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Marika Sipola-Leppänen

PRETERM BIRTH AND CARDIOMETABOLIC RISK FACTORS IN ADOLESCENCE AND EARLY ADULTHOOD

UNIVERSITY OF OULU GRADUATE SCHOOL;
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Abstract

About 11% of infants are born preterm (before 37 weeks of gestation) worldwide. Adults born preterm with very low birth weight show enhancement of cardiometabolic risk factors such as elevated blood pressure and impaired glucose regulation compared with their peers born at term. Not all the cardiometabolic risk factors related to preterm birth are known, or whether they apply to those born less preterm, although about 80% of premature infants are born late preterm.

The association between preterm birth and cardiometabolic risk factors in adolescence and adulthood was investigated in three cohort studies: The Helsinki Study of Very Low Birth Weight Adults, the Northern Finland Birth Cohort 1986, and the ESTER study.

Preterm birth over its whole range has a long-term impact on a child's health in later life: adults born preterm with very low birth weight had lower resting energy expenditure, but higher resting energy expenditure per unit lean body mass than their peers born at term. Adolescent girls born before 34 weeks of gestation had higher blood pressure and boys have elevated levels of LDL cholesterol and apolipoprotein B. Adults born preterm were more likely to be obese and to have hypertension or metabolic syndrome than their peers born at term. In addition to conventional biomarkers of cardiometabolic disorders, they had alterations in other cardiometabolic biomarkers, such as uric acid and liver transaminases.

Adolescents and adults born preterm are at greater risk of developing cardiometabolic disorders than their peers born at term. Most of the cardiometabolic risk factors related to preterm birth are modifiable. Favorable early life circumstances of premature infants, such as optimal nutrition and reduction of stress in neonatal intensive care units, might reduce the risk of later cardiometabolic disorders. In addition, children and adults born preterm might particularly benefit from primary prevention such as screening for additional risk factors and promotion of healthy lifestyles.

Keywords: cardiometabolic risk factor, metabolic syndrome, premature infant, preterm birth

Sipola-Leppänen, Marika, Ennenaikaisesti syntyneiden nuorten ja aikuisten sydän- ja verisuonitautien riskitekijät.
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Tiivistelmä

Noin joka yhdeksäs lapsi maailmassa syntyy ennenaikaisesti, ennen 37. raskausviikkoa. Keskosena syntyneillä aikuisilla on todettu enemmän joitakin sydän- ja verisuonisairauksien riskitekijöitä kuin heidän täysaikaisena syntyneillä ikätovereillaan. Näistä eniten on tutkittu etenkin kohonneen verenpaineen ja heikentyneen sokerin siedon esiintyvyyttä, mutta kaikkia myöhempien sairauksien riskitekijöitä ei tunneta. Suurin osa aiemmista keskostutkimuksista on tehty hyvin tai erittäin ennenaikaisesti syntyneillä, vaikka yli 80% keskosista syntyy lievästi ennenaikaisena. Ei ole juurikaan tutkimuksia siitä, ovatko sydän- ja verisuonitautien riskitekijät lisääntyneet myös tässä suuressa lievemmin ennenaikaisesti syntyneiden joukossa.

Eriasteisen ennenaikaisen syntymän vaikutuksia nuoruus- ja aikuisiän sydän- ja verisuonitautien riskitekijöihin tutkittiin kolmessa kohorttitutkimuksessa: Helsingin Pikku-K -tutkimuksessa, Pohjois-Suomen syntymäkohortti 1986 -tutkimuksessa sekä ESTER-tutkimuksessa.

Ennenaikaisella syntymällä sinänsä on pitkäaikaiset vaikutuksen syntyneen lapsen terveyteen myös nuoruudessa ja aikuisuudessa: Hyvin pienipainoisena ennenaikaisesti syntyneillä on korkeampi lepoenergian kulutus rasvatonta painoyksikköä kohden kuin täysiaikaisena syntyneillä ikätovereilla. Hyvin ennenaikaisena (ennen 34. raskausviikkoa) syntyneillä tytöillä on 16-vuotiaina korkeampi verenpaine, ja pojilla suuremmat LDL-kolesterolin ja apolipoproteiini B:n pitoisuudet. Keskosena syntyneet puolestaan täyttivät aikuisina todennäköisemmin lihavuuden, verenpainetaudin ja metabolisen oireyhtymän kriteerit. Perinteisten sydän- ja verisuonitautien riskitekijöiden lisäksi heillä oli muutoksia myös monissa muissa sydän- ja verisuonitautien merkkiaineissa, kuten uraatin ja maksa-arvojen pitoisuuksissa.

Ennenaikaisesti syntyneillä nuorilla ja aikuisilla on suurentunut riski sairastua sydän- ja verisuonitauteihin myöhemmällä iällä. Näitä riskejä on mahdollista ennaltaehkäistä, minkä vuoksi ennenaikaisesti syntyneet nuoret ja aikuiset voivat hyötyä terveellisistä elämäntavoista erityisen paljon.

Asiasanat: ennenaikainen syntymä, keskonen, metabolinen oireyhtymä, sydän- ja verisuonitaudit

To my loved ones

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Oulu, March 2015 Marika Sipola-Leppänen

Abbreviations

ABP	Ambulatory blood pressure
AGA	Appropriate for gestational age
ApoA1	Apolipoprotein A1
ApoB	Apolipoprotein B
BIA	Bioimpedance analysis
BP	Blood pressure
CI	Confidence interval
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
DOHaD	Developmental origins of health and disease
DXA	Dual X-ray absorptiometry
ELBW	Extremely low birth weight
EPT	Early preterm
FLI	Fatty liver index
FMBR	Finnish Medical Birth Register
GA	Gestational age
HDL-C	High-density lipoprotein cholesterol
HeSVA	the Helsinki Study of Very Low Birth Weight Adults
HOMA-IR	Homeostasis model assessment of insulin resistance
hsCRP	High-sensitivity C-reactive protein
ICD-10	International Classification of Diseases
IUGR	Intrauterine growth retardation
LBM	Lean body mass
LBW	Low birth weight
LDL-C	Low-density lipoprotein cholesterol
LGA	Large for gestational age
LPa	Lipoprotein (a)
LPT	Late preterm
METh	Metabolic equivalent hour
MRI	Magnetic resonance imaging
NICU	neonatal intensive care unit
NFBC	Northern Finland Birth Cohort
OGTT	Oral glucose tolerance test
OR	Odds ratio
REE	Resting energy expenditure

SBP	Systolic blood pressure
SD	Standard deviation
SGA	Small for gestational age
TC	Total cholesterol
TG	Triglyceride
VLBW	Very low birth weight
VLGA	Very low gestational age
WHO	World Health Organization

List of original articles

This thesis is based on the following publications, which are referred throughout the text by their Roman numerals:

I Sipola-Leppänen M, Hovi P, Andersson S, Wehkalampi K, Vääräsmäki M, Strang-Karlsson S, Järvenpää AL, Mäkitie O, Eriksson JG & Kajantie E. Resting energy expenditure in young adults born preterm ─ the Helsinki study of very low birth weight adults. PLoS One.6(3):e17700.

II Sipola-Leppänen M, Vääräsmäki M, Tikanmäki M, Hovi P, Miettola S, Ruokonen A, Pouta A, Järvelin M & Kajantie E (2014) Cardiovascular risk factors in adolescents born preterm. Pediatrics 2014: 134(4): 1072—1081.

III Sipola-Leppänen M, Vääräsmäki M, Tikanmäki M, Matinolli H, Miettola S, Hovi P, Wehkalampi K, Ruokonen A, Sundvall J, Pouta A, Eriksson JG, Järvelin M, Kajantie E. Cardiometabolic risk factors in adults born preterm. Am J Epidemol. 2015: In press.

IV *Sipola-Leppänen M, *Karvonen R, Tikanmäki M, Matinolli H, Martikainen S, Pesonen A, Räikkönen K, Järvelin M, Hovi P, Eriksson JG, Vääräsmäki M, Kajantie E. Ambulatory blood pressure and its variability in adults born preterm. Hypertension 2015;65:615—621.

*Equal contribution.

Contents

1 Introduction

Each year, 14.9 million infants worldwide, approximately one in nine live-born, are born preterm, i.e. before 37 weeks of gestation (Goldenberg *et al.*. 2008, Blencowe *et al.*. 2012, EUROCAT 2013). In Finland the proportion of premature infants is smaller, 5.7% of all infants in 2013 (Vuori & Gissler 2014). Owing to the development of neonatal intensive care in recent decades, the prognosis of infants born preterm has changed dramatically and most of them survive to adulthood. However, compared with the natural environment of the fetus, preterm infants continue their development and growth in a substantially different environment such as a neonatal intensive care unit (NICU). A growing body of evidence shows that pre- and postnatal events have long-lasting effects on a child's health: those born smallest and most immature, such as those born with very low birth weight (<1500 g) or very preterm (before 32 weeks of gestation), show enhancement of cardiometabolic risk factors as adults, for example elevated blood pressure (Hack *et al.* 2005, Hovi *et al.* 2010, Keijzer-Veen *et al.* 2010b, de Jong *et al.* 2012, Parkinson *et al.* 2013), impaired glucose regulation (Hofman *et al.* 2004, Hovi *et al.* 2007), and atherogenic lipid profiles (Parkinson *et al.* 2013). However, most of this evidence is limited to these conventional cardiometabolic risk factors in the extreme groups of adults with very low birth weight or born very preterm.

Most (about 70–80%) preterm infants are born moderately (at 32–36 weeks of gestation) or late preterm (at 34–36 weeks of gestation) (EUROCAT 2013, Martin *et al.* 2013, Vuori & Gissler 2014). However, only a few studies concerning adult cardiometabolic risks have included the whole range of preterm births. The results of these studies suggest that a linear relationship exists between shorter length of gestation and higher blood pressure in adulthood (Järvelin *et al.* 1993b, Johansson *et al.* 2005). If a similar "dose-response" relationship exists as regards other cardiometabolic risk factors, even moderately increased risks in the much larger group of people born late or moderately preterm could potentially reflect a larger public health burden.

The focus of this thesis was to evaluate the association between preterm birth and cardiometabolic risk factors in healthy adolescents and adults in three cohort studies, using conventional risk factors, such as body mass and blood pressure, the established components and criteria of metabolic syndrome, as well as emerging risk factors that may reflect specific pathophysiological pathways, such as resting energy expenditure, body composition, plasma apolipoproteins, uric acid, and markers of inflammation and fatty liver disease.

2 Review of the literature

2.1 Preterm birth

Normal pregnancy usually takes an average of 40 weeks (or 280 days) counted from the beginning of the woman's last menstrual period. However the range in length of gestation of live-born infants is wide, from 22 to over 43 weeks (Fig. 1). It is based on the assumption that the length of the menstrual cycle is 28 days and ovulation occurs on the 14th day after the last menstrual period. However, there are several limitations of dating based on last menstrual period, such as uncertainty regarding the last menstrual period date, menstrual disturbances including oligomenorrhea and delayed ovulation and bleeding disturbance in early pregnancy. In recent decades it has become increasingly common to verify the expected delivery date by means of ultrasonography, usually in the first trimester, or at the latest before 20 weeks of gestation.

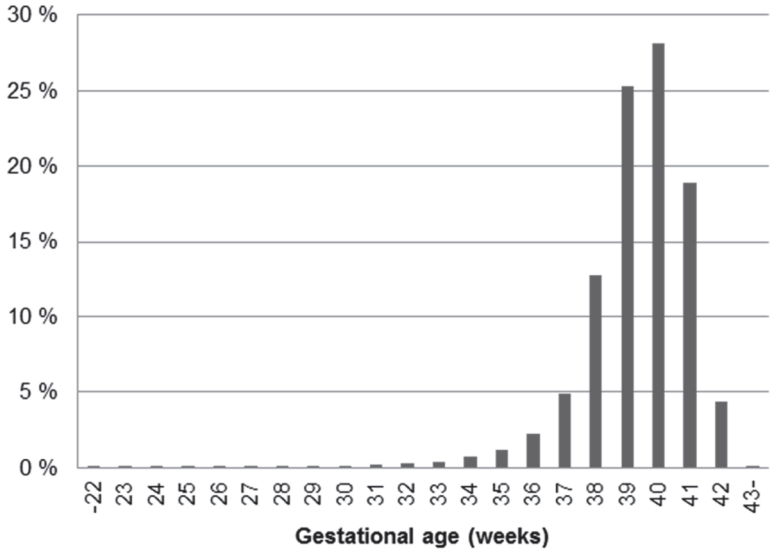

Fig. 1. Gestational age distribution of live-born infants in Finland in 2013 (Vuori & Gissler 2014).

According to the International Classification of diseases: tenth revision (ICD-10) a live birth occurs when a fetus, irrespective of gestational age, exits the maternal body and subsequently shows any sign of life, such as voluntary movement, heartbeat, or pulsation of the umbilical cord, for however brief a time and regardless of whether the umbilical cord or placenta are intact (World Health Organization 2004). The cut-offs for live birth vary between countries from 20 to 28 weeks (Blencowe *et al.* 2012). In Finland the cut-off for live birth is 22+0 gestational weeks or birth weight ≥ 500 g (Vuori & Gissler 2014). According to the number of completed gestational weeks World Health Organization (WHO) categorizes births in three groups:

- preterm (<37 gestational weeks)
- term (37 to 41 gestational weeks)
- post-term (≥42 gestational weeks). (WHO 1977)

An infant born too early (before 37 full gestational weeks) is called a preterm or premature infant. Preterm birth is also traditionally categorized in smaller groups according to length of gestation:

- extremely preterm (<28 weeks)
- very preterm (28 to 31 weeks)
- moderately preterm (32 to 36 weeks) (Engle *et al.* 2007, Blencowe *et al.* 2012).

As most preterm infants are born at between 34 to 36 weeks, moderate preterm birth was further split to focus on late preterm birth (34 to 36 completed weeks) by the American College of Obstetricians and Gynecologists (Engle *et al.* 2007).
Especially before the time when ultrasonography was widely used, categorization of preterm infants was based on birth weight:

- extremely low birth weight, ELBW (<1000 g)
- very low birth weight, VLBW (<1500 g)
- low birth weight, LBW (<2500 g).

However, in this categorization low birth weight can be due to prematurity or being born small for gestational age, or both. Birth weight in relation to gestational age has been used as an indicator of intrauterine growth (Lee *et al.* 2003). There are several national criteria used and they are very different from each other (Hadlock *et al.* 1991, Ioannou *et al.* 2012, Papageorghiou *et al.* 2014):

- small for gestational age, SGA (more than two standard deviations (SDs) below the mean, or <10th percentile)
- appropriate for gestational age, AGA (within ± 2SDs around the mean, or within the 10th and 90th percentiles)
- large for gestational age, LGA (more than 2SDs above the mean, or >90th percentile).

2.1.1 Causes of preterm birth

The obstetric precursors of preterm delivery are categorized in three groups: 1) spontaneous labor (40–45% of preterm births), 2) rupture of membranes (25–30% of preterm births), and 3) "indicated"/iatrogenic labor (30–35% of preterm births) in conditions that threaten the health or life of the mother or fetus (Goldenberg *et al.* 2008). Preterm birth is thought to be a pathological condition or syndrome with multiple etiologies including inflammation, infection, uteroplacental ischemia or hemorrhage, uterine over-distension, stress, and an immunological process (Romero *et al.* 2006). The etiology is not fully understood and a precise mechanism cannot be defined in most of the cases.

The risk factors of preterm birth include demographic characteristics, medical history and lifestyle, pregnancy history, and medical conditions in the present pregnancy (1.1.1.1.Table 1). Some of these risk factors may not be related to preterm birth independently and preterm birth may be the outcome of the interaction of several risk factors. There is also evidence of a genetic background to birth timing (Plunkett *et al.* 2009) and spontaneous preterm birth (Plunkett & Muglia 2008, Wilcox *et al.* 2008, Haataja *et al.* 2011): women with a history of preterm labor have a more than 5-fold risk of preterm labor in the next pregnancy (Bezold *et al.* 2013). The results of register studies concerning siblings, half-siblings and/or twins have suggested that both maternal and fetal genes have an effect on the length of gestation and/or the risk of preterm birth (Lunde *et al.* 2007, York *et al.* 2013).

Although there have been many efforts to predict and prevent preterm birth, means to avoid prematurity are scanty. Screening and minimization of the risks, for example by treatment of bacterial vaginosis or urinary tract infections, may help in reaching the optimal length of gestation. Bed rest has been a traditional non-pharmacologic treatment to prevent preterm births, but there is a lack of evidence for its effectiveness. In addition, tocolytic therapy can be used to inhibit contractions in cases of threatened preterm labor (Committee on Practice Bulletins—Obstetrics 2012).

Table 1. Risk factors of preterm birth.

Characteristics of the of mother
Low socioeconomic status or low educational attainment
Age <18 or >35 years
Low body mass index or poor nutritional status
Unmarried life
Smoking, alcoholism or drug use
Hard working conditions
High levels of psychological or social stress or exposure to objectively stressful conditions
Depression
Chronic disease
Ethnic background
Pregnancy history
Primipara
Previous second-trimester miscarriage or stillbirth
Previous preterm labor or infant with low birth weight
Previous operation of uterine cervix
Present pregnancy
Multiple pregnancy
Cervical insufficiency
Low inter-pregnancy interval (< 6 months)
Polyhydramnion or oligohydramnion
Abdominal surgery in the second or third trimester
Contractions
Placenta previa
Placental abruption
Hypertensive pregnancy disorder
Intrauterine growth retardation or malformation
Hepatic cholestasis of pregnancy
Vaginitis or cervicitis
Premature rupture of membranes

References: Olsen *et al.* 1995, Goldenberg *et al.* 2008, Blencowe *et al.* 2012, Romero *et al.* 2014.

2.1.2 Epidemiology of preterm birth

More than one in ten of all infants are born preterm: the worldwide prevalence of preterm birth is 11.1%, i.e. 14.9 million births in 2010. However, the prevalence ranges from 5% to 18% depending on the country (Blencowe *et al.* 2012). For example, in Europe the rate varies from about 5% to 10% (EUROCAT 2013). In Finland it has been low and relatively stable during the last ten years, being highest

(6.3%) around 2000, and in 2013 it was 5.7% (Vuori & Gissler 2014). In 2010 the highest rates of preterm birth were in Southeast Asia (13.6%), South Asia (13.3%), and Sub-Saharan Africa (12.3%) (Blencowe *et al.* 2012). The USA also has a high preterm birth rate (12%) (Blencowe *et al.* 2012, Martin *et al.* 2013). There are also differences in preterm birth rates between ethnic groups within countries: for example among black Americans the rate was as high as 17.5%, when the rate was 10.9% among white Americans (Blencowe *et al.* 2012). The incidence of preterm birth is rising worldwide (Blencowe *et al.* 2012, Zeitlin *et al.* 2013).

Most preterm infants are born late preterm: For example in Finland 75.5% of preterm infants (and 4.2% of all infants) were born late preterm in 2013 (Vuori & Gissler 2014) and in the USA the rate was 70.8% (8.5% of all infants) in 2010 (Fig. 2) (Martin *et al.* 2013).Preterm birth is more common among boys than girls – about 55% of all preterm infants are boys (Zeitlin *et al.* 2002). Boys born preterm are also at a higher risk of neonatal mortality and long-term impairment (Smith 2000, Stevenson *et al.* 2000, Kent *et al.* 2012).

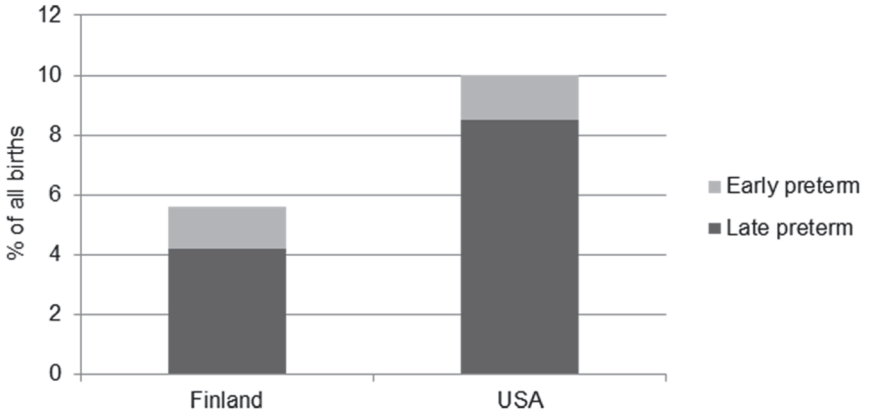

Fig. 2. Proportions of early and late preterm births of all births in Finland (2011–2012) and the United States of America (2010) (Martin *et al.* 2013, Vuori & Gissler 2013).

