stress responses in everyday life. Are the stress responses different also in real life, not only in laboratory settings? Another important direction for future research is the lower NA in VLBW women after stress. Our study group size is somewhat small for evaluating sex differences in stress response. If replicated, this may be a protective finding regarding hypertension and CVD.

Finally, it would be very interesting to combine the topics of Studies I-V, and measure cortisol responses after a) intense physical exercise and b) a nutritional challenge.
7 Conclusions

1. Based on self-report, healthy adults born preterm at VLBW undertake markedly less conditioning LTPA than controls born at term. The lower conditioning LTPA is not explained by differences in personality characteristics. This difference in physical activity was not captured by accelerometer measurement. Accelerometer measurement probably captures different aspects of physical activity than self-report; all types of physical activity cannot be measured by accelerometer measurement.

2. VLBW adults have unhealthier dietary habits than controls, with lower intake of fruits, vegetables, berries and dairy products. This is accompanied by lower intake of calcium and vitamin D.

3. A sedentary lifestyle and an unhealthy diet are modifiable features and offer a target for prevention of chronic NCDs, including osteoporosis, diabetes and CVD, in this high-risk population.

4. Our findings suggest that VLBW adults have a blunted HPAA response to psychosocial stress. This is accompanied by a lower insulin response.

5. We found no evidence of higher SAM stress response in VLBW adults. If replicated, our result of lower NA in VLBW women may be a protective finding.

6. Our results on stress response in VLBW adults reinforce previous suggestions that stress response is programmed early in life.
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Physical activity, nutrition and stress response in young adults born preterm – determinants of health and disease


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87