Mortality related to preterm birth

The intensive care of neonates born preterm has improved remarkably since the 1960s. In the late 1960s assisted ventilation was introduced, in the 1970s the use of antenatal and postnatal glucocorticoids was started and in the 1980s the use of

exogenous surfactant started to prevent bronchopulmonary dysplasia and many other conditions (Philip 2005). Most of the treatments were primarily focused on improving the outcomes related to pulmonary problems. However, monitoring of the infant by physiological and biochemical measurements the ability to provide nutrition intravenously, and pharmacological manipulation were also important (Philip 2005). In addition to advances in technology, skin-to-skin care (kangaroo mother care) and breastfeeding have reduced infant mortality and morbidity (Lawn *et al.* 2010, Flacking *et al.* 2012). However, over one million infants every year die as a result of complications related to preterm birth. It is estimated that every third neonatal death (<28 days after birth) is caused by preterm birth and it is the largest direct cause of neonatal mortality and the second most common cause of death after pneumonia in children under 5 years old (Liu *et al.* 2012). In the U.S. in 2010, 35.2% of infant deaths were related to preterm birth (Mathews & MavDorman 2013) and in Europe the neonatal mortality of infants born at <32 weeks accounts for 48% of all neonatal deaths (EUROCAT 2013). Overall neonatal mortality is highest in developing regions including Southeast Asia. However, the proportion of deaths related to preterm birth is similar worldwide, about 30–36% of all neonatal deaths (Liu *et al.* 2012). In Finland the perinatal mortality rate in preterm infants was 3.8% as in all infants it was 0.35% in 2013 (Vuori & Gissler 2014).

Most neonatal deaths occur during the 7 days after birth ("early neonatal" or perinatal mortality). Gestational age correlates negatively to the perinatal and neonatal mortality rate (Fig. 3). In infants born at <34 weeks the perinatal mortality rate was 3.5% and in infants born at 34–36 gestational weeks the rate was 0.6% in Finland in 2012. Although infants born late preterm are often referred to as "near term", mortality rates are higher than in term infants. For example, in the United States the mortality rate of late-preterm infants was found to be 4.6 times higher than in term infants (Engle *et al.* 2007). Those born preterm have an increased risk of mortality throughout childhood, but not in adolescence (Swamy *et al.* 2008, Crump C 2011). Again, in young adulthood, preterm birth has been associated with increased mortality, even among individuals born late preterm (Crump C 2011). In spite of increased mortality rates, most infants born preterm survive to adulthood.

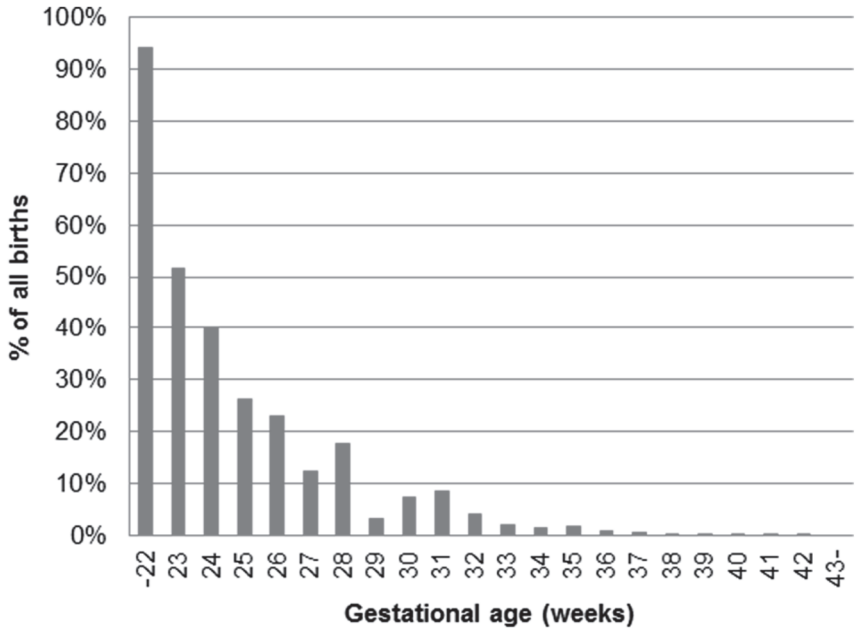

Fig. 3. Perinatal mortality rate by gestational age in weeks in Finland in 2013 (Vuori & Gissler 2014).

Morbidity related to preterm birth

Despite the developments in intensive care of preterm infants in past decades, preterm survivors still have higher morbidity rates than infants born at term. Some of the factors associated with preterm birth, such as intrauterine growth retardation (IUGR), are related to morbidity of preterm infants. However, preterm infants are exposed to a very different environment in their first weeks of postnatal life than if they would have been in utero till term. In addition, most organs, such as the lung, brain and kidneys, are immature and especially susceptible to the consequences of preterm birth (Saigal & Doyle 2008). As with neonatal mortality, morbidity rates are also lower the higher the gestational age is at birth (Bastek *et al.* 2008). However, late-preterm infants are much more likely to show newborn morbidity than term infants (Bastek *et al.* 2008, Committee on Obstetric 2008, Saigal & Doyle 2008, Shapiro-Mendoza *et al.* 2008, Kugelman & Colin 2013). Common neonatal complications of preterm neonates are presented in Table 2.

In the first years of life, children born preterm with VLBW, and also those born late-preterm, have more hospital readmissions than children born at term. Rates of acute hospitalization decreases in adolescence (Saigal *et al.* 2001, Bird *et al.* 2010, Korvenranta *et al.* 2010) and in early adulthood rates of hospitalization are similar to those among term-born peers (Saigal *et al.* 2007), though they have higher rates of chronic conditions than controls (Hack *et al.* 2002). The most frequently occurring medical conditions in children and adults born preterm are asthma, recurrent bronchitis, cerebral palsy, mental retardation, neurosensory impairment, and epilepsy (Hack *et al.* 2002, Saigal *et al.* 2007, Moster *et al.* 2008, Korvenranta *et al.* 2010). However, most of those who survive after preterm birth to reach adolescence and adulthood are healthy.

Table 2. Common neonatal complications after preterm birth.

Respiratory distress syndrome and bronchopulmonary dysplasia
Persistent pulmonary hypertension of newborns
Pneumothorax
Patent ductus arteriosus
Apnea/bradycardia
Hyperbilirubinemia
Intraventricular or periventricular hemorrhage
Sepsis and other infections
Temperature instability
Hypoglycemia
Dehydration
Feeding difficulties and under-nutrition
Necrotizing enterocolitis

References: Wang *et al.* 2004, Philip 2005, Engle *et al.* 2007, Saigal & Doyle 2008.

2.2 Cardiometabolic risk factors

Cardiometabolic risk refers to a high lifetime risk for cardiovascular disease (CVD) (Sipola-Leppänen *et al.* 2015). CVDs include diseases of the heart, vascular diseases of the brain, and diseases of blood vessels. They can be categorized into two groups according to their etiology to those developed as a result of atherosclerosis (ischemic heart disease or coronary artery disease, cerebrovascular disease, diseases of the aorta and arteries – including hypertension and peripheral vascular disease) and others (congenital heart disease, rheumatic heart disease, cardiomyopathies, cardiac arrhythmias) (Mendis

et al. 2011). The present work is concentrated on cardiovascular disease risks related to atherosclerosis. Atherosclerosis is the underlying complex pathological process in the walls of blood vessels that results in coronary heart disease and cerebrovascular disease.

Table 3. Conventional cardiometabolic risk factors.

Behavioral
Tobacco smoking, including second-hand smoke
Physical inactivity
Unhealthy diet (e.g. rich in salt and calories)
Harmful use of alcohol
Metabolic risk factors
Raised blood pressure
Raised blood sugar
Dyslipidemias
Overweight and obesity
Inflammation
Hypercoagulation
Other
Low socioeconomic status
Advancing age
Male sex
Genetic disposition
Psychological factors (e.g. stress, depression)
Air pollution

References: Berenson *et al.* 1998, Brunzell *et al.* 2008, Mendis *et al.* 2011, Lim *et al.* 2012.

Atherosclerosis starts to develop as early as in childhood and adolescence due to the overall effect of a number of risk factors (presented in Table 3) (Järvisalo *et al.* 2001, Raitakari *et al.* 2003, Koskinen *et al.* 2009, Lewandowski *et al.* 2014). Behavioral and metabolic risk factors play a key role in the etiology of atherosclerosis (Mendis *et al.* 2011). Previous studies have shown that the fetal period and childhood have a substantial effect on an individual's risk of later cardiovascular disease (see section 2.3). CVDs are the leading cause of death worldwide, representing about 30% of all deaths globally and 47% of all deaths in Europe, and the numbers are increasing (World Health Organization 2011, Nichols *et al.* 2012). In Finland ischemic heart disease causes more than every fifth death (21%, about 11,000 deaths [add time period], 53% men), though the

numbers have decreased in the past twenty years (Statistics Finland 2012). Most cardiovascular diseases could be prevented by reducing the risk factors.

Metabolic syndrome is a combination of factors that multiply a person's risk of heart disease, diabetes and stroke (Lakka *et al.* 2002, Onat *et al.* 2002). The risk factors include central (abdominal) obesity, raised blood pressure, elevated fasting plasma glucose levels, and dyslipidemias (high serum triglyceride, and low high-density cholesterol (HDL-C) levels). Various diagnostic criteria for metabolic syndrome have been in use, decided upon by different organizations (the WHO, the National Cholesterol Treatment panel III, the International Diabetes Foundation and the American Heart Association/National Heart, Lung, and Blood Institute), with the same risk factors but different cut-off points. However, in 2009 these major organizations proposed a Joint Interim Statement in an attempt to unify the criteria (Alberti *et al.* 2009). The cut-off levels of these criteria are presented in section 4.3.7. Obesity, particularly abdominal obesity, is a key component underlying many characteristics of metabolic syndrome.

The prevalence of metabolic syndrome varies depending on the criteria used and the population. In 2001–2002 , among adolescents born in Northern Finland, the overall prevalence of metabolic syndrome according to the International Diabetes Foundation pediatric definition was 2.4% (95% CI 2.0 to 2.8%) and according to the International Diabetes Foundation adult definition the overall prevalence was lower, 1.7% (95% CI 1.3 to 2.0%) (Pirkola *et al.* 2008). In Finland the overall prevalence of metabolic syndrome in young adults aged 24–39 years in 2001 was 10–15% and 6 years later in 30- to 45-year-old adults it was 15–23% depending on the metabolic syndrome definition used. The prevalence of metabolic syndrome increased from 1.0% to 7.5% in 24-year-old participants between the years 1986 and 2001. The increase was mostly driven by an increase in central obesity (Mattsson *et al.* 2007).

Cardiometabolic syndrome, on the other hand, is a constellation of metabolic dysfunctional characteristics – cardiovascular, renal, metabolic, hemodynamic, prothrombotic and inflammatory abnormalities (Castro *et al.* 2003, Govindarajan *et al.* 2005).

2.3 Developmental Origins of Health and Disease (DOHaD)

In the 1980's David Barker and his colleagues presented the theory that undernutrition during gestation was an important early origin of adult cardiac and metabolic disorders due to fetal programming that permanently shaped the body's

structure, function and metabolism and contributed to adult disease (Gillman 2005, Barker 2007). This theory was based on epidemiological studies of birth and death records that revealed a high geographic correlation between rates of infant mortality and certain classes of later adult deaths as well as an association between birth weight and rates of adult death from ischemic heart disease (Barker & Osmond 1986, Barker *et al.* 1989, Barker *et al.* 1993). The theory is often called "Barker's hypothesis" and it stimulated interest in the fetal origins of adult disorders, which expanded and led to the formation of an International Society for Developmental Origins of Health and Disease (DOHaD).

The hypothesis has been supported by a worldwide series of animal (Mcmillen & Robinson 2005, Nuyt 2008) and epidemiological studies. These studies have shown that those who are born with low birth weight have, for example, increased incidences of cardiovascular disease and mortality (Barker *et al.* 1989, Osmond *et al.* 1993, Forsen *et al.* 1997, Rich-Edwards *et al.* 1997, Kaijser *et al.* 2008), higher blood pressure (Law *et al.* 1993, Law & Shiell 1996, Barker *et al.* 2001), increased rates of hypertension (Barker & Osmond 1988, Barker 1992, Huxley *et al.* 2000, Järvelin *et al.* 2004b, Johansson *et al.* 2005), and impaired glucose regulation or type 2 diabetes (Hales *et al.* 1991, Robinson *et al.* 1992, Barker *et al.* 2002, Eriksson *et al.* 2006, Whincup *et al.* 2008, Kaijser *et al.* 2009). In addition, length of gestation seems to be associated with mortality from cardiovascular disease (Koupil *et al.* 2005) and diabetes (Kaijser *et al.* 2009), which indicates similar metabolic consequences in adults born preterm and those born with low birth weight.

2.4 Long-term cardiometabolic risk factors related to preterm birth

As with morbidity and mortality in infancy, the long-term impact of preterm birth is usually inversely related to the gestational age at birth, with the greatest effects being seen in those born very or extremely preterm. Most of the relevant follow-up studies have been focused mainly on health during childhood.

In Swedish cohort studies low gestational age at birth was independently associated with increased mortality in early childhood and young adulthood (Crump C 2011), and preterm birth before 32 weeks was associated with an almost twofold increased risk of cerebrovascular disease compared with that among term-born individuals, while individuals born at 32–36 weeks were not at increased risk (Ueda *et al.* 2014). In addition, in older people shorter length of gestation has been associated with an elevated risk of cerebrovascular disease (Koupil *et al.* 2005), but not with later ischemic heart disease (Koupil *et al.*

2005), or the association was found only when adjusted for birth weight (Kaijser *et al.* 2008). However, studies on older people might be affected by survival bias, as the survival rate of preterm infants was much lower several decades ago.

Because ischemic heart disease is not prevalent in young adults, relevant studies are often concentrated on risk factors, not the full-blown syndrome. There are several cohort studies of survivors who have been followed longitudinally from birth into adolescence or adulthood. Most of them include subjects born with VLBW or VLGA and subjects have been selected according to birth weight rather than gestational age, mainly because gestational age was more uncertain in the era before routine antenatal ultrasonographic examination. In addition, those individuals whose length of gestation was determined ultrasonographically are now young adults.

2.4.1 Body size and composition

In the early postnatal period infants born preterm show substantial growth failure, which is usually followed by a period of catch-up growth. The catch-up starts in early infancy and usually stops at 2–3 years of age (Hack *et al.* 2003, Saigal *et al.* 2006). Despite the catch-up, adults born preterm are on average shorter (Kistner *et al.* 2000, Peralta-Carcelen *et al.* 2000, Weiler *et al.* 2002, Bonamy *et al.* 2005, Rogers *et al.* 2005, Saigal *et al.* 2006, Hovi *et al.* 2007, Rotteveel *et al.* 2008a, Indredavik Evensen *et al.* 2009) and lighter (Kistner *et al.* 2000, Peralta-Carcelen *et al.* 2000, Rogers *et al.* 2005, Indredavik Evensen *et al.* 2009) than their controls (**Virhe. Viitteen lähdettä ei löytynyt.**), and the catch-up for weight is more pronounced than that for height (Hack *et al.* 2003, Saigal *et al.* 2006).

Catch-up in weight may lead to altered body composition in adulthood. For example, in term-born individuals, the early catch-up weight gain has been shown to be associated with later obesity (Ong *et al.* 2000), which is a key component underlying many characteristics of metabolic syndrome and is a major health problem throughout the world. Most of the studies on the body size of former preterm infants concern adults born with VLBW or VLGA and they have reported lower weight in adolescents and adults born preterm with VLBW or ELBW, which was explained by lower lean body mass (LBM, aka fat-free mass, Table 5) (Peralta-Carcelen *et al.* 2000, Hovi *et al.* 2007). Although one group reported more adipose tissue in adults born preterm (≤33 w) (Thomas *et al.* 2011), two others reported no difference in body composition between adults born preterm (<32 wk or <1500 g) and those born at term (Weiler *et al.* 2002, Rotteveel *et al.* 2008a). However, in studies on adults born

Table 4. Mean differences (with 95% CI or P value) in body size in adolescents and adults born preterm compared with term-born controls.

Authors	Age	Subjects	Height (cm)	Weight (kg)	BMI
Women					
Rogers *et al.* 2005	~17	≤800 g	-7.9 (P<0.001)	-2.3 (P<0.01)	0.51 (NS)
Saigal *et al.* 2006	21.5—26.5	<1000 g	-6.2 (-8.3, -4.0)	-7.1 (-11.8, -2.4)	-0.75 (-2.5, 0.99)
Hack *et al.* 2003	~20	<1500 g	-1.2 (-3.2, 0.9)	-2.0 (-6.9, 2.8)	-0.5 (-2.1, 1.0)
Hovi *et al.* 2007	18–27	<1500 g	-5.3 (-7.3, -3.2)	W: -8.5% (-12.9, -3.8)	-2.4% (-6.7, 2.1)
Rotteveel *et al.* 2008	~20	<32 w	-2.0 (P=0.003)	-2.1 (P=0.12)	0.3 (P=0.94)
Edstedt Bonamy et al 2005	~16	≤34 w	-3 (P=0.03)	1 (P=0.76)	1 (P=0.23)
Men					
Rogers *et al.* 2005	~17	≤800 g	-10.2 (P<0.001)	-9.1 (P<0.01)	-0.35 (NS)
Saigal *et al.* 2006	21.5—26.5	<1000 g	-7.2 (-10.3, -4.1)	-6.5 (-11.7, -1.2)	-0.15 (-1.8, 1.5)
Hack *et al.* 2003	~20	<1500 g	-3.1 (-5.2, -1.1)	-10.5 (-14.8, -6.2)	-2.6 (-3.8, -1.3)
Hovi *et al.* 2007	18—27	<1500 g	-5.9 (-8.3, -3.5)	-12% (-16.9, -8.8)	-5.9% (-10.4, -1.1)
Rotteveel *et al.* 2008	~20	<32 w	-2.8 (P=0.003)	0.8 (P=0.12)	0.8 (P=0.94)
Mathai *et al.* 2013	35.7	<37 w	All: -1.5 (P=0.44)	M: 20 P=0.01)	5.8 (P=0.021)
Women and men					
Peralta-Carcelen *et al.* 2000	14.8 (1.8)	≤1000 g	-4.8 (P<0.05)	-9.1 (P<0.05)	NR
Inderavik Evensen *et al.* 2009	~18	<1500 g	-3.8 (P<0.01)	-5.6 (P<0.01)	1.0 (NS)
Weiler *et al.* 2002	16—19	<1500 g	-7.3 (P<0.05)	-5.7 (NS)	0.0 (NS)
Lewandowski *et al.* 2013	23—28	<1850g	-4.4 (P<0.001)	3.7 (P=0.33)	2.0 (P=0.003)
Irving *et al.* 2000	~24	<2000 g	2 (NS)	6.8 (NS)	NR-
Kistner *et al.* 2000	23—30	<32 w	-3.2 (P<0.01)	-4.0 (P<0.01)	-0.5 (NS)
Thomas *et al.* 2011	18—27	≤33 w	-0.02 (-0.06, 0.03)	-1.69 (-6.8, 3.4)	-0.12 (-1.6, 1.4)
Mathai *et al.* 2013	35.7	<37 w	-1.5 (P=0.44)	5.1 (P=0.28)	2.2 (P=0.14)
Skilton *et al.* 2011	~32	<37 w	NR	NR	0.0 (P=0.66)

Abbreviations: NR, not reported; NS, not statistically significant.

preterm within the whole spectrum of preterm birth, adults born preterm have been found to have a higher body mass index (BMI) and a more adipose body composition (Table 5) (Breukhoven *et al.* 2012, Lewandowski *et al.* 2013, Mathai *et al.* 2013). In addition, adults born preterm (<37 weeks) were more obese compared with those born at term (39% vs. 14%, P=0.049) (Mathai *et al.* 2013). However, some studies did not reveal any difference in body size (Irving *et al.* 2000, Thomas *et al.* 2011, Parkinson *et al.* 2013), or a difference was seen only in men (Hack *et al.* 2003, Hovi *et al.* 2007). In addition to lower LBM and possibly a more adipose body composition, adults born preterm have lower bone mineral density (Hovi *et al.* 2009).

The body composition of adolescents and adults born preterm has been studied by bioimpedance analysis (BIA), dual X-ray absorptiometry (DXA) and magnetic resonance imaging (MRI) in previous studies. MRI allows determination of anatomically defined compartments – for example, intra-abdominal versus subcutaneous fat, and is one of the "gold standard" methods to assess body composition. DXA is also a precise method that provides detailed information on body composition (Woodrow 2007). BIA is used to measure the resistance to a weak current (impedance) applied across extremities and provides an estimate of body fat using an empirically derived equation. Although compared with MRI and DXA, BIA is more likely to be affected by other factors such as position and posture of the subject, the precision of the technique is high (Woodrow 2007). DXA and BIA do not distinguish between visceral and subcutaneous fat tissue.

2.4.2 Resting energy expenditure

The mechanisms behind the altered body composition in former preterm infants are not clear. Lean body mass is positively related to resting energy expenditure (REE, or resting metabolic rate), which means the number of calories burned to maintain basic life functions at rest (Weinsier *et al.* 1992, Wang *et al.* 2000). Having a lower LBM, adults born preterm with VLBW would be expected to have lower REE. However, the REE of adults born preterm has not been reported before. There are inconsistent findings in studies comparing REE in children born preterm and SGA with those born preterm and AGA (Mericq *et al.* 2009, Sepúlveda *et al.* 2013). The association between LBW and REE in adulthood is also unclear: in young adults there was no statistically significant difference in REE between those born LBW compared with those born with normal birth

weight (Weitz *et al.* 2013). However, a study on Finnish adults (mean age 61.6 years) showed that birth weight is positively associated with adult REE (Sandboge *et al.* 2012).

Within-individual REE is a very stable measurement: individual variability ranges from 3% to 7.5% (Compher *et al.* 2006). However, between individuals there are differences in REE and the results of previous studies have suggested that these differences could be important contributors to the development of obesity (Ravussin *et al.* 1988, Astrup *et al.* 1999). REE accounts for about two thirds of daily total energy expenditure (Fig. 4) (Levine 2004). The remainder depends on an individual's thermogenesis and physical activity, the amount of which varies substantially between individuals according to their physical activity levels (Lowell & Spiegelman 2000). Young adults born preterm with VLBW were reported to have lower rates of physical activity energy expenditure in the Helsinki Study of Very Low Birth Weight Adults (HeSVA) (Kaseva *et al.* 2012).

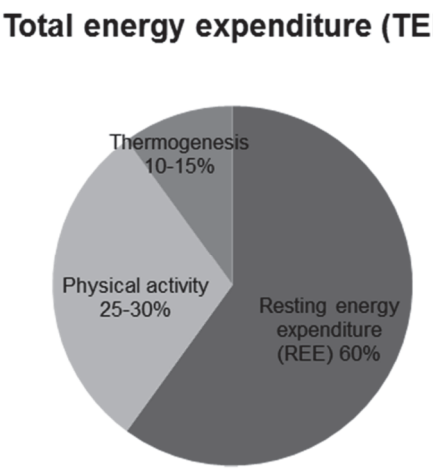

Fig. 4. Components of daily total energy expenditure.

Table 5. Mean differences in body composition measurements of adolescents and adults born preterm compared with their peers born at term.

Authors	Age (y)	Study group	Method	Lean body mass (kg) (95% CI or P value)	Fat mass (kg) (95% CI or P value)	Percentage body fat (95% CI or P value)
Peralta-Carcalen *et al.* 2000	14.8 (SD 1.8)	≤1000 g	DXA	-4.6 (P≤0.01)	-4.1 (P≤0.01)	-2.9 (NS)
Hovi *et al.* 2007	18—27	<1500 g	DXA	W: -9.5% (-13.1, -5.7)	NR	W: -0.5 (-2.3, 1.2)
				M: -12.7% (-17.1, -8.0)		M: 0.0 (-2.1, 2.2)
Weiler *et al.* 2002	16—19	<1500 g	DXA	-1.9 (NS)	NR	2.5 (NS)
Rotteveel *et al.* 2008	~20	<32 w	BIA	W: -1.2	W: -1.0 (NS)	W: 0.7 (NS)
				M: 0.2 (NS)	M: 0.7 (NS)	M: -0.4 (NS)
Thomas *et al.* 2011	18—27	≤33 w	MRI	NR	Total adipose tissue: 2.2 (0.3, 4.1)	NR
Breukhoven *et al.* 2012	18—24	<36 w	DXA	3.4 (P<0.01)	0.9 (P<0.05)	NR
Mathai *et al.* 2013	33.4—38.0	<37 w	DXA	NR	NR	6.0 (P=0.011)

BIA, bioelectrical impedance analysis; DXA, dual X-ray absorptiometry; MRI, Magnetic resonance imaging; NR, not reported; NS, not statistically significant.

2.4.3 Blood pressure

Office-measured blood pressure

An association between preterm birth and elevated blood pressure in later life has been shown in many previous studies (Table 6). Most studies on adults born preterm with low, very low or extremely low birth weight have shown higher systolic blood pressure (SBP) in preterm subjects versus controls (Irving *et al.* 2000, Doyle *et al.* 2003, Hovi *et al.* 2007, Indredavik Evensen *et al.* 2009, Vohr *et al.* 2010) and higher diastolic blood pressure (DBP) (Irving *et al.* 2000, Doyle *et al.* 2003, Hovi *et al.* 2007, Vohr *et al.* 2010), and this has also been seen in adolescents (Pharoah *et al.* 1998). However, Hack *et al.* found no statistically significant difference in BP in adults born preterm with VLBW compared with controls born at term (Hack *et al.* 2005). Studies on adolescents and adults born preterm at low gestational age have shown an association between preterm birth and higher SBP levels in later life (Irving *et al.* 2000, Kistner *et al.* 2000, Rotteveel *et al.* 2008a, Keijzer-Veen *et al.* 2010b, Thomas *et al.* 2011). The association is not particularly clear in studies including all subjects born preterm (<37 weeks) (Table 6) (Barros & Victora 1999, Singhal *et al.* 2001b, Järvelin *et al.* 2004a, Johansson *et al.* 2005, Dalziel *et al.* 2007, Cooper *et al.* 2009, Lazdam *et al.* 2010, Rossi *et al.* 2011, Skilton *et al.* 2011, Tauzin *et al.* 2014). In addition, in a meta-analysis that included 10 studies on children and adults born preterm (mean age 17.8 years, range 6.3–22.4 years) and a mean gestational age of 30.2 weeks (range 28.8–34.1 weeks), the estimated office-measured SBP difference was 2.5 mm Hg (95% CI 1.7–3.3 mm Hg) higher among preterm subjects versus term-born controls (de Jong *et al.* 2012). In another meta-analysis that included preterm adults, preterm birth was associated with an elevation of SBP of 4.2 mm Hg (95% CI 2.8–5.7) (Parkinson *et al.* 2013).

An inverse linear association between gestational age and SBP has also been shown. For example, -0.1 to -0.5 mm Hg changes in SBP per one-week increase in gestational age have been reported (Siewert-Delle & Ljungman 1998, Leon *et al.* 2000, Järvelin *et al.* 2004b, Dalziel *et al.* 2007).

A few studies have revealed higher relative risks of hypertension in adults born preterm compared with adults born at term, ranging from 1.2 to 2.5 (Johansson *et al.* 2005, Dalziel *et al.* 2007, Crump *et al.* 2011b). In addition, in the Northern Finland Birth Cohort 1966, women born preterm had an approximately twofold risk of

gestational hypertension during their first pregnancies, but no increased risk of preeclampsia (Pouta *et al.* 2004).

Several studies have concerned sex-specific analysis and most (Doyle *et al.* 2003, Järvelin *et al.* 2004b, Hack *et al.* 2005, Cooper *et al.* 2009), but not all (Rotteveel *et al.* 2008a, Thomas *et al.* 2011) have revealed a greater difference in women than in men. A statistically significant interaction between preterm birth and sex on blood pressure was seen in the Northern Finland Birth Cohort 1966 (Järvelin *et al.* 2004b). In brief, both women and men born preterm had higher levels of office-measured blood pressure than their peers born at term, but the difference was greater in women.

Ambulatory blood pressure

Studies on adults born preterm with VLBW (Doyle *et al.* 2003, Hovi *et al.* 2010, Roberts *et al.* 2014) and born at <28 weeks (Roberts *et al.* 2014) have shown elevated mean 24-h systolic ambulatory blood pressures (ABPs) (0). Doyle *et al.* (2003) reported a statistically significant difference in all preterm subjects born before 28 weeks, and also a difference between women and men in a gender-specific analysis. Again, in the Helsinki Study of Very Low Birth Weight Adults, gender-specific analysis revealed a statistically significant difference in ABP in women only. A gender-specific association in a meta-analysis was similar: women born preterm had a 3.5-mmHg (95% CI 1.4–5.6) higher systolic ABP than women born at term, but such a difference was not seen in men (Parkinson *et al.* 2013). In contrast, another study of young women born preterm (<32 weeks) did not reveal any statistically significant difference in ABP (Kistner *et al.* 2000) (0). In a study on Turkish children (5–17 y), preterm birth was associated with higher nocturnal systolic blood pressure, but not with daytime or 24-hour BP (Cruickshank *et al.* 2013).

Variability of blood pressure

The variability of ABP is less studied. In HeSVA, the variability of daytime SBP, as expressed by the SD of each individual's measurements, was 1.1 mmHg (P=0.03) higher in men born with VLBW compared with men born at term (Hovi *et al.* 2010). In addition, a study concerning late preterm birth and BP in 4- to 13-year-old children revealed higher 24-hour SBP and DBP, and higher daytime SBP and nighttime SBP and DBP than in controls, but the investigators did not present the mean values of ambulatory blood pressure (Gunay *et al.* 2014). The variability of 24-hour BP (Parati

1987, Frattola 1993) and SBP when awake (Tatasciore *et al.* 2007) independently predicts organ damage, 24-hour SBP predicts atherosclerosis (Mancia *et al.* 2001), and nighttime SBP variability is associated with cardiac event incidence in hypertensive patients (Verdecchia *et al.* 1994).

2.4.4 Lipid metabolism

Dyslipidaemias represent a major risk as regards ischemic heart disease and stroke. Globally, one third of cases of ischemic heart disease is attributable to high cholesterol levels and hypercholesterolemia is one of the leading risk factors causing burden of disease (Lim *et al.* 2012). Previous findings concerning later life serum lipid levels of former preterm infants are inconsistent. Several studies have reported no association between preterm birth and serum lipid levels in adulthood (Irving *et al.* 2000, Kistner *et al.* 2004, Finken *et al.* 2006, Rotteveel *et al.* 2008a, Hovi *et al.* 2011, Skilton *et al.* 2011, Thomas *et al.* 2011). However, there are also findings that have indicated a more atherogenic lipid profile in adults born preterm: Adults (aged 33.4–38.0 years) born preterm (<37 w) had lower HDL-C concentrations and greater total cholesterol (TC) to HDL-C ratios (Mathai *et al.* 2013). In a British cohort study young adults (23–28 y) born preterm <1850 g had higher total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C) and TG levels than their peers born at term (Lewandowski *et al.* 2013). In addition, a study concerning measurement of lipids after a meal showed that postprandial triacylglycerol levels were increased in men born SGA (Rotteveel *et al.* 2008a). In the detailed HeSVA analysis of lipoprotein profiles by nuclear magnetic resonance, young adults born with VLBW had triglyceride-related differences in both VLDL and HDL-C subclasses compared with their peers born at term (Hovi *et al.* 2013). In a meta-analysis, adults born preterm had 0.15 mmol/l (95% CI 0.01–0.30) higher fasting LDL-C concentrations (Parkinson *et al.* 2013), but the difference was explained with one study (Lewandowski *et al.* 2013).

Furthermore, a one-week increase in gestational age (GA) has been associated with 0.02 mmol/l lower TC levels in women, but not in men (Cooper *et al.* 2009) and TG levels have been found to be inversely associated with GA in 11- to 15-year-old children (Morley *et al.* 2000), but not in young adults (Dalziel *et al.* 2007).

Table 6. Unadjusted mean differences (mmHg) in office-measured blood pressure in adolescents and adults born preterm compared with controls born at term.

Authors and year	Birth years	No. of subjects + controls	Age (years)	Study group	Mean difference	
					SBP (95% CI or P)	DBP (95% CI or P)
Vohr *et al.* 2010	1989—1992	296 + 95	~16	600–1250 g	4 (P=0.003)	1.9 (P=0.001)
Doyle *et al*. 2003	1977—1982	156 + 38	18+	<1500 g	8.6 (3.4, 13.9)	4.3 (1.0, 7.6)
Indredavik Evensen *et al*. 2009	1986—1988	37 + 63	~18	<1500 g	6.5 (P<0.01)	2.2 (NS)
Hack *et al.* 2005	1977—1999	195 + 208	~20	<1500 g	1.9 (-0.2, 4.1)	0.4 (-1.4, 2.1)
Hovi *et al*. 2007	1978—1985	163 + 169	18–27	<1500g	4.0 (1.5, 6.5)	3.5 (1.7, 5.3)
Pharoah *et al*. 1998	1980—1981	128 + 128	~15	≤1500 g	3.2 (0.4, 6.0)	1.1 (−0.7, 2.9)
Lewandowski *et al.* 2013	1982—1985	102+102	23–28	<1850 g.	8.4 (P<0.001)	4.2 (P<.001)
Irving *et al.* 2000	1973—1975	19 + 27	~24	<2000 g	7 (P<0.001)	5 (P<0.05)
Johansson *et al.* 2005	1973—1981	14 192 + 275 892	~18	24–28 wk.	1.9 (1.3, 2.8)	NR
				29–32 wk.	1.5 (1.3, 1.7)	
				33–36 wk.	1.3 (1.2, 1.3)	
Keijzer-Veen *et al*. 2010	1983	29 + 30	~20	<32 wk.	8.4 (4.1,12.7)	2.0 (-1.9, 5.9)
Kistner *et al.* 2000	1970—1974	15 + 17	23–30	<32 wk.	13 (P<0.001)	5 (P=0.155)
Rotteveel *et al.* 2008	1983	29 + 30	~20	<32 wk.	W: 9	W: 6
					M: 19 (P<0.0001)	M: 9 (P=0.001)
Thomas *et al.* 2011	NR	19 + 18	18–27	≤33 wk.	6.5 (2.2, 10.8)	5.9 (1.8, 10.1)
Edstedt Bonamy *et al.* 2005	1982—1989	34 + 32	~16	≤34 wk.	9 (P<0.001)	5 (P<0.001)
Kerkhof *et al.* 2012	NR	163 + 243	18–24	<36 wk.	2.3 (P<0.01)	-2.8 (P<0.001)
Barros *et al.* 1999	1982	44 + 770	14–15	<37 wk.	0.1 (P=0.9)	0.1 (P=0.9)
Cooper *et al*. 2009	1958	279 + 2177	44–45	<37wk.	NR	2.44 (1.04, 3.84)
Dalziel *et al.* 2007	1969—1974	311 + 147	~30	<37 wk.	3.5 (0.9, 6.1)	NR
Järvelin *et al.* 2004	1966	273 + 4356	~31	<37 wk.	W: 2.7 (P=0.015)	W: 1.0 (P=0.25)
					M: 1.0 (P=0.59)	M: 0.0 (P=0.96)

Authors and year	Birth years	No. of subjects + controls	Age (years)	Study group	Mean difference	
					SBP (95% CI or P)	DBP (95% CI or P)
Lazdam *et al.* 2010	1982—1985	52 + 32	22–26	<37 wk.	6.7 (P=0.006)	5.5 (P=0.0001)
Rossi *et al.* 2011	NR	25 + 41	13–14	<37 wk.	6 (P=0.04)	4 (P=0.03)
Siewert-Delle *et al.* 1998	1926—1927	44 + 336	~49	≤37 wk.	3 (NR)	0 (NR)
Skilton *et al.* 2011	NR	253 + 835	~32	<37 wk.	1.5 (P=0.11)	0.4 (P=0.55)
Tauzin *et al.* 2014	1984—1985	16 + 15	~21	<37 wk.	10 (P<0.05)	4 (P<0.05)
Singhal *et al.* 2001	1982—1985	216 + 61	13–16	preterm	0.5 (NS)	0 (NS)

Abbreviations: BP, blood pressure; DBP, diastolic BP; M, men; NR, not reported; NS, not statistically significant, SBP, systolic BP; W, women.

Table 7. Ambulatory blood pressure in children and adults born preterm compared with controls born at term.

Authors and year	No.*	Age (years)	Study group	Mean difference in mmHg (95% CI or P value)					
				24-hour BP		BP when awake		BP when asleep	
				SBP	DBP	SBP	DBP	SBP	DBP
Women									
Hovi *et al.* 2010	69+72	18—27	<1500 g	3.4 (0.4, 6.4)	2.1 (0.0, 4.3)	2.6 (P=0.05)	1.4 (P=0.10)	2.7 (P=0.05)	1.8 (P=0.08)
Doyle *et al.* 2003	83+18	~18	<28 wk	3.8 (0.2, 7.8)	0.6 (-2.3, 3.6)	4.5 (0.2, 8.6)	1.3 (-2.0, 4.5)	3.2 (-1.7, 8.1)	0.6 (-3.0, 4.2)
Kistner *et al.* 2000	15+17	23—30	<32 wk	4 (P=0.23)	3 (P=0.26)	5 (P=0.12)	3 (P=0.26)	1 (P=0.92)	2 (P=0.31)
Men									
Hovi *et al.* 2010	49+48	18—27	<1500 g	-0.4 (-3.4, 2.9)	-1.3 (-3.7, 1.1)	0.6 (P=0.78)	1.1 (P=0.38)	0.3 (P=0.84)	0.2 (P=0.92)
Doyle *et al.* 2003	73+20	~18	<28 wk	6.4 (1.6, 1.1)	1.5(-2.4, 5.3)	6.7 (1.7, 11.7)	1.6 (-2.4, 5.7)	5.2 (0.5, 10.0)	1.2 (-2.8, 5.1)
Women and men									
Hovi *et al.* 2010	118+120	18—27	<1500 g	2.4 (0.2, 4.6)[a]	-0.8 (-0.8, 2.5)a	NR	NR	NR	NR
Doyle *et al.* 2003	156+38	~18	<28 wk	4.7 (1.4, 8.0)	1.1 (1.2, 3.5)	5.0 (1.6, 8.5)	1.5 (-1.0, 4.1)	3.6 (0.05, 7.1)	0.9 (-1.7, 3.6)
Roberts *et al.* 2014	136+120	~18	<28 wk	3.2 (0.1, 6.4)	2.1 (0.3, 4.0)	3.9 (0.7, 7.2)	2.8 (0.8, 4.8)	2.0(-1.4, 5.5)	1.3 (-0.7, 3.3)
Keijzer-Veen *et al.* 2010	29+30	20	<32 wk	3.5 (P=0.04)	0.9 (P=0.60)	4.2 (0.4, 8.0)	0.5 (P=0.82)	3.6(-0.9, 8.1)	0.8 (P=0.56)
Bayrakci *et al.* 2012	41+27	5—17	<37 wk	2.2 (NS)	0.8 (NS)	2.1 (NS)	-0.1 (NS)	3.9 (P < 0.05)	0.3 (NS)

*No. of subjects + controls.

Abbreviations: BP, blood pressure; DBP, diastolic BP; M, men; NR, not reported; NS, not statistically significant; SBP, systolic BP; W, women.

[a]Adjusted for BMI

2.4.5 Glucose regulation

Insulin resistance is a key component of type 2 diabetes and metabolic syndrome, and low birth weight is associated with altered glucose regulation and diabetes (Eriksson *et al.* 2006, Harder *et al.* 2007). However, the association between GA or preterm birth and altered glucose metabolism in later life is inconsistent. Some studies have revealed no difference in glucose regulation between adults born preterm vs. term (Irving *et al.* 2000, Skilton *et al.* 2011, Thomas *et al.* 2011), because of a lack of power, or a difference has been found only in those born preterm and SGA but not in those born AGA (Rotteveel *et al.* 2008a). However, studies in prepubertal children (Hofman *et al.* 2004, Kistner *et al.* 2012) and adults (Dalziel *et al.* 2007, Hovi *et al.* 2007, Pilgaard *et al.* 2010, Mathai *et al.* 2012) born preterm have shown decreased insulin sensitivity, also shown by way of intravenous glucose tolerance tests (2004, Kajantie *et al.* 2014), and higher fasting glucose (Lewandowski *et al.* 2013) and insulin levels (Hovi *et al.* 2007, Lewandowski *et al.* 2013). Although GA was not found to be associated with later diabetes in Finnish children and young adults (Lammi *et al.* 2009), preterm birth increased the risk of diabetes in adulthood in other studies (Lawlor *et al.* 2006a, Kaijser *et al.* 2009, Kajantie *et al.* 2010a, Pilgaard *et al.* 2010, Crump *et al.* 2011a).

2.4.6 Other cardiometabolic biomarkers

In addition to the established risk factors of cardiovascular disease listed in Table 3 (section 2.2) and those included in the criteria of metabolic syndrome, there are many other measurable markers related to elevated CVD risk. Some previous studies have concerned unconventional cardiometabolic risk factors possibly associated with preterm birth and reflecting different underlying pathophysiological pathways of CVD.

Inflammation seems to be a strong, independent risk factor of metabolic syndrome and CVD in adults (Danesh *et al.* 1998, Pearson *et al.* 2003). However, the predictive utility of high-sensitivity C-reactive protein (hsCRP) concentrations has been questioned in a previous meta-analysis (Shah *et al.* 2009). Some investigators have reported no difference in hsCRP or CRP levels in adults born preterm compared with adults born at term (Skilton *et al.* 2011, Lewandowski *et al.* 2013).

Uric acid stimulates oxidative stress, endothelial dysfunction, inflammation and vasoconstriction and is a strong predictor of type 2 diabetes and CVD, independent of

metabolic syndrome components (Fang & Alderman 2000). Liver transaminases and non-alcoholic fatty liver disease are also biomarkers of these disorders, although the literature is less consistent as to whether or not they are independent indicators of pathology or general markers of metabolic syndrome (Sniderman *et al.* 2011, Lv *et al.* 2013). No reports have been published concerning uric acid and liver enzymes in adults born preterm. However, one group reported differences in the levels of (premorbid) urinary biomarkers (elevated levels of methylamines and acetylglycoproteins; lower hippurate levels), metabolites associated with inflammation in young adults born preterm (≤33 w) (Thomas *et al.* 2011).

2.4.7 Vascular structure and function

Some changes in vascular structure have been reported in young adults born preterm, such as increased left ventricular mass and reduced function (Lewandowski *et al.* 2013) and impaired retinal vascularization in women (Kistner *et al.* 2002). Findings concerning early markers of the atherosclerotic process, such as endothelial dysfunction or arterial stiffness in adolescents and adults born preterm are conflicting. Some studies have shown no association (Singhal *et al.* 2001b, Indredavik Evensen *et al.* 2009, Kerkhof *et al.* 2012, Parkinson *et al.* 2013), and in contrast, some studies have indicated a positive association (Bonamy *et al.* 2005, Bassareo *et al.* 2010, Hovi *et al.* 2011), although in one of them the finding was limited to those with concurrent fetal growth restriction (Skilton *et al.* 2011). Arterial stiffness is a key factor as regards increased systolic and pulse pressure in adults.

2.4.8 Lifestyle

Many aspects of cardiovascular disease (see section 2.2) could be prevented by way of a healthy lifestyle. Previous studies have suggested that the lifestyle of adults born preterm, at least in those born with VLBW, is different from that in adults born preterm. Adolescents and adults born preterm are less physically active than their peers born at term (Rogers *et al.* 2005, Hack *et al.* 2007, Saigal *et al.* 2007, Andersen *et al.* 2009, Kajantie *et al.* 2010b, Kaseva *et al.* 2012) and they have lower cardiorespiratory and muscle strength (Rogers *et al.* 2005, Saigal *et al.* 2007). Low physical activity level is a well-known risk factor of CHD and CVD (Shiroma & Lee 2010). In addition, adults born with VLBW have reported consuming fewer fruits, vegetables, berries and milk products (HeSVA) (Kaseva *et al.* 2013). Low consumption of fruit has been ranked among the five most important factors causing

the worldwide disease burden (Lim *et al.* 2012). In contrast, the results of some studies suggest that adults born preterm are more cautious and show less risk-taking behavior (Hack *et al.* 2002, Pesonen *et al.* 2008), lower rates of smoking (Strang-Karlsson *et al.* 2008) and use of alcohol (Hack *et al.* 2002, Strang-Karlsson *et al.* 2008). These factors may protect them from CVD.

2.4.9 Summary

There is a lot of evidence that adolescents and adults born preterm have many risk factors for later cardiovascular disease, such as higher blood pressure, impaired glucose regulation, and altered body composition and lifestyle. However, the evidence is not that consistent as regards all cardiometabolic risk factors, e.g. energy metabolism, lipid metabolism and emerging cardiometabolic risk factors. In addition, it is not clear whether these risks are similar in those born moderately versus late preterm. Fig. 5 summarizes the main points of the association between preterm birth and later cardiometabolic risk factors.

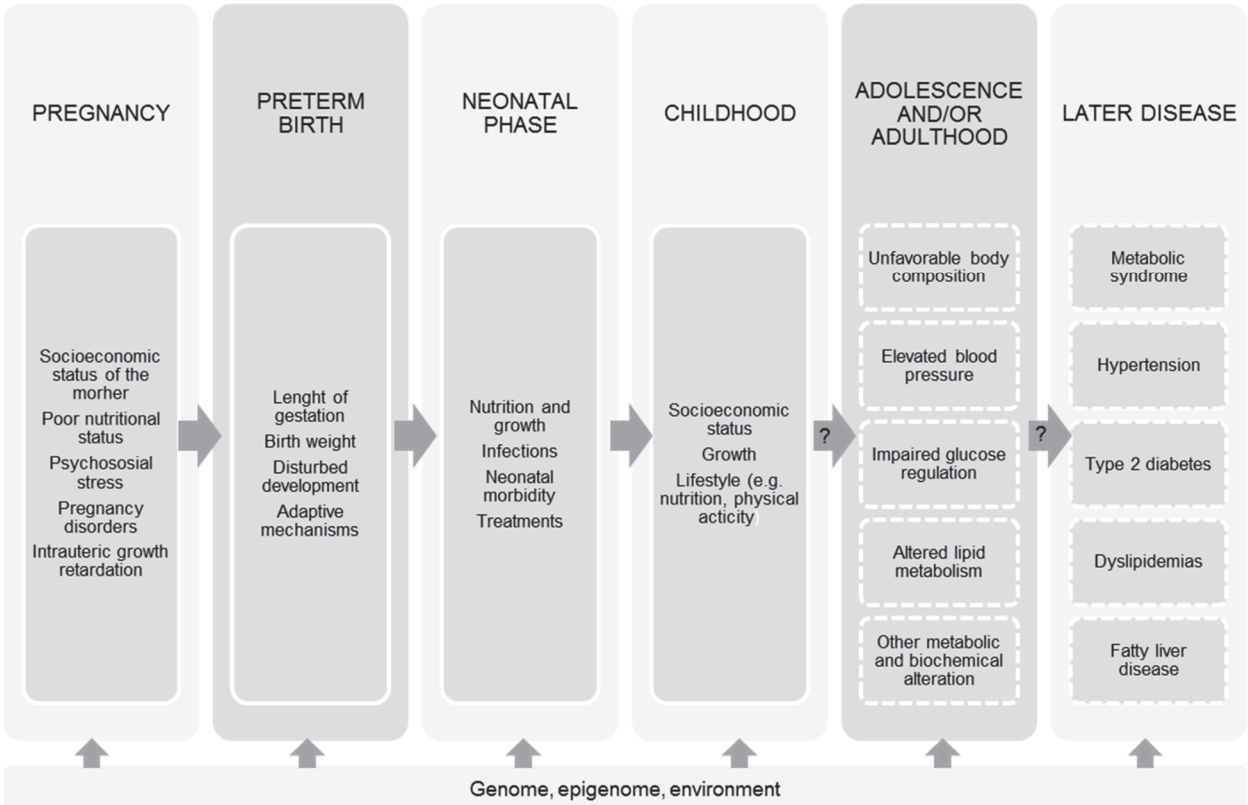

Fig. 5. Study framework.

3 Aims

The present study was designed to evaluate the cardiometabolic risk factors of adolescents and young adults born preterm. The specific aims were:

1. To study whether adolescents/adults born preterm differ from those born at term as regards cardiometabolic risk factors such as lower resting energy expenditure, unfavorable body composition, elevated blood pressure, higher plasma lipid levels, and altered glucose regulation (I–IV).
2. To examine whether these risk factors are present and similar in adolescents/adults born early preterm (<34 weeks) and late preterm (34 to 36 weeks) (II–IV).
3. To see if these risk factors are different in men and women born preterm (I–IV).
4. To see if these risks are attributable to perinatal factors, childhood socioeconomic status or lifestyle (I–IV).

4 Subjects and methods

The thesis is based on data from three different studies: 1) the Helsinki Study of Very Low Birth Weight Adults (I), 2) the Northern Finland Birth Cohort 1986 (NFBC 1986, II–IV) and 3) the ESTER Preterm Birth study *("Preterm birth and early life programming of adult health and disease"*, III, IV). Half of the subjects (585) in the ESTER study are also members of the NFBC 1986 cohort.

4.1 Helsinki Study of Very Low Birth Weight Adults (I)

The Helsinki Study of Very Low Birth Weight Adults is a prospectively collected longitudinal birth cohort study, the clinical assessment of which was conducted in 2004–2005 in Helsinki.

4.1.1 The study population

The original study cohort consisted of 335 VLBW infants who were born between January 1978 and December 1985 and were discharged alive from the NICU of the Children's Hospital at Helsinki University Central Hospital, the only tertiary neonatal care center in the province of Uusimaa, Finland (Järvenpää & Granström 1987). For each VLBW survivor, the next available singleton term infant (gestational age >37 weeks), who was of the same sex and was not SGA was selected as a control.

Most (95.1%) of the VLBW individuals and 96.8% of the controls were traced through the National Population Register Center of Finland. 255 VLBW individuals and 314 control individuals born at term who were living in the greater Helsinki area were invited to the first clinical visit and 166 (65.1%) of the VLBW individuals and 172 (54.8%) of the control individuals agreed to participate. The clinical study participants had a lower rate of cerebral palsy at 15 months of age than the non-participants, but otherwise they did not differ as regards perinatal and neonatal data (birth weight, length of gestation, maternal preeclampsia, and days of age at discharge from the NICU) (Hovi *et al.* 2007).

In this study we included those with data on resting energy expenditure (REE) assessed by indirect calorimetry and body composition assessed by dual energy X-ray absorptiometry (DXA). REE could be measured in three of the four to five participants per day because there was only one calorimeter available. Subjects were selected randomly for the measurement and no one refused. DXA required a separate visit and was not carried out in participants who were pregnant or had a foreign object

in the body, or had severe cerebral palsy or were unwilling to undergo the examination. As a result, 116 VLBW individuals and 118 controls born at term had data on REE and DXA and were included in this study.

We compared the subjects included in the analysis with those who did not have appropriate data. Included subjects did not differ from the remaining subjects who attended the clinical examination in any of the prenatal and birth characteristics, except that they were more likely to be born from a singleton pregnancy (P=0.046). In addition, their mean age, height, BMI, parental education, and smoking habits were similar.

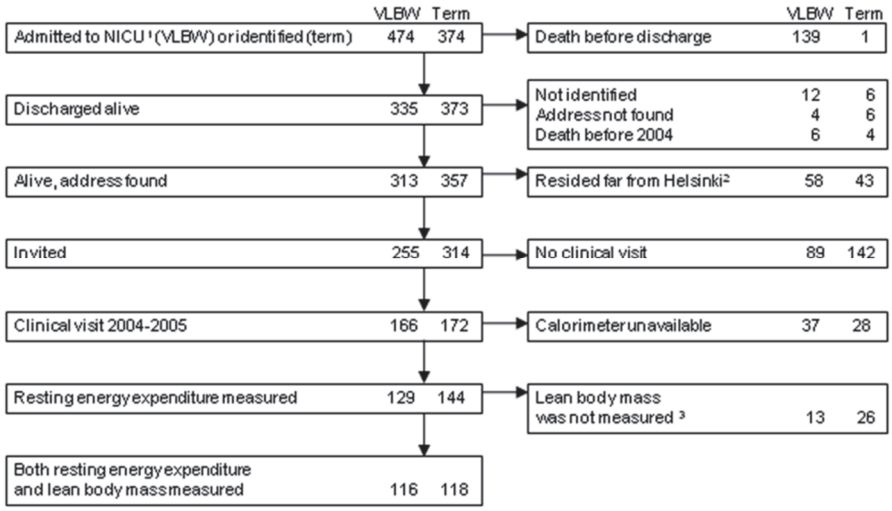

Fig. 6. Flow chart showing participants selected for the study (article I). Participants who had both resting energy expenditure and lean body mass measured had similar characteristics compared to those invited but who did not undergo these measurements. [1]NICU denotes neonatal intensive care unit. Term subjects were identified from the birth-hospital records for each very low birth weight (VLBW) infant. [2]Only those residing within distance of 110 km were invited. [3]Lean body mass was not measured, if the subject was pregnant, had foreign object in the body, had severe cerebral palsy or was unwilling to undergo the examination. Reprinted with permission; the same figure appears in PLoS One. 6(3):e17700.

4.1.2 Perinatal and neonatal data

Perinatal and neonatal data were collected from the hospital records. Gestational age was assessed by last menstruation date or by Dubovitz score (Hovi 2011). The infants born with VLBW had been weighed daily during their hospital stay. If the weight at 40 weeks of gestational age was missing from the records, we included the interpolated value based on measurements available within 10 days before and 20 days after this time point in our analysis. We converted the weights into standard deviation scores according to Finnish birth weight charts (Pihkala *et al.* 1989).

4.1.3 Questionnaire

The participants completed a detailed questionnaire on medical history, use of medication, current smoking, parents' education (as an indicator of socioeconomic status, categorized into four levels according to information on the parent with the higher education) and leisure-time physical activity assessed by means of questions on exercise intensity (four categories), duration, and frequency (Hovi *et al.* 2007, Kajantie *et al.* 2010b).

4.1.4 Clinical examination

The participants attended a clinical examination at a mean age of 22.5 y (range from 18.5 to 27.0). It was performed in the clinic at the National Public Health Institute (now the National Institute for Health and Welfare) in Helsinki. The participants fasted for at least 8 hours (Hovi *et al.* 2007). When the participant was in underwear, nurses measured height and weight and BMI was calculated (weight/height^2, kg/m^2). The nurses used a soft tape to measure waist and hip circumference: waist circumference midway between the lowest rib and the iliac crest and hip circumference at the level of the great trochanters.

4.1.5 Resting energy expenditure and lean body mass

Resting energy expenditure was measured by indirect calorimetry (Deltatrac II, Datex, Helsinki, Finland) at rest. Indirect calorimetry is the most commonly used method to measure REE, and Deltatrac equipment is well-established as being valid and reliable (Tissot *et al.* 1995, Wells & Fuller 1998, Compher *et al.* 2006). The reproducibility is very good: For example in young (18–35 y) non-lactating

Bangladeshi women the mean within-subject within-session variations was 3.0% and within-subject between-sessions variation was 4.5% (Alam *et al.* 2005). The measurement was performed after an overnight fast, after the subject had completed the consent forms and undergone anthropometric and blood pressure measurements, usually approximately 30 minutes after coming to the clinic. The measurement was performed by one of the two trained nurses. At first the subject was connected to the calorimetry device and rested about 10 minutes before the measurement started. During the measurement the subject was wearing light indoor clothing, was still fasting and lying in a bed in a comfortable semi-recumbent position and holding a transparent plastic canopy, which covers the head of the participant. The device has a computerized, open-circuit system to measure gas exchange by the air-dilution method. REE was expressed as the amount of energy used in 24 hours (Dulloo & Jacquet 1998, Jørgensen *et al.* 1998, Wang *et al.* 2000, Eriksson *et al.* 2002, Heymsfield *et al.* 2002, Johnstone *et al.* 2005).

Lean body mass was measured at a separate visit by DXA (Hologic® Discovery A, software version 12.3:3, Bedford, MA, USA) (Hovi *et al.* 2007, Hovi *et al.* 2009). During the measurements the subjects were wearing underwear alone and they were not allowed to wear any jewelry and other personal effects that could interfere with the DXA measurement. If measurements contained artifacts which could affect the accuracy of DXA they were excluded from the analysis. The ratio of REE to LBM (REE/LBM) was calculated (Eriksson *et al.* 2002). Originally DXA was developed for diagnosis of osteoporosis, but it also provides detailed and precise information about body composition. It is a clinically applicable if not "bedside" method (Mazess *et al.* 1990). It involves measurement of the relative attenuation of two different energy X-rays and produces a three-component model of body composition including fat, bone mineral, and lean tissue. Scans are relatively fast, with minimal radiation exposure (Woodrow 2007). DXA is reliable and reproducible in the estimation of LBM, and reproducibility of measurements is excellent, with r value of 0.98 (Lohman *et al.* 2009). However, it does not distinguish between visceral and subcutaneous fat tissue (Haarbo *et al.* 1991, Svendsen *et al.* 1993, Glickman *et al.* 2004).

4.2 Northern Finland Birth Cohort 1986 (II–IV)

The Northern Finland Birth Cohort 1986 (NFBC 1986) is a prospectively collected longitudinal cohort of all births in the two northernmost provinces of Finland, with mothers and children whose expected delivery date was between July 1st 1985 and June 30th 1986. In total 9 479 children were born into the cohort, and 9 432 of them

were live-born. Mothers and children have been followed up since the mothers enrolled at their first antenatal clinic visit, usually by the twelfth week of gestation (Järvelin *et al.* 1993a, Pirkola *et al.* 2008).

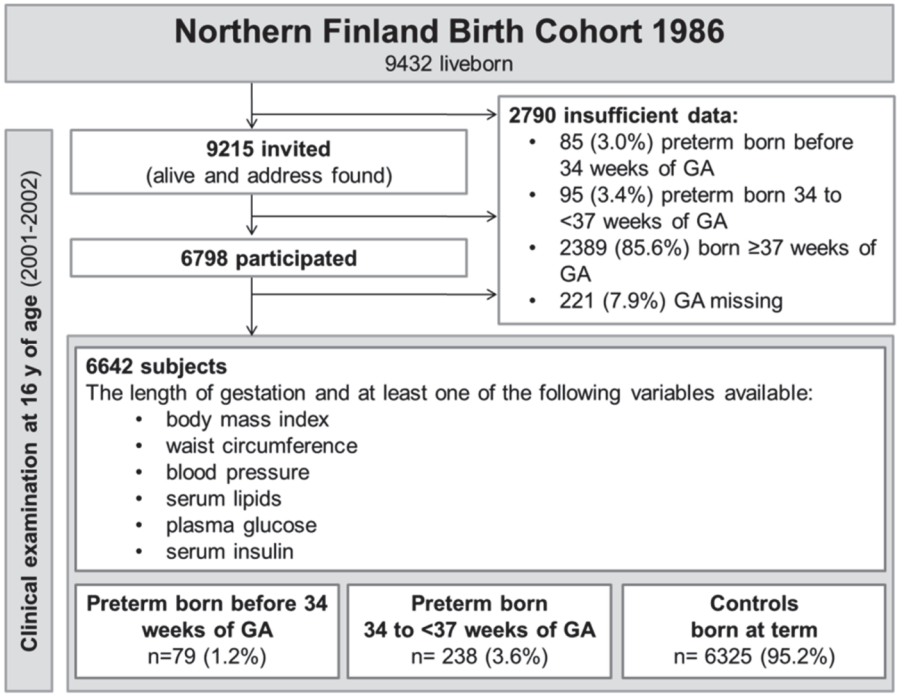

Fig. 7. Participants in the study (article II).

4.2.1 The study population

At a mean age of 16 years, 6798 (74%) cohort members residing in Finland participated in a clinical examination, which was conducted in 2001–2002 (Fig. 7). In our analysis we included those 6642 subjects with data on length of gestation and at least one of the following variables: BMI, waist circumference, blood pressure, plasma lipids, plasma glucose and serum insulin. In total, 79 (1.2%) of the study subjects included in the analysis were born early preterm (<34 weeks), 238 (3.6%) were born late preterm (34 to <37 weeks) and 6325 (95.2%) were controls (≥37 weeks).

Subjects with insufficient data for analysis had a shorter length of gestation (0.27 weeks, P<0.001), were more likely to be born preterm (P<0.001), had a lower birth

weight (77 g, P<0.001) and a lower birth weight SD score (0.1 SD, P<0.001) and were more likely to be born SGA (P=0.006).

4.2.2 Perinatal and neonatal data

Perinatal data were collected from healthcare records and questionnaires. The overall incidence of preterm deliveries was 4.8%, of which 70.8% were spontaneous preterm deliveries (Olsen *et al.* 1995). We confirmed length of gestation by reviewing original hospital records (Vääräsmäki *et al.* 2009, Miettola *et al.* 2013). We calculated the birth weight SD score on the basis of Finnish standards (Pihkala *et al.* 1989) and SGA was defined as lower than 2 SD below the mean.

In 1985–1986, when the study subjects were born, routine determination of length of gestation by ultrasonography was the practice in a number of towns and municipalities in the region, but not in all. The cohort database included data indicating length of gestation, which were collected from three sources:

1. If the length of gestation was estimated or confirmed by ultrasonography (before 20 weeks of gestation), it was obtained from maternal welfare clinic records.
2. If ultrasonography was not performed, the length of gestation was estimated on the basis of the last menstrual period, and it was collected from maternal welfare clinic records.
3. The length of gestation was based on clinical decision-making and recorded in full completed weeks in birth hospital records.

We looked at these variables and if there was a discrepancy, we reviewed the data and medical records if needed.

The length of gestation was determined by ultrasonography in 3699 (39.2%) cases, by last menstrual period in 5358 (56.8%) cases, and according to data in hospital records, based on clinical decision-making with no information as to whether this was based on ultrasonography or last menstrual period in 154 (1.6%) cases. We were unable to confirm the length of gestation in 221 cases (2.3%).

We categorized the subjects into three groups according to their gestational age:

1. <34 weeks of gestation (early preterm)
2. 34 to <37 weeks of gestation (late preterm) (Engle *et al.* 2007)
3. ≥37 weeks of gestation (controls).

4.2.3 Questionnaire

At the age of 16 the participants (and their parents) completed questionnaires on medical history, medication, socioeconomic status and lifestyle. We used parental educational attainment as an indicator of socioeconomic status and it was categorized into four levels (dummy coded). Regular smoking ("Have you ever smoked regularly?") was transformed to a dichotomous variable. Physical activity was based on questions on daily time spent in commuting and weekly time in light or moderate-to-vigorous physical activity and transformed to total metabolic equivalent hours per week (METh/wk), assuming 3 MET for light activity, 4 MET for commuting, and 5 MET for moderate-to-vigorous physical activity. The subjects assessed their pubertal stage with the help of drawings representing different stages of the Tanner classification (Tanner 1962).

4.2.4 Clinical examination

At the clinical examination weight (kg), height (cm), waist (cm) and hip circumferences (cm) were measured. Blood pressure was measured from the right arm after 15 minutes of rest with the subject sitting, by use of an automated oscillometric device (Omron 705CP, Omron Corporation, Shiokoji, Horikawa, Kyoto, Japan) or mercury sphygmomanometer if the first one failed. The mean of two measurements taken two minutes apart was calculated.

4.2.5 Laboratory analyses

Fasting blood samples collected between 8:00 and 11:00 were analyzed within 24 hours of sampling at Oulu University Hospital laboratory by using a Cobas Integra 700 automatic analyzer (Roche Diagnostics, Basel, Switzerland): plasma glucose by using an enzymatic reference method with hexokinase, TC, HDL-C, LDL-C, and TG concentrations with an enzymatic, colorimetric method, and ApoA1 and ApoB with an immunoturbidimetric method (Vääräsmäki *et al.* 2009). Samples for serum insulin measurement were stored at -20 °C and analyzed by radioimmunoassay with commercial reagents (Pharmacia Diagnostics, Uppsala, Sweden) within 7 days. We used homeostasis model assessment values for insulin resistance (HOMA-IR) by calculating them from paired fasting glucose and insulin levels by way of the validated calculator program available at www.dtu.ox.ac.uk (Wallace *et al.* 2004).

4.3 The ESTER Study (III, IV)

The ESTER study ("Preterm birth and early life programming of adult health and disease" and Maternal pregnancy disorders and child's health in adulthood) is a birth cohort study conducted in 2009 to 2011 in the two northernmost provinces of Finland. The study has been carried out as a collaborative effort between the National Institute for Health and Welfare, the Institute of Health Science in the University of Oulu, the Northern Ostrobothnia Hospital District and the University of Helsinki. The ESTER study consists of two sub-studies:

1. Preterm birth and early life programming of adult health and disease (the ESTER Preterm Birth Study), and
2. Maternal pregnancy disorders and child's health in adulthood.

Subjects born in 1985–1986 were recruited from NFBC 1986 and subjects born in 1987–1989 from The Finnish Medical Birth Register (FMBR), born in the same geographical area. We selected all the subjects from NFBC 1986 who were born preterm (<37 weeks of gestation), and those who were exposed to maternal hypertension, preeclampsia or diabetes. In addition, we selected subjects randomly from the FMBR with same criteria. Control group subjects were selected randomly from both NFBC 1986 and FMBR. The total number of subjects who attended the examination is 1161.

4.3.1 The study population

The present work is focused on the effects of preterm birth on cardiovascular risk factors, so we included those born preterm and their randomly selected controls.

Subjects were categorized into three groups according to their gestational age:

1. <34 weeks of gestation (early preterm, n=149),
2. 34 to <37 weeks of gestation (late preterm, n=248) (Engle *et al.* 2007), and
3. ≥37 weeks (controls, n=380). The control group also includes 16 subjects technically born post-term (at 42 weeks 1 day or later).

The selection of the subjects included in the analysis is presented in Fig. 8 (for article III) and Fig. 9 (for article IV).

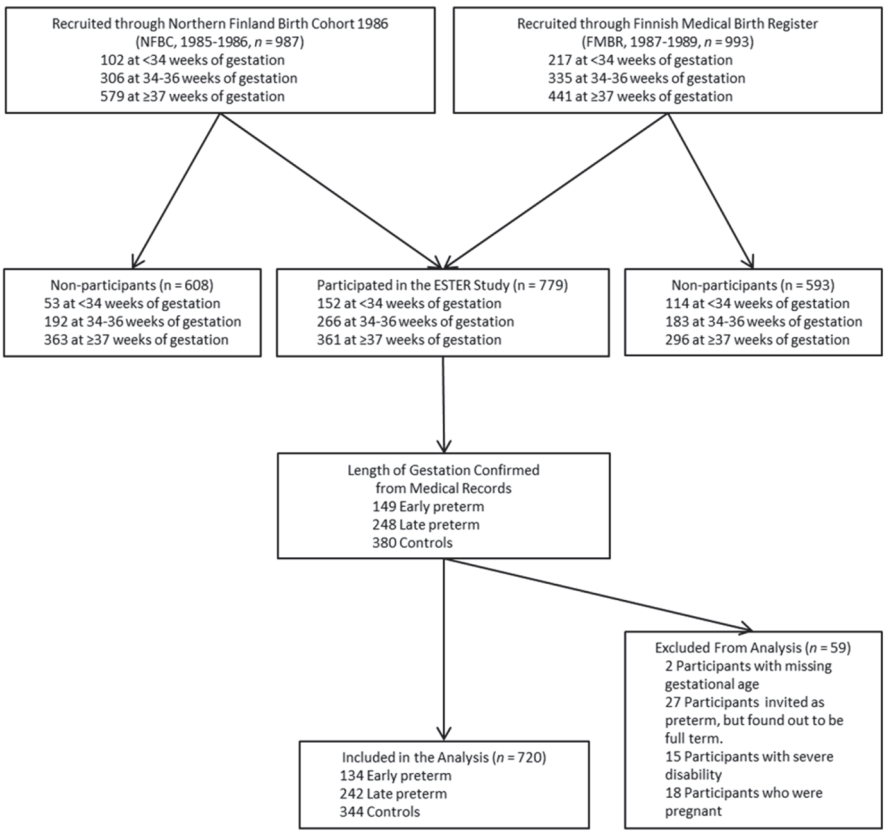

Fig. 8. Flow chart of the study population (article III). All subjects recruited to the study are born in Northern Finland in 1986-1989. In the Finnish Medical Birth Register data 83 individuals in the random control group with missing gestational age of whop 58 individuals did not participate and 25 participated to the ESTER study. 10 subjects born early preterm, 1 subject born late preterm and 4 controls reported severe disability and were excluded from the analysis. 5 subject born early preterm, 5 subjects born late preterm and 8 controls reported being pregnant and were excluded from the analysis. 3 excluded subjects had more than one reason for exclusion. Abbreviations: FMBR, Finnish Medical Birth Register; NFBC, Northern Finland Birth Cohort. Printed with permission; the same figure appears in Am J Epidemiol 2015: In press.

4.3.2 Perinatal and neonatal data

Perinatal data on members of the NFBC 1986 were collected as described previously in section 4.2.2 (Järvelin *et al.* 1993b). We collected similar peri- and neonatal variables concerning FMBR subjects from the patient records of hospitals and maternal welfare clinics. We determined the length of gestation of NFBC and FMBR subjects as described above (section 4.2.2). We recorded diagnoses of maternal gestational diabetes, hypertension (gestational or chronic) and preeclampsia (including superimposed) retrospectively according to prevailing medical guidelines. The birth weight SD score was calculated according to Finnish standards (Pihkala *et al.* 1989) and SGA was defined as lower than 2 SD below the mean.

4.3.3 Questionnaire

The participants completed questionnaires before the clinical visit electronically or during or after the visit on paper. The questionnaire included questions about medical history and medication including hormonal contraception, socioeconomic status and lifestyle. We used parental educational attainment as an indicator of socioeconomic status and it was categorized and dummy-coded (four levels). Physical activity was assessed as described above (section 4.2.3). Daily smoking (yes/no) and the amount of alcohol doses per week (0; 1 to 3; 4 to 9; ≥10) were categorized.

4.3.4 Clinical examination

The subjects participated in clinical examination at clinics in Oulu, Kemi, Kuusamo, Raahe, Rovaniemi and Ylivieska. The participants had fasted overnight before the clinical visit.With the subject in a sitting position and after five minutes' rest, a trained study nurse measured blood pressure (mm Hg) from the upper right arm, using an automatic oscillometric blood pressure monitor (Intellisense M10-IT, cuff size 22–42 cm; Omron Healthcare Co., Ltd., Kyoto, Japan). Three measurements were taken and the mean was calculated. Height (cm) was measured three times; waist circumference (cm, midway between the lowest rib and the iliac crest) and hip circumference (cm, at the widest point of the hip) were measured twice. Using the means of repeated measurements, BMI and the waist-hip ratio (WHR=waist circumference/hip circumference) were calculated. We measured body composition (weight, plus lean body mass, fat mass and percentage body fat) by segmental multi-frequency bioelectrical impedance analysis (BIA; InBody 3.0, Biospace Co., Ltd.,

Seoul, Korea). It is based on the principle that lean mass, which is primarily an electrolyte solution, conducts current better than fat mass. The method gives a measure of the resistance to a weak current (impedance) applied across extremities and provides an estimate of body fat using an empirically derived equation. BIA has been shown to give accurate estimates of body components in different populations with high reliability in repeated measurements (Bedogni *et al.* 2002, Malavolti *et al.* 2003, Sartorio *et al.* 2005, Gibson *et al.* 2008) and is practical in large epidemiological studies . Correlations between BIA and DXA as regards percentage body fat are generally good (Bolanowski & Nilsson 2001), but BIA tends to overestimate percentage body fat in lean subjects and underestimates it in obese subjects (Sun *et al.* 2005).

4.3.5 Laboratory analyses

The subjects fasted overnight and blood samples were collected at 8:00–11:00 a.m. and 2 hours after a 75-gram oral glucose load. Some of the analyses were performed at Oulu University Hospital laboratory: Plasma glucose (fasting and 2-hour), TC, HDL-C and LDL-C, TG, uric acid, alanine aminotransferase, aspartate aminotransferase, gamma glutamate, albumin and urea were analyzed by using an Advia 2400 automatic chemical analyzer (Siemens Diagnostics, Terrytown, NY, USA) and blood leukocytes by an automatic electronic cell counter (Abbott CELL-DYN Sapphire, Abbott Diagnostics, USA).

Remaining samples were stored at -70 ºC. Other analyses were performed later at the Disease Risk Unit of the National Institute for Health and Welfare: Serum concentrations of insulin, lipoprotein (a) (LPa), ApoA1, ApoB, and hsCRP (values >10 mg/l were excluded from analysis) were measured by using an Architect ci8200 analyzer (Abbott Laboratories, USA). The following methods were used: chemiluminescent microparticle immunoassay (CMIA, Abbott Laboratories, USA) for insulin, immunoturbidimetric methods (Abbott Laboratories, USA) for LPa, ApoA1 and ApoB and a latex immunoassay (Sentinel Diagnostics, Italy) for hsCRP. HOMA-IR values from paired fasting glucose and insulin levels were defined by using a validated calculator program available at www.dtu.ox.ac.uk (Wallace *et al.* 2004).

4.3.6 Ambulatory measurements

To measure 24-hour blood pressure, volunteer subjects were given ambulatory blood pressure (ABP) monitors with operating instructions (Spacelabs 90207, Spacelabs Medical, Inc., WA, U.S.A.) after the clinical examination, if there were available devices. The subjects wore the cuff on the non-dominant upper arm and carried the device for 24 hours. The monitors measured their blood pressure every 20 minutes during the day (7:00 to 22:00 h) and every 30 minutes at night (22:00 to 7:00 h).

Thirty-two (76.2%) subjects born early preterm, 47 (65.3%) subjects born late preterm and 78 (75.7%) controls agreed to wear an accelerometer (GT1M; ActiGraph, Inc., Pensacola, FL) on the wrist to measure the sleep–wake rhythm simultaneously with the ABP monitor (Fig.9). They were instructed to keep a sleep log reporting their bedtimes and wake-up times. After the measurements, the participants returned the devices to the researchers for data download. We visually inspected the accuracy of the sleep log against the raw accelerometry data. We removed the night-time data with inconsistent (e.g., the participant was already sleeping at the reported bedtime) or missing information on bedtimes. If the reported wake-up time was inconsistent (e.g., the participant was still asleep after the reported wake-up time) or missing, it was visually estimated from the raw accelerometry data. Sleep onset time was estimated by using ActiLife software (ActiLife 5.10.0; ActiGraph Pensacola, FL, USA), with the Sadeh algorithm (Sadeh *et al.* 1994). For the 60 (27.6%) subjects who had no accelerometry data, BP when sleep was defined as that between 01:00 and 07:00 h, and BP when awake was defined as that between 09:00 and 23:00 h. In other words, we excluded measurements taken between 07:00 and 09:00 h and between 23:00 and 01:00 h, because of the potential individual variability in bedtimes and wake-up times.

We excluded from the analysis subjects with fewer than 15 BP measurements when awake or fewer than eight BP measurements when asleep (O'Brien *et al.* 2000) and these subjects were also excluded from 24-hour BP analysis. We calculated the means of the subjects' 24-hour, awake and asleep ABPs (mmHg) and SDs of BP (mmHg, indicators of individual BP variability).

4.3.7 Definitions of pre-hypertension, hypertension, fatty liver index, obesity and metabolic syndrome

The cut-off values of office-measured, ambulatory-measured and white-coat hypertension are presented in Table 8. The definition of office-measured hypertension

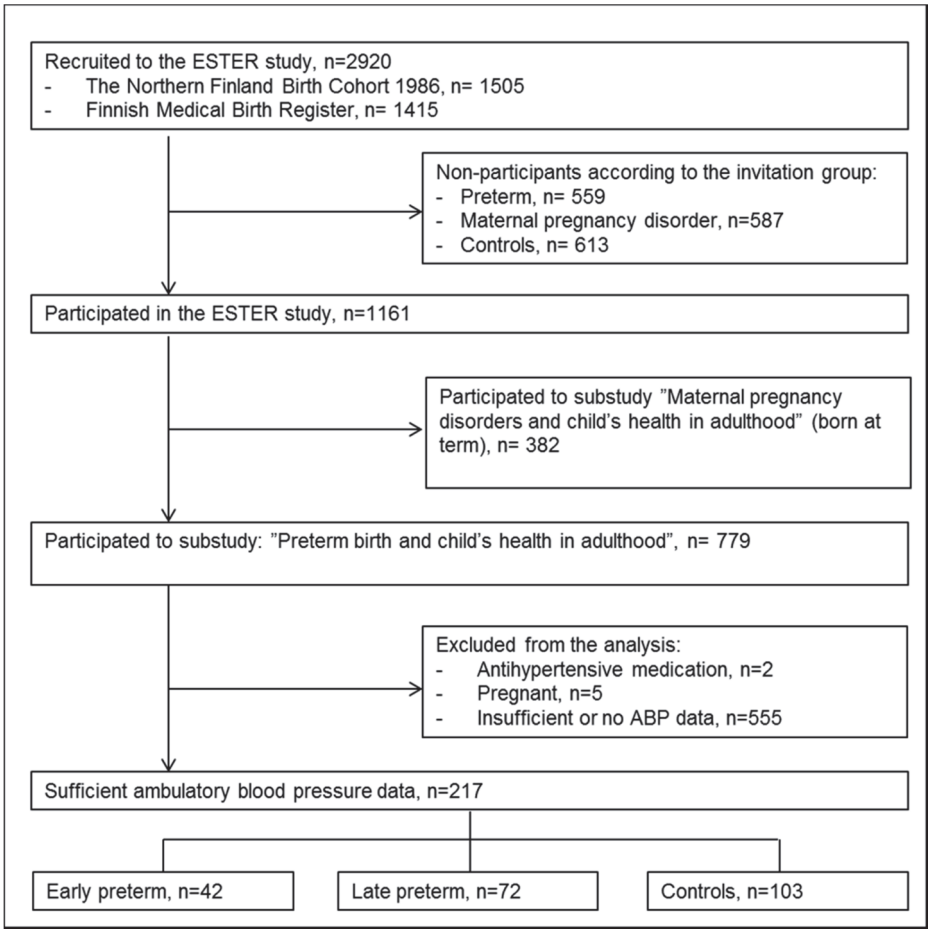

Fig. 9. Flowchart of the study population (article IV). Printed with permission; the same figure appears in Hypertension 2015;65: 615-621.

was based on the criteria of the European Society of Hypertension (ESH), the European Society of Cardiology (ESC) and the American Heart Association (Pickering *et al.* 2005, Mancia *et al.* 2013). We defined abnormal mean values of ABP and white-coat hypertension according to criteria of the American Heart Association and the British Hypertension Society (O'Brien *et al.* 2000, Urbina *et al.* 2008). We calculated the fall (or "dip", %) of mean blood pressure from awake to sleep blood pressure as: (mean awake blood pressure - mean sleep blood pressure)/mean awake blood pressure * 100 (Verdecchia *et al.* 1994). If blood pressure when asleep was less than 10% lower than when awake, the subject was

categorized as a "non-dipper" (Verdecchia *et al.* 1994). We defined the metabolic syndrome according to the Joint Interim Statement (Table 8) (Alberti *et al.* 2009).

We calculated the fatty liver index (FLI), a proposed marker of non-alcoholic fatty liver disease (Bedogni *et al.* 2006) as:

$$FLI = \frac{e^{0.953\times ln\,(TG) + 0.139\times BMI + 0.718\times ln\,(GGT) + 0.053\times WC - 15.745}}{1 + e^{0.953\times ln\,(TG) + 0.139\times BMI + 0.718\times ln\,(GGT) + 0.053\times WC - 15.745}} \times 100$$

Abbreviations (units) in equation:
TG, triglycerides (mg/dl); 1 mg/ml = 18.0182 mmol/l
BMI, body mass index (kg/m^2)
GGT, gamma glutamate (U/l)
WC, waist circumference (cm)

An FLI value of <30 rules out hepatic steatosis with 87% sensitivity and a negative likelihood ratio of 0.2 and a value of ≥60 rules out hepatic steatosis with 86% sensitivity and a positive likelihood ratio of 4.3 (Bedogni *et al.* 2006). We used an FLI value of >30 as a marker of intermediate or high FLI.

4.3.8 Subjects included in the analysis and the attrition analyses

We excluded those who were pregnant (n=21) or who reported having cerebral palsy (n=8), mental disability (n=11) and/or several physical disability (n=5) from the analysis of cardiometabolic risk factors (publication III), because these conditions might have an effect on cardiometabolic risk factors. Finally, we had sufficient data on cardiometabolic risk factors among 134 individuals born early preterm, 242 born late preterm, and 344 controls who were born at term.

We compared those who participated with those who did not participate or who were excluded from the analysis. In the late-preterm group and in the controls, women were more likely to participate. In addition, among the late-preterm adults, those who participated were more likely to be born to primiparous mothers. The participants and non-participants did not differ as regards mothers' age at birth, maternal hypertension in pregnancy, maternal smoking, maternity hospital, length of gestation, birth weight or birth weight SD score. We looked at the clinical data at 16 years of age among the NFBC 1986 members. Those who participated in this study were more likely to have

Table 8. Definitions and cut-off values for hypertension, obesity and metabolic syndrome.

Definition	Cut-off values
Pre-hypertension	≥120/80 mmHg
Hypertension (office-measured)	≥140/90 mmHg
Abnormal ambulatory blood pressure	
24-hour	>135/85 mmHg
Awake	>140/90 mmHg
Sleep	>125/75 mmHg
White-coat hypertension	Both of the following criteria:
Office blood pressure	≥140/90 mmHg
Day-time ambulatory BP	<135/85 mmHg
Obesity	
Body mass index	>30 kg/m^2
Metabolic syndrome	3 of the 5 following criteria:
Waist circumference	≥94 cm in men; ≥80 cm in women
Triglycerides	≥1.7 mmol/l
HDL-C	<1.03 mmol/l in men;
	<1.29 mmol in women
Blood pressure	≥130/85 mm Hg
Fasting plasma glucose	≥5.6 mmol/l or type 2 diabetes

participated in clinical examination at 16 years, but the participants and non-participants did not differ as regards BMI and parental educational attainment, and the rates of physical and mental disability were similar within the groups.

Not all the participants wanted to wear an ABP monitor after the clinical visit, or ABP data were missing for some other reason. We also excluded five pregnant subjects (one early preterm, two late preterm, and two controls) and two controls who were taking beta-blocker medication from the ABP analysis. Altogether, we had sufficient data on ambulatory blood pressure measurements on 42 (28.2%) participants in the early-preterm group, 72 (29.0%) participants in the late-preterm group and 103 (28.9%) controls (P=0.98). The proportion of subjects with sufficient ABP data was similar in every group. Women were more likely to have sufficient ABP data than men in the control and early-preterm groups. The subjects invited to the ESTER study who did not participate or who did not have sufficient ABP data were more likely to have been exposed to maternal smoking during pregnancy

(P=0.04). Participants with and without sufficient ABP data were of similar age and had similar parental educational attainment, BMI and office-measured BP. In the early-preterm group and in controls, those without sufficient data were more likely to smoke, and in the early-preterm group men without sufficient data were 3.1 cm shorter than those with ABP data (P=0.02). To control for possible differences in blood pressure levels in those without accelerometry we adjusted the mean differences in ABP outcomes for use of an accelerometer.

4.4 Statistical methods

We performed statistical analyses with SPSS for Windows software, versions 16.0 (SPSS Inc., Chicago, Illinois) to 22.0 (IBM SPSS Statistics Version 22, USA). We used logarithmic transformation to normalize skewed distributions to achieve normality of all outcome variables except blood pressure, height and concentrations of uric acid, albumin and urea. We also calculated the geometric means of those variables which are the *n*th roots of the product of *n* values. Geometric standard deviation corresponds to the relative change in a variable corresponding to one standard deviation unit change in the logarithm of the variable. We assessed group differences in background characteristics by using Student's *t* test for continuous data and Pearson's $\chi 2$ test for categorical data. To assess differences between preterm (VLBW/early-preterm/late-preterm) subjects and controls we used linear or logistic regression models to adjust for covariates described in Fig. 10 and Table 9:

Covariates in linear regression models assessing the association between preterm birth vs. REE and the REE/LBM ratio in adults born preterm with VLBW (I):

- Model 1: Age and sex.
- Model 2: Variables in Model 1and parental education and daily smoking.
- Model 3: Variables in Model 2 and body fat percentage and self-reported intensity, frequency and duration of leisure-time physical activity.

Covariates in linear regression models assessing cardiovascular risk factors in adolescents born preterm (II):

- Model 0: Unadjusted.
- Model 1: Age.
- Model 2: Variables in Model 1 and BMI and height.
- Model 3: Variables in Model 2 and birth weight SD score, maternal smoking during pregnancy, and educational level of more educated parent.

- Model 4: Variables in Model 3 and smoking, physical activity and Tanner pubertal stage.

Covariates in linear regression models assessing cardiometabolic risk factors in adults born preterm (III):

- Model 1: Age, cohort (NFBC or FMBR), and sex.
- Model 2: Variables in Model 1 and parental and prenatal confounding factors (including parental educational attainment as a proxy of childhood socioeconomic position, maternal smoking during pregnancy, and birth weight SD scores as indicators of fetal conditions during pregnancy), and, for analyses of dichotomous and biochemical outcomes, parental history of hypertension, diabetes, and myocardial infarction or stroke as proxies of genetic susceptibility.
- Model 3: Variables in Model 1 and current characteristics: height (for body composition and blood pressure) or BMI (for blood pressure and biochemical risk factors), physical activity, and smoking. For fatty liver index, these adjustments also included current alcohol use.
- Model 4: variables in Models 2 and 3.

Covariates in linear regression models assessing ambulatory blood pressure and its variability in adults born preterm (IV):

- Model 1: Age and sex. In addition, models for BP when awake and sleep also included whether sleep was assessed by accelerometry.
- Model 2: Variables in Model 1 and parental educational level, mother's BMI before pregnancy, gestational or chronic hypertension, preeclampsia, GDM, and birth weight SD score.
- Model 3: Model 1 and parental educational attainment, height, BMI, physical activity, and smoking.

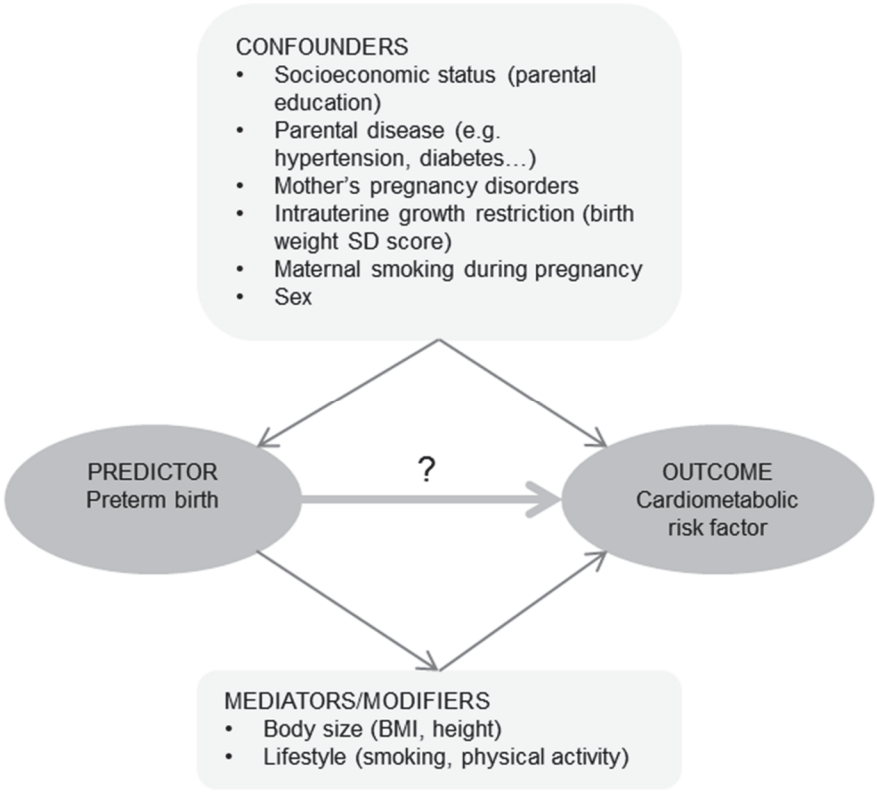

Fig. 10. Causal diagram (or direct acyclic graph) for the linear and logistic regression models (Textor *et al.* 2011).

In addition, we reported some of the analyses with length of gestation as a continuous variable. We tested whether the associations between preterm birth and outcomes were similar in men and women by adding the interaction terms sex*VLBW or sex*early preterm birth or sex*late preterm birth to the model. All P-values were 2-sided.

Table 9. Study design in Articles I–IV.

Variable	I	II	III	IV
Cohort	(HeSVA)	NFBC	ESTER	ESTER
Mean age (SD), years	22.5 (2.2)	16.0 (0.4)	23.3 (1.3)	23.3 (1.2)
Predictor	VLBW (<1500 g)	Early preterm (<34 wk); late preterm (34 to 36 wk); GA at birth (wk)	Early preterm (<34 wk); late preterm (34 to 36 wk); GA at birth (wk)	Early preterm (<34 wk); late preterm (34 to 36 wk); GA at birth (wk)
Controls	≥37 weeks not SGA	≥37 weeks	≥37 weeks	≥37 weeks
Main outcome variables				
Energy metabolism	REE, REE/LBM ratio			
Body size and composition		Height, weight, BMI, waist circumference	Height, BMI, waist circumference, waist-hip ratio, lean body mass, fat mass, percentage body fat, obesity	
Blood pressure		Office-measured systolic and diastolic blood pressure	Office-measured systolic and diastolic blood pressure, hypertension	Means and SDs of 24-hour, awake and asleep systolic and diastolic ABP
Lipid metabolism		TC, LDL-C, HDL-C, TG, ApoA1, ApoB	TC, LDL-C, HDL-C, TG, LPa, ApoA1, ApoB	
Glucose regulation		Fasting glucose and insulin	Fasting and 2-hour glucose, fasting and 2-hour insulin, HOMA-IR	
Inflammatory markers			hsCRP, blood leukocytes	

Variable	I	II	III	IV
Fatty liver markers			Alanine aminotransferase, aspartate transaminase, gamma glutamate, FLI	
Other biomarkers			Uric acid, albumin, and urea	
Covariates				
Confounders	Age, sex, parental education	Age, sex, parental education, maternal smoking during pregnancy, and birth weight SD score	Age, source cohort (NFBC or FMBR), sex, parental education, parental history of a) hypertension, b) diabetes, c) coronary heart disease and/or stroke, maternal smoking during pregnancy, birth weight SD score	Age, use of accelerometry, sex, parental education, mother's BMI before pregnancy, gestational or chronic hypertension, preeclampsia (including superimposed), gestational diabetes, birth weight SD score
Mediators/modifiers	Body fat percentage, smoking, self-reported intensity, frequency and duration of leisure time physical activity	BMI, height, smoking of the subject, self-reported physical activity, pubertal stage	BMI, height, self-reported physical activity, daily smoking, hormonal contraception	Height, BMI, self-reported physical activity, daily smoking

Variable	I	II	III	IV
Additional analyses	Comparison of VLBW subjects born SGA vs. AGA; exposed to maternal preeclampsia. Additional adjustment for weight gain (SD) from birth to term	Exclusion of subjects a) born post-term; b) with uncertain length of gestation; c) born SGA; d) exposed to maternal gestational diabetes; e) excluding those exposed to maternal preeclampsia or gestational or chronic hypertension. Additional adjustment a) birth weight SD score; b) adjustment of the full regression model for maternal gestational diabetes, preeclampsia, gestational or chronic hypertension	Exclusion of subjects born a) SGA, b) from multiple pregnancies. Additional adjustment for a) maternal gestational or chronic hypertension, and preeclampsia, b) gestational diabetes	Exclusion of subjects a) exposed to maternal hypertensive pregnancy disorder; b) born SGA

Abbreviations: ABP, ambulatory blood pressure; AGA, appropriate for gestational age; ApoA1, apolipoprotein A1, ApoB, apolipoprotein B; BMI, body mass index; ESTER, Preterm birth and early life programming of adult health and disease ; FMBR, Finnish Medical Birth Register; FLI, fatty liver index; GA, gestational age; HDL-C high-density lipoprotein cholesterol; HeSVA, The Helsinki Study of Very Low Birth Weight Adults; HOMA-IR, homeostasis model assessment values for insulin resistance; hsCRP, high-sensitivity C-reactive protein; LBM, lean body mass; LDL-C, low-density lipoprotein cholesterol; LPa, lipoprotein (a); NFBC, Northern Finland Birth Cohort 1986; REE, resting energy expenditure; SD, standard deviation; SGA, small for gestational age; TC, total cholesterol; TG, triglycerides; VLBW, very low birth weight (<1500 g) .

5 Results

The perinatal and neonatal characteristics of the study groups are presented in Table 11. In every cohort, subjects born preterm were more likely to be exposed to preeclampsia of the mother, born from multiple pregnancy and be SGA, as expected. To summarize the current findings, the results of each outcome variable group are presented together.

5.1 Body size and composition (I, II, III)

5.1.1 Body size and composition in adults born preterm with VLBW (I)

Differences in body size and composition in adults born preterm compared with their peers born at term (HeSVA) have been published before and are presented in the Review of the literature (section 2.4.1). In short, adults born preterm with VLBW were shorter and lighter and had lower lean body mass than their peers born at term (Table 10).

Table 10. Mean values (SD) of lean body mass in women and men born with VLBW and in controls born at term.

Measurement	Women			Men		
	VLBW	Term	P value	VLBW	Term	P value
Height (cm)	162.4 (8.0)	167.6 (6.3)	<0.001	175.9 (8.5)	180.7 (6.1)	0.003
BMI	21.8 (3.7)	23.0 (3.9)	0.064	22.1 (4.0)	23.9 (3.2)	0.020
Body fat percentage (%)	31.9 (6.2)	32.0 (5.6)	0.92	19.9 (6.4)	19.9 (5.4)	0.97
Lean body mass (kg)	38.9 (5.9)	43.5 (5.5)	<0.001	54.4 (8.9)	62.2 (8.4)	<0.001

5.1.2 Body size in adolescents born preterm in NFBC (II)

In NFBC, adolescent girls and boys born preterm had similar weight, height, BMI, waist and hip circumference as their peers born at term (Table 12), even when adjusted for SD for birth weight, age, parental education, smoking and physical activity, and Tanner Pubertal Stage.

Table 11. Perinatal and neonatal characteristics of the subjects in the Helsinki Study of Very Low Birth Weight Adults (HeSVA), the Northern Finland Birth Cohort 1986 (NFBC 1986) and the ESTER Preterm Birth Study ("Preterm birth and early life programming of adult health and disease").

Study	HeSVA		NFBC 1986			ESTER		
Groups	VLBW	Controls	Early preterm	Late preterm	Controls	Early preterm	Late preterm	Controls
N	116	118	79	238	6325	134	242	344
Male, n (%)	44 (37.9)	45 (38.1)	33 (41.8)	131 (55.0)	3105 (49.1)	65 (48.5)	120 (49.6)	168 (48.8)
Maternal preeclampsia, n (%)	24 (20.7)**	10 (8.5)	12 (15.2)***	24 (10.1)***	289 (4.6)	32 (23.9)***	22 (9.3)***	16 (4.7)
Multiple pregnancy, n (%)	21 (18.1)	0 (0)	22 (27.8)***	43 (18.1)***	86 (1.4)	32 (23.9)***	34 (14.0)***	4 (1.2)
Gestational age (weeks)	29.2 (2.3)***	40.1 (1.1)	32.0 (1.6)***	36.0 (0.8)***	40.0 (1.2)	31.8 (2.0)***	35.8 (0.8)***	40.1 (1.2)***
Birth weight (g)	1125 (223)***	3606 (469)	1788 (461)***	2696 (494)***	3619 (476)	1786 (493)***	2674 (515)***	3576 (483)
Birth weight SD score	-1.38 (1.6)***	0.08 (1.0)	-0.82 (1.4)***	-0.65 (1.2)***	0.08 (1.0)	-0.73 (1.4)***	-0.63 (1.3)***	-0.02 (1.0)
SGA, n (%)	25 (21.6)	0 (0)	15 (19.0)***	21 (8.8)***	114 (1.8)	22 (16.4)***	30 (12.4)***	7 (2.0)

Abbreviations: SGA, small for gestational age; VLBW, very low birth weight (<1500g).

P values for the differences compared with controls: * P < 0.05; ** P < 0.01; *** P < 0.001.

Table 12. Mean (SD) in body sizes of girls and boys born early and late preterm, and controls born at term.

Measurement	Sex	Early preterm		Late preterm		Controls
		Mean (SD)	P value	Mean (SD)	P value	Mean (SD)
Height (cm)	Girls	163.6 (6.3)	0.90	163.6 (5.3)	0.73	163.9 (6.0)
	Boys	174.7 (7.9)	0.70	174.6 (7.1)	0.56	174.8 (6.8)
Body mass index (kg/m^2)	Girls	20.9 (1.2)	0.25	20.9 (1.2)	0.53	21.0 (1.2)
	Boys	20.2 (1.1)	0.85	20.9 (1.2)	0.95	20.9 (1.2)
Waist circumference (cm)	Girls	72.2 (1.1)	0.45	71.6 (1.1)	0.39	71.5 (1.1)
	Boys	74.3 (1.1)	0.58	75.8 (1.1)	0.91	75.3 (1.1)

5.1.3 Body size and composition of young adults born preterm (III)

In the ESTER study, adults born early and late preterm had similar heights as their peers born at term (Table 13.Fig. 11). However, when adjusted for confounders in order to assess the total effect (sex, age, cohort, parental education, maternal smoking during pregnancy, birth weight SD score) and direct effect (in addition to the covariates in the total effect model, for height, physical activity, daily smoking) of preterm birth, they were taller than the controls. Adults born early preterm also had similar BMIs and LBMs as their peers born at term. However, they had higher waist circumferences, waist-hip ratios, fat mass and body fat percentages (Table 13), but the difference in fat mass was statistically significant in the model assessing the direct effect of preterm birth on adult body composition. Adults born late preterm had higher BMIs, waist circumferences, waist-hip ratios, fat mass and percentage body fat (Table 13.Fig. 11). The differences remained similar when controlled for the covariates. They also had higher LBMs, but the difference [3.6% (1.4, 5.8)] was statistically significant only in the model assessing the total effect of preterm birth on adult body composition. Adults born early and late preterm were about 2-fold more likely to be obese than the controls: OR 2.2 (95% CI 1.1, 4.1) for early preterm and OR 1.7 (95% CI 1.0, 3.1) for late preterm group when adjusted for age, sex and source cohort (Table 22.Fig. 16).

Table 13. Means for height and geometric means (SD) of body size and composition measurements in adults born early and late preterm and mean differences in percent, except for height in cm, (95% CIs, adjusted for age, sex and cohort) between preterm groups compared with controls born at term.

Measurement	Early preterm			Late preterm			Controls	
	Women	Men	Mean difference (95% CIs)	Women	Men	Mean difference (95% CIs)	Women	Men
Height (cm)	163.4 (5.2)	178.6 (7.0)	0.4 (-0.9, 1.6)	164.6 (5.8)	177.7 (6.7)	0.5 (-0.6, 1.5)	164.0 (6.0)	177.6 (7.0)
BMI	22.8 (0.24)	22.9 (0.17)	1.8% (-1.8, 5.3)	22.4 (0.18)	23.9 (0.19)	2.9% (0.1, 5.8)	22.0 (0.19)	23.0 (0.19)
Waist circumference (cm)	77.3 (0.17)	83.5 (0.13)	3.6% (1.2, 6.1)	75.8 (0.12)	84.7 (0.13)	3.3% (1.3, 5.3)	73.7 (0.13)	82.3 (0.10)
Waist-hip ratio	0.83 (0.05)	0.90 (0.04)	1.8% (0.7, 2.9)	0.82 (0.04)	0.91 (0.05)	1.3% (0.4, 2.1)	0.81 (0.05)	0.90 (0.05)
Lean body mass (kg)	42.6 (0.17)	61.6 (0.15)	-0.2% (-2.8, 2.5)	43.7 (0.14)	61.8 (0.14)	1.3% (-0.9, 3.5)	43.2 (0.13)	61.5 (0.15)
Fat mass (kg)	17.9 (0.59)	11.6 (0.65)	8.5% (-0.1, 18.9)	16.8 (0.46)	13.2 (0.68)	11.7% (3.7, 20.4)	15.7 (0.52)	11.5 (0.57)
Percentage body fat	28.7 (0.30)	15.5 (0.42)	6.2% (-0.4, 13.2)	27.1 (0.27)	17.1 (0.48)	8.0% (2.4, 13.8)	26.0 (0.32)	15.4 (0.42)

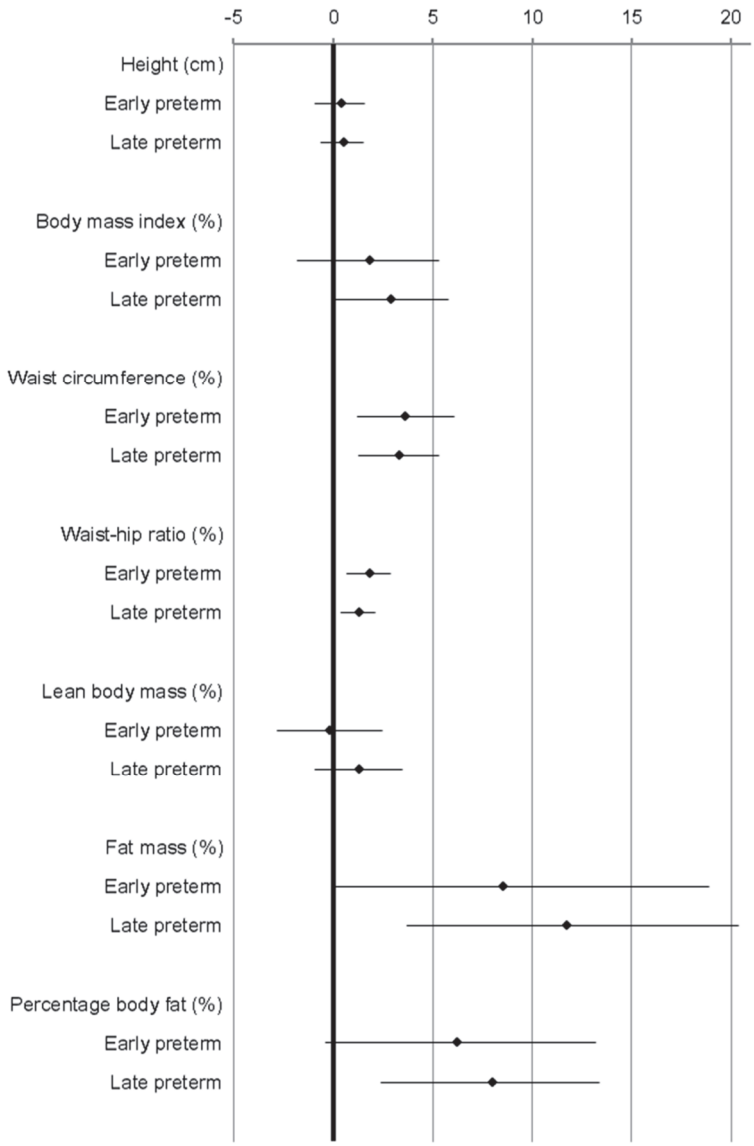

Fig. 11. Mean percentage differences (except for height in cm) and 95% confidence intervals (error bars) in body size and composition in adults born early and late preterm compared with controls (zero line), adjusted for age, sex and cohort (whether they are recruited from the Northern Finland Birth Cohort or the Finnish Medical Birth Register).

To study whether or not perinatal conditions that may accompany preterm birth contributed to later body size and composition, we reanalyzed the data by 1) excluding those born SGA, 2) excluding those born after multiple pregnancy, and 3) adjusting the analyses for maternal gestational diabetes. This did not alter any of the conclusions. We further adjusted the analyses for maternal hypertension in pregnancy, and the differences in fat mass and body fat percentage attenuated the differences among those born early preterm.

Further, we compared those born SGA to those born AGA within the preterm groups. Adults born early preterm and SGA (EPT-SGA) were 4.0 cm (95% CI 1.2, 6.8) shorter and had 9.3% (95% CI 3.1, 15.2) lower LBM than adults born early preterm and AGA (EPT-AGA) when adjusted for age, sex and cohort. Adults born late preterm and SGA (LPT-SGA) were 4.9 cm (05% CI 2.6, 9.2) shorter and had 9.4% (95% CI 5.1, 13.7) lower LBM than adults born late preterm and AGA (LPT-AGA). However, we found no statistically significant difference in BMI, waist circumference, fat mass, or percentage body fat between SGA and AGA subjects in early and preterm groups.

5.2 Resting energy expenditure (I)

We found that adults born preterm with VLBW had 6.3% (95% CI 3.2, 9.3) lower REE, but 6.1% (95% CI 3.4, 8.6) higher REE per unit lean body mass (REE/LBM ratio) compared with peers born at term when adjusted for age and sex (Table 14, HeSVA). The differences in REE and the REE/LBM ratio were little affected after adjustment for age, sex, parental education, daily smoking, body fat percentage and the intensity, frequency and duration of self-reported leisure time physical activity. The interaction between VLBW and sex on these outcomes was not statistically significant (all P values >0.27), meaning that the association between preterm birth with VLBW on REE and the REE/LBM ratio was similar in women and men. Therefore we presented the results pooled for both sexes.

We carried out additional analyses to examine the effects of perinatal and other clinical characteristics on energy metabolism. We reanalyzed the data after exclusion of subjects a) born from multiple pregnancies, b) subjects with cerebral palsy, developmental delay, or severe sensorineural deficit, or c) with regular usage of beta-sympathomimetic drugs. The results were similar.

Table 14. Mean (SD) resting energy expenditure (REE) and resting energy expenditure per unit lean body mass (REE/LBM ratio) in women and men born preterm with very low birth weight (VLBW) and controls born at term, and mean percentage differences in percent (95% CIs) between adults born with VLBW vs. controls.

Measurement	VLBW; mean (SD)		Term; mean (SD)		Mean difference
	Women	Men	Women	Men	(95% CI)
REE (kcal/24h)	1442 (207)	1834 (253)	1520 (172)	1977 (237)	-6.3% (-10.4 to -2.0)
REE/LBM ratio (kcal/24h/kg)	37.4 (4.4)	33.9 (2.6)	35.1 (3.0)	31.9 (2.3)	6.2% (3.5 to 9.0)

Further, we carried out additional subgroup analysis within the VLBW group. Subjects born SGA (n=25) had a 6.2% (95% CI 0.15%, 11.5%) lower REE, but a similar REE/LBM ratio as those born AGA (n=91) when adjusted for age and sex. The difference in REE was attenuated after further adjustment for other covariates. Within the VLBW group, individuals whose mothers had preeclampsia during pregnancy, as compared with those whose mothers did not, had similar REE values and similar REE/LBM ratios. In VLBW subjects a one SD unit higher score in body weight at what would have been term (40 weeks of postmenstrual age) corresponded to a 3.3% (95% CI 0.6%, 6.1%) increase in REE and was not related to the REE/LBM ratio. However, the change in SD score from birth to term was not related to REE or the REE/LBM ratio.

5.3 Blood pressure (II–IV)

The association between preterm birth and blood pressure in adolescence or adulthood was reported in three articles: office-measured BP in Articles II and III and ambulatory BP in Article IV.

5.3.1 Blood pressure in adolescents born preterm (II)

In NFBC 1986 we found statistically significant interactions between the associations of early preterm birth and sex on SBP levels (P=0.009) meaning the association of preterm birth on blood pressure in adolescence. Therefore we performed analyses separately in boys and girls.

Girls born early preterm had higher SBP higher DBP than control girls (Table 15, Fig. 12). The difference remained after adjusting for BMI, height, birth weight SD score, maternal smoking during pregnancy, educational level of the more educated

parent, smoking of the subject, physical activity, and Tanner Pubertal Stage (full model). However, we found no statistically significant difference in BP in girls born late preterm compared with girls born at term. In addition, the difference in BP was not statistically significant in boys born preterm (early or late) compared with controls.

The association between length of gestation and blood pressure was inverse in adolescent girls: a one-week greater length of gestation corresponded to 0.5 mmHg (95% CI 0.3, 0.8) lower SBP and 0.2 mmHg (95% CI 0.0, 0.3) lower DBP. However, this association was not seen in boys. We found no quadratic relationship between the length of gestation and BP in either sex (all P >0.1).

Table 15. Means (SD) of systolic and diastolic blood pressure (SBP and DBP) in adolescent girls and boys born early and late preterm, and controls born at term and mean differences (95% CI) between preterm groups and controls adjusted for age.

Measurement	Early preterm		Late preterm		Controls
	Mean (SD)	Mean difference (95% CI)	Mean (SD)	Mean difference (95% CI)	Mean SD
Girls					
SBP (mmHg)	116.7 (9.5)	6.7 (3.2, 10.2)	111.8 (10.4)	1.7 (-0.6, 3.9)	109.9 (10.7)
DBP (mmHg)	70.3 (6.7)	3.5 (1.1, 5.8)	67.6 (6.7)	0.6 (-0.9, 2.1)	66.8 (7.2)
Boys					
SBP (mmHg)	121.6 (15.4)	0.8 (-7.5, 5.8)	122.6 (14.1)	1.3 (-1.4, 3.5)	121.0 (12.1)
DBP (mmHg)	68.9 (9.2)	-0.1 (-3.6, 3.4)	68.4 (8.2)	-0.4 (-1.9, 1.2)	68.6 (7.9)

However, girls born EPT-SGA had 8.4 mmHg (95% CI 1.5, 15.4) lower SBP and 4.9 mmHg (95% CI 0.0, 9.7) lower DBP than girls born EPT-AGA. Girls born LPT-SGA did not have statistically significant difference in blood pressure when compared to girls born LPT-AGA. In addition, no statistically significant difference was found in boys born EPT-SGA vs. EPT-AGA or in boys born LPT-SGA vs LPT-AGA. We further reran the comparisons after excluding those born SGA from preterm and control groups and the difference in BP was even greater in girls born early preterm compared with controls. The results were similar when subjects exposed to maternal GDM or maternal hypertensive pregnancy disorders were excluded.

5.3.2 Blood pressure in young adults born preterm (III)

In the ESTER study adults born early preterm had higher SBP and DBP than the controls (Table 16). The difference remained statistically significant when further adjusted for

1. age, sex, cohort, height, BMI, parental educational attainment, maternal smoking during pregnancy, parent's history of hypertension, diabetes, and coronary heart disease or stroke, and birth weight SD score (*total effect*)
2. age, sex, cohort, height, BMI, self-reported physical activity and daily smoking to control the bias caused by possible *intermediate factors*
3. total effect and intermediate factors (*direct effect*).

The interaction between preterm birth and sex on BP was not statistically significant. For this reason we carried out the analysis simultaneously for women and men.

We further adjusted the analyses for maternal hypertension in pregnancy. Subjects exposed to maternal hypertension had 3.6 mm Hg higher systolic and 2.7 mm Hg higher diastolic blood pressure compared with those not exposed (adjusted for the direct effect model). When adjusted for maternal hypertension, the differences in systolic/diastolic blood pressures vs. those in the controls became attenuated to 1.9 (95% CI -0.3, 4.0)/1.7 mmHg (0.1, 3.3) for early preterm and 0.5 mmHg (-1.2, 2.3)/0.02 mmHg (-1.1, 1.6) for late preterm infants. However, the results remained similar when we reran the analysis excluding those born SGA or born from multiple pregnancy or those exposed to maternal GDM. We also compared those born SGA to those born AGA within the early and late preterm groups and there were no statistically significant difference in systolic or diastolic blood pressure.

Table 16. Mean systolic and diastolic blood pressures (SBP and DBP) in adults born early and late preterm compared with controls born at term, and mean differences (95% CI) between preterm groups and controls adjusted for age, sex and cohort (NFBC or FMBR).

Measurement	Early preterm		Late preterm		Controls
	Mean (SD)	Mean difference (95% CI)	Mean (SD)	Mean difference (95% CI)	Mean (SD)
SBP (mmHg)	118.9 (12.9)	3.0 (0.9, 5.1)	117.7 (13.4)	1.7 (-0.1, 3.4)	116.3 (12.7)
DBP (mmHg)	77.8 (8.9)	2.6 (0.9, 4.2)	76.5 (8.2)	1.2 (-0.1, 2.5)	75.5 (7.6)

5.3.3 Ambulatory blood pressure in young adults born preterm (IV)

In the ESTER study, adults born early preterm had higher 24-hour SBP and DBP, higher SBP and DBP when awake and higher DBP when asleep versus controls when adjusted for age, sex and use of an accelerometer (Table 17). The difference in 24-hour and awake SBP remained similar when further adjusted for covariates (parental educational level, mother's BMI before pregnancy, gestational or chronic hypertension, preeclampsia [including superimposed preeclampsia], gestational diabetes, birth weight SD score, height, BMI, physical activity and daily smoking). However, the differences in 24-hour DBP, and awake DBP and sleep SBP were not statistically significant when controlled for perinatal factors (parental educational level, mother's BMI before pregnancy, gestational or chronic hypertension, preeclampsia gestational diabetes and birth weight SD score). Adults born late preterm had no statistically significant difference in mean ABP (0). A one-week increase in the length of gestation was associated with approximately 0.6 mmHg (0.1, 1.0) lower 24-hour and awake SBP and 0.3 mmHg (0.04, 0.6) lower 24-hour DBP and 0.4 mmHg (0.1, 0.7) lower awake DBP. However, no statistically significant association between length of gestation and sleep SBP or DBP was found.

We found no statistically significant interactions between the associations of early or late preterm birth and sex on ambulatory blood pressure levels ($P \geq 0.08$), except for awake SBP among late preterm ($P=0.05$). However, we further performed analyses separately in women and men. Differences between adults born early preterm and controls were seen in both sexes in awake SBP. In addition. women born early preterm had higher 24-hour DBP and awake DBP than controls. However, men born early preterm had higher 24-hour SBP than controls. Differences between adults born late preterm and controls were seen only among men: men born late preterm had higher 24-hour SBP and DBP than men born at term.

Maternal chronic and gestational hypertension during pregnancy was independently associated with higher ABP, while maternal preeclampsia was not. Therefore, we reanalyzed the data after excluding subjects exposed to maternal hypertension during pregnancy, and the difference between adults born early preterm and controls in 24-hour SBP attenuated to 5.4 mm Hg (95% CI 1.6, 9.2). Otherwise, the differences remained similar. When subjects born with SGA were excluded from the analyses, the differences in mean ABP between the early preterm and control groups increased by 0.1–0.5 mm Hg,

Variability of ambulatory blood pressure

Adults born early preterm also had higher SDs of 24-hour SBP and DBP, SD of awake SBP and DBP and SD of sleep DBP (Table 17). The differences were similar when adjusted for covariates (parental educational level, mother's BMI before pregnancy, gestational or chronic hypertension, preeclampsia [including superimposed preeclampsia], gestational diabetes, birth weight SD score, height, BMI, physical activity and daily smoking), except for the SD of wake DBP adjusted for perinatal factors (parental educational level, mother's BMI before pregnancy, gestational or chronic hypertension, preeclampsia, gestational diabetes and birth weight SD score). Adults born late preterm had 0.8 mmHg (0.1, 1.4) higher SD of 24-hour DBP, 0.8 mmHg (0.0, 1.6) higher sleep SBP and 0.6 mmHg (-0.2, 1.4) higher SD of sleep DBP when adjusted for age, sex and use of an accelerometer (Table 17). Otherwise, no statistically significant difference in SD of ambulatory blood pressure was found between the late preterm group and controls. A one-week increase in the length of gestation was associated with approximately 0.1–0.2 mmHg lower SD of 24-hour SBP and DBP, SBP and DBP and sleep DBP. We reanalyzed the data after excluding subjects exposed to maternal hypertension during pregnancy, and the differences in SDs of ABP remained similar. We further reran the analyses after excluding subjects born SGA. The differences in the SDs of ABP attenuated by up to 0.2 mm Hg.

Table 17. Means (SD) and SDs of ambulatory blood pressure and mean differences (95 CIs) in means and standard deviations (SDs) between early and late preterm adults compared with controls.

Measurement	Early preterm, n = 42		Late preterm, n = 72		Controls, n = 103
	Mean (SD)	Mean difference (95% CI)	Mean (SD)	Mean difference (95% CI)	Mean (SD)
Mean ambulatory BP, mm Hg					
24-hour SBP	121.4 (12.7)	5.5 (1.9, 9.3)	119.1 (12.0)	2.7 (-0.5, 5.8)	116.3 (8.9)
24-hour DBP	71.2 (7.4)	3.2 (0.7, 5.7)	69.8 (6.2)	0.9 (-1.3, 3.1)	68.2 (6.6)
Awake SBP	126.8 (13.1)	6.4 (2.8, 10.1)	122.9 (12.0)	2.0 (-1.2, 5.1)	120.8 (9.4)
Awake DBP	76.5 (8.4)	4.2 (1.6, 6.7)	73.9 (6.5)	1.9 (-0.2, 4.1)	72.7 (7.1)
Sleep SBP	110.1 (11.8)	3.9 (0.3, 7.5)	108.5 (11.5)	1.3 (-1.8, 4.4)	106.4 (8.9)
Sleep DBP	59.2 (6.0)	1.2 (-1.3, 3.7)	58.7 (7.0)	0.6 (-1.5, 2.7)	58.2 (6.5)
SD of ambulatory BP, mm Hg					
24-hour SBP	12.6 (3.0)	1.7 (0.8, 2.7)	11.5 (2.7)	0.5 (-0.3,1.4)	11.0 (2.6)
24-hour DBP	12.3 (2.3)	1.7 (0.9, 2.5)	11.4 (2.1)	0.8 (0.1, 1.4)	10.7 (2.1)
Awake SBP	10.3 (2.5)	1.3 (-0.5, 2.1)	9.6 (2.5)	0.5 (-0.2, 1.2)	9.1 (2.1)
Awake DBP	9.6 (2.5)	1.0 (0.2, 1.7)	9.5 (2.4)	0.5 (-0.1, 1.2)	8.6 (1.9)
Sleep SBP	7.9 (2.5)	0.7 (-0.2, 1.7)	8.2 (3.2)	0.8 (0.0, 1.6)	7.3 (2.4)
Sleep DBP	8.0 (2.5)	1.5 (0.6, 2.4)	7.2 (3.0)	0.6 (-0.2, 1.4)	6.4 (2.1)

Abbreviations: DBP, diastolic blood pressure; SBP, systolic blood pressure.

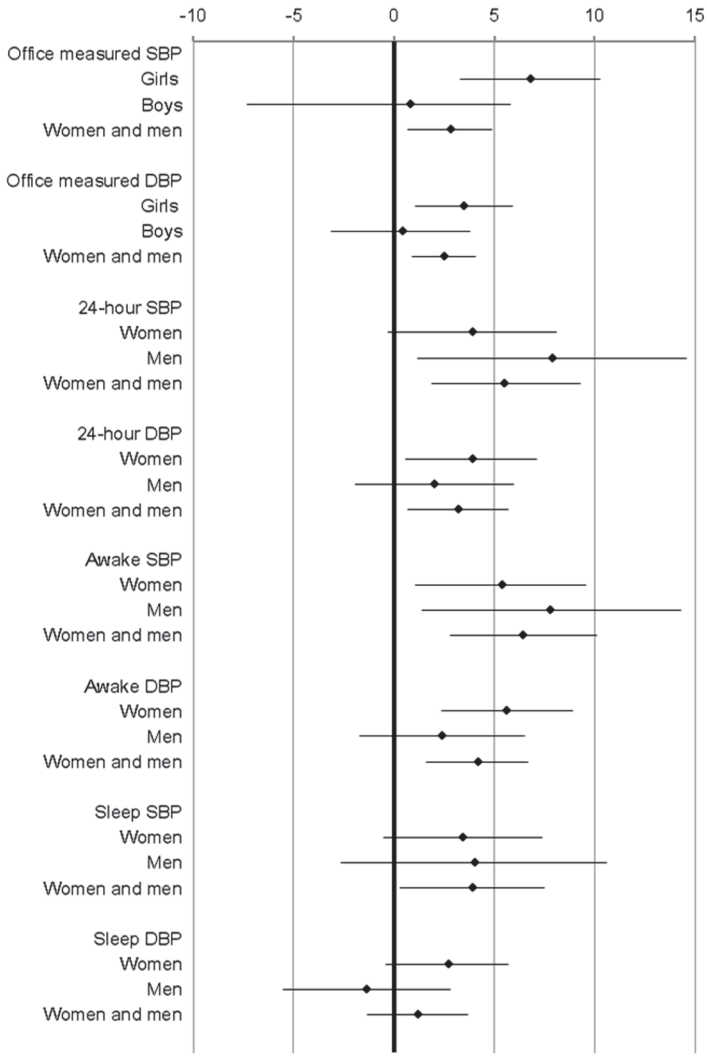

Fig. 12. The mean difference and 95% confidence intervals (error bars) in office and ambulatory measured blood pressure in adolescents and adults born *early preterm* compared to controls (zero line) adjusted for age (and sex and cohort).

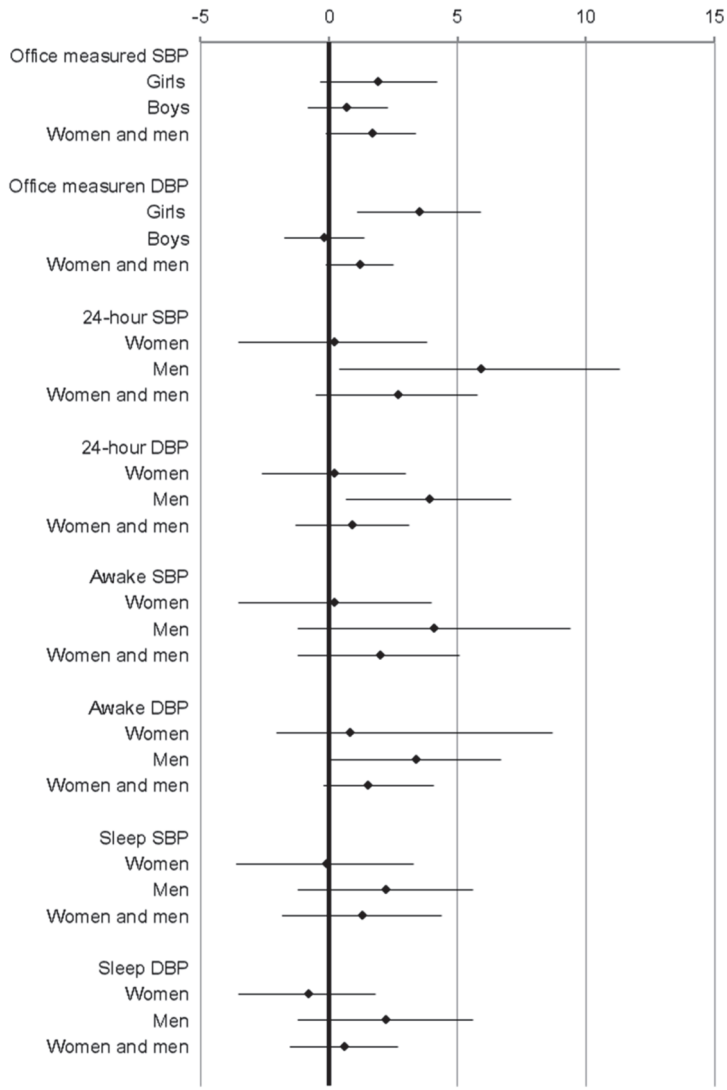

Fig. 13. The mean difference and 95% confidence intervals (error bars) in office and ambulatory measured blood pressure in adolescents and adults born *late preterm* compared to controls (zero line) adjusted for age (and sex and cohort).

5.3.4 Hypertension (II, III)

In the NFBC 1986 study we did not observe a pronounced risk of hypertension in adolescents born preterm, but pre-hypertension was more common in the early preterm group (17.7%) than in the controls (9.6%) (P<0.01). However, in the ESTER study, adults born preterm were about two- to threefold more likely to have hypertension, but the OR was statistically significant only in the early preterm group (Table 22.Fig. 16): OR for the early preterm group 2.7 (95% CI 1.3, 5.3) and for the late preterm group 1.7 (0.9, 3.2) adjusted for age, sex and cohort. In addition, adults born early preterm were more likely to have hypertensive ABP when awake: OR 3.8 (95% CI 1.1, 13.7). However, the OR was not statistically significant when adjusted for other covariates (age, sex, use of an accelerometer, parental educational level, mother's BMI before pregnancy, gestational or chronic hypertension, preeclampsia [including superimposed preeclampsia], birth weight SD score, height, BMI, physical activity and smoking).

5.4 Lipid metabolism (II, III)

The association between preterm birth and lipid profile in adolescence or adulthood was different in women and men, so we performed analyses separately for both sexes. In the adolescents the P value for interaction between early preterm birth and sex was 0.02 for LDL-C and it was 0.03 for ApoB. In addition, the P values for the interaction terms sex and early preterm birth were 0.035 for HDL-C and 0.019 for ApoA1 (when adjusted for age and sex).

5.4.1 Lipid profile of adolescents born preterm (II)

Among girls in NFBC, the lipid profiles were similar in all study groups. As for boys, those born early preterm had higher mean TC, LDL-C, ApoB and TG levels than controls when adjusted for age (Table 18). The differences remained similar when controlled for covariates (age, BMI, birth weight SD score, maternal smoking during pregnancy, parental education, smoking of the subject, physical activity and pubertal stage), except for the TGs when adjusted for current lifestyle factors. Boys born late preterm also had higher levels of TGs (Table 18), and when controlled for covariates as well. Levels of HDL-C and ApoA1 were similar in boys born early/late preterm and controls. In addition, among boys, a one-week greater length of gestation

corresponded to 0.5% (95% CI 0.1, 0.9%) lower TC, 1.0% (0.4, 1.6%) lower LDL-C and 1.0% (0.4, 1.5%) lower ApoB levels, adjusted for covariates. There were no quadratic relationships between length of gestation and lipid concentrations (all P >0.1).

Table 18. Geometric means (geometric SD) of lipid levels in adolescent girls and boys born early and late preterm and controls born at term, and mean percentage differences (95% CIs) between preterm groups and controls adjusted for age.

Measurement	Early preterm		Late preterm		Controls
	Geometric mean (SD)	Mean percentage difference (95% CI)	Geometric mean (SD)	Mean percentage difference (95% CI)	Geometric mean (SD)
Girls					
Total cholesterol	4.46 (1.18)	2.5 (-2.8, 8.1)	4.39 (1.46)	0.9 (-2.5, 4.5)	4.36 (1.19)
HDL-C	1.54 (1.23)	5.6 (-0.5, 12.1)	1.46 (1.22)	0.2 (-3.6, 4.2)	1.46 (1.21)
LDL-C	2.21 (1.34)	-0.8 (-8.1, 7.2)	2.27 (1.26)	2.0 (-3.0, 7.2)	2.24 (1.29)
ApoA1	1.45 (1.13)	2.9 (-1.3, 7.2)	1.42 (1.126)	0.3 (-2.4, 3.1)	1.41 (1.15)
ApoB	0.67 (1.34)	1.5 (-5.4, 8.9)	0.67 (1.24)	1.2 (-3.4, 6.0)	0.66 (1.27)
Triglycerides	0.72 (1.64)	-7.4 (-18.2, 4.7)	0.80 (1.55)	3.3 (-4.6, 11.9)	0.77 (1.49)
Boys					
Total cholesterol	4.46 (1.18)	6.7 (0.2, 13.7)	4.39 (1.19)	2.2 (-1.0, 5.5)	4.36 (1.19)
HDL-C	1.54 (1.24)	-0.1 (-7.1, 7.4)	1.46 (1.22)	-2.6 (-6.1, 1.0)	1.46 (1.21)
LDL-C	2.21 (1.34)	11.7 (2.1, 22.3)	2.27 (1.26)	4.4 (-0.2, 9.3)	2.24 (1.29)
ApoA1	1.45 (1.13)	0.9 (-3.6, 5.7)	1.42 (1.16)	-1.0 (-3.3, 1.3)	1.41 (1.15)
ApoB	0.67 (1.3)	12.3 (3.1, 22.4)	0.67 (1.24)	5.0 (0.5, 9.6)	0.66 (1.27)
Triglycerides	0.72 (1.64)	19.2 (2.1, 39.1)	0.80 (1.56)	13.2 (4.7, 22.4)	0.77 (1.49)

Abbreviations: ApoA1, apolipoprotein A1; ApoB, apolipoprotein B; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein protein cholesterol.

Boys born EPT-SGA had 17.6% (95% CI 2.9, 30.2) lower TC, 24.7% (95% CI 3.2, 41.4) lower LDL-C levels, and 24.5% (95% CI 5.1, 40.0) lower ApoB levels than boys born EPT-AGA. We found no difference between boys born LPT-SGA compared to boys born LPT-AGA in lipid levels. In addition, after excluding those born SGA, among boys born early preterm, levels of TC were 10.4% (95% CI 2.7–18.6%) higher, those of LDL-C 19.3% (7.7–32.2%) and those of ApoB 18.0% (7.2–29.9%) higher than in their controls. In addition, we reran the

analysis with adjustment only for birth weight SD score to assess the effect of birth weight separately from the effect of other covariates: In boys born early preterm, TC was 5.4% (-1.0–2.2%) higher, LDL-C was 10.3% (0.9–20.6%) higher, ApoB was 8.7% (-0.2–18.4%) higher and TGs 16.7% (0.1–35.9%) higher compared with controls. In boys born late preterm TG levels were 12.8% (4.2, 22.0%) higher. To assess the effect of maternal gestational disorders and hypertensive pregnancy disorders, we reran the analyses after 1) excluding subjects exposed to maternal gestational diabetes and 2) excluding those exposed to maternal hypertension or preeclampsia, and the results remained similar. Moreover, after further adjustment for a) maternal gestational diabetes, b) preeclampsia and gestational or chronic hypertension with other covariates, the results again remained similar.

5.4.2 Lipid profile of young adults born preterm (III)

In the ESTER study, women born early preterm had lower HDL-C and ApoA1 concentrations than the control women when adjusted for age and cohort (Table 19). The differences attenuated when further adjusted for covariates (BMI, parental educational attainment, maternal smoking during pregnancy, parental history of hypertension, diabetes and acute myocardial infarction or stroke, self-reported physical activity, daily smoking, birth weight SD score and hormonal contraception, direct effect model): Levels of HDL-C were 7.2% (1.1, 12.9%) lower and those of ApoA1 7.7% (2.3, 12.8%) lower in the early preterm group compared with controls. No differences in triglyceride or total or LDL-cholesterol concentrations were found in women born preterm compared with controls. Associations between preterm birth and lipid profile were not present among men. Within the subjects, no one used lipid-lowering medication.

We further compared adults born EPT-SGA to adults born EPT-AGA, and adults born LPT-SGA to those born LPT-AGA, and no statistically significant difference was found between groups. In addition, after exclusion of those born SGA or those exposed to maternal antenatal disorders, or additional adjustment for maternal antenatal disorders, the results remained similar.

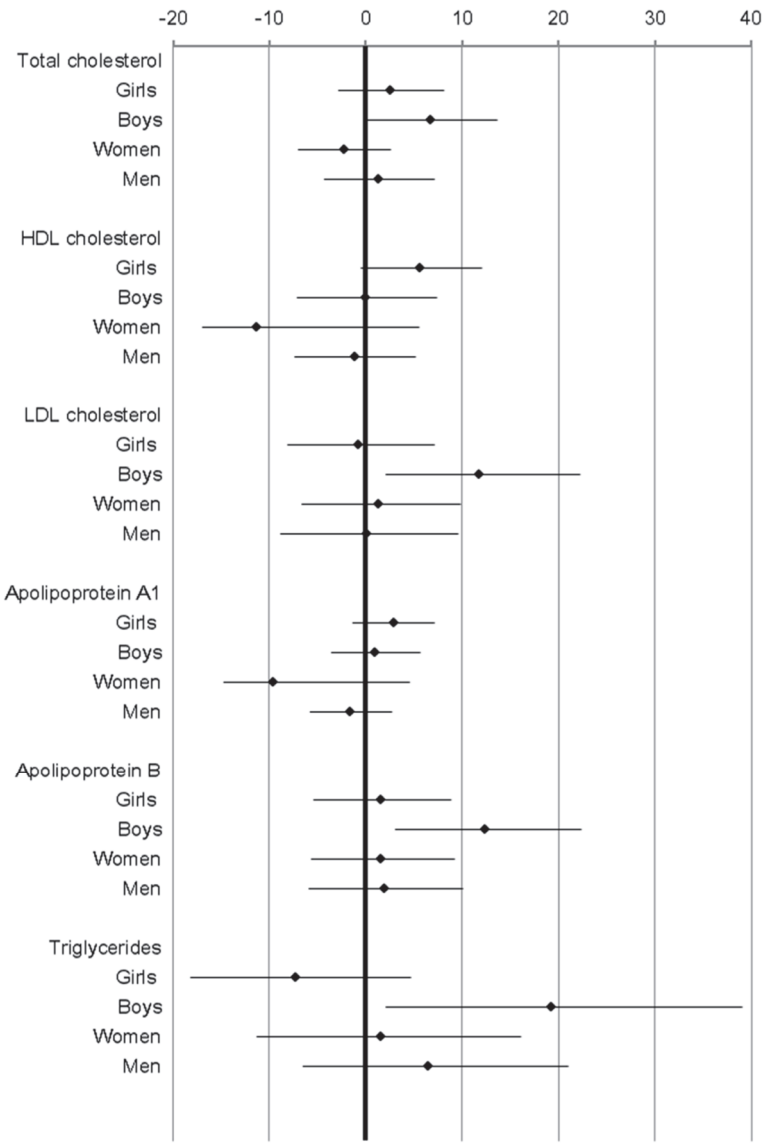

Fig. 14. Mean percentage differences and 95% confidence intervals (error bars) in lipid levels in adolescent girls and boys and young adult women and men born *early preterm* compared with controls (zero line) adjusted for age, and in adults of the source cohort (the Northern Finland Birth Cohort 1986 or the Finnish Medical Birth Register.

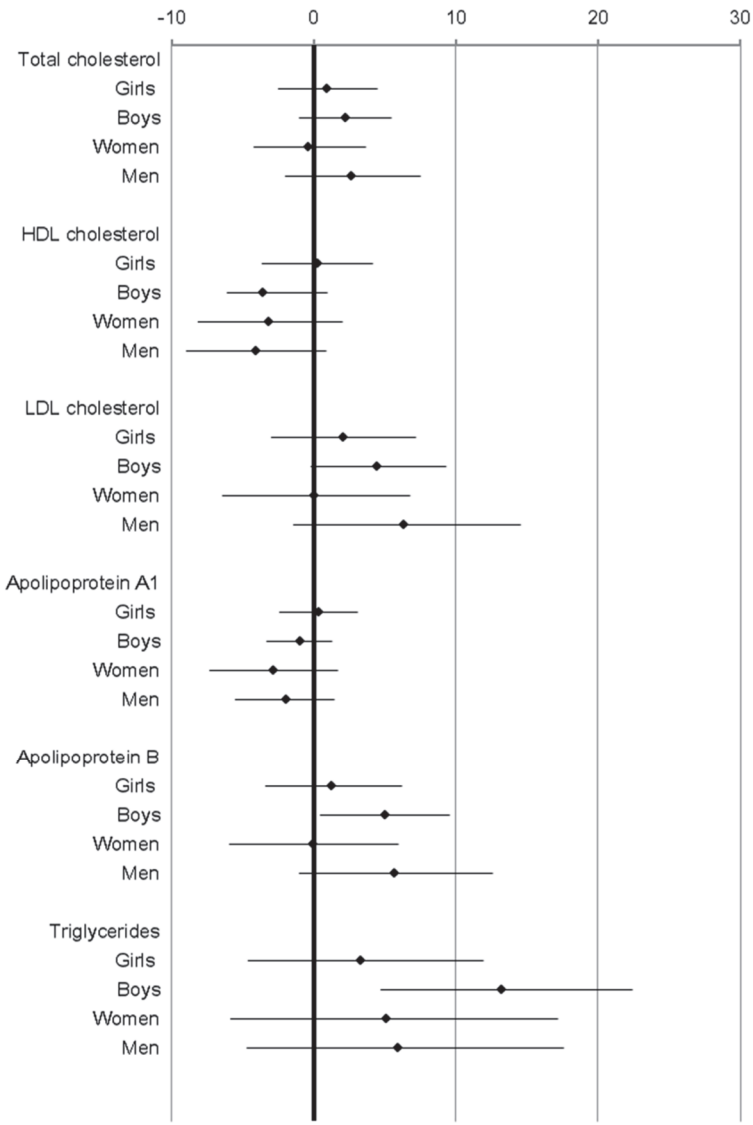

Fig. 15. Mean percentage differences and 95% confidence intervals (error bars) in lipid levels in adolescent girls and boys and young adult women and men born *late preterm* compared with controls (zero line) adjusted for age, and in adults of the source cohort (the Northern Finland Birth Cohort 1986 or the Finnish Medical Birth Register).

Table 19. Geometric means (geometric SD) of lipid levels in young adult women and men born early and late preterm and controls born at term, and mean percentage differences (95% CIs) between preterm groups and controls adjusted for age, sex and cohort (NFBC or FMBR).

Measurement	Early preterm		Late preterm		Controls
	Geometric mean (SD)	Mean percentage difference (95% CI)	Geometric mean (SD)	Mean percentage difference (95% CI)	Geometric mean (SD)
Women					
TC	4.58 (1.16)	-2.3 (-7.0, 2.6)	4.68 (1.17)	-0.4 (-4.2, 3.7)	4.70 (1.20)
HDL-C	1.59 (1.27)	-11.4 (-16.9, -5.6)	1.73 (1.23)	-3.2 (-8.1, 2.0)	1.79 (1.24)
LDL-C	2.70 (1.31)	1.3 (-6.6, 9.8)	2.66 (1.28)	0.0 (-6.4, 6.8)	2.66 (1.35)
ApoA1	1.53 (1.23)	-9.7 (-14.7, -4.5)	1.65 (1.20)	-2.9 (-7.3, 1.7)	1.69 (1-21)
ApoB	1.53 (1.-23)	1.5 (-5.6, 9.2)	0.75 (1.24)	-0.1 (-5.9, 6.0)	0.75 (1.31)
LPa, mg/l	99,9 (3.24)	4.9 (-25.5, 47.7)	88.7 (2.98)	-6.5 (-29.5, 23.9)	93.9 (3.25)
Triglycerides	0.97 (1.56)	1.5 (-11.3, 16.1)	1.01 (1.58)	5.1 (-5.8, 17.2)	0.97 (1.61)
Men					
TC	4.49 (1.23)	1.3 (-4.3, 7.2)	4.55 (1.20)	2.6 (-2.0, 7.5)	4.46 (1.22)
HDL-C	1.36 (1.25)	-1.2 (-7.3, 5.2)	1.32 (1.21)	-4.1 (-8.9, 0.9)	1.37 (1.26)
LDL-C	2.76 (1.49)	0.0 (-8.8, 9.6)	2.91 (1.32)	6.3 (-1.4, 14.6)	2.76 (1.37)
ApoA1	1.35 (1.15)	-1.7 (-5.8, 2.7)	1.34 (1.14)	-2.0 (-5.5, 1.5)	1.36 (1.17)
ApoB	0.77 (1.38)	1.8 (-5.9, 10.1)	0.80 (1.27)	5.6 (-1.0, 12.6)	0.76 (1.31)
LPa, mg/l	85.8 (3.25)	-4.9 (-33.0, 34.8)	94.4 (3.17)	2.4 (-23.1, 36.4)	91.0 (3.19)
Triglycerides	0.95 (1.63)	6.4 (-6.5,21.0)	0.95 (1.56)	5.9 (-4.7, 17.6)	0.90 (1.51)

Abbreviations: ApoA1, apolipoprotein A1; ApoB, apolipoprotein B; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein protein cholesterol; LPa, lipoprotein (a); TC, total cholesterol.

5.5 Glucose regulation (II, III)

5.5.1 Glucose metabolism of adolescents born preterm (II)

We found statistically significant interaction between late preterm birth and sex on HOMA-IR values (P=0.036) in the adolescents, so we analyzed the differences separately in girls and boys (NFBC). Girls did not show any difference in fasting plasma glucose or serum insulin levels, or in HOMA-IR values, compared with their controls.

Boys born late preterm had higher insulin HOMA-IR values than boys born at term (Table 20). The differences became attenuated when adjusted for age, BMI, height, birth weight SD score, maternal smoking during pregnancy, educational level of the more educated parent, smoking of the subject, physical activity and Tanner

Pubertal Stage. The mean levels of fasting plasma glucose were similar between the groups. When adjusted only for birth weight SD score, in boys born late preterm, fasting insulin levels were13.2% (3.1, 24.3%) higher and HOMA-IR values 12.6% (2.6, 23.6%) higher than in controls. Otherwise, within the boys born early preterm or boys born late preterm, there was no statistically significant difference between SGA and AGA in glucose metabolism. In addition, after exclusion of those born SGA or those exposed to maternal antenatal disorders, or additional adjustment for maternal antenatal disorders, the results remained similar.

Table 20. Geometric means (geometric standard deviations, SDs) concerning glucose metabolism in adolescent girls and boys born early and late preterm, and controls born at term, and mean percentage differences (95% CIs) between preterm groups and controls adjusted for age.

	Early preterm		Late preterm		Controls
	Geometric mean (SD)	Mean percentage difference (95% CI)	Geometric mean (SD)	Mean percentage difference (95% CI)	Geometric mean (SD)
Girls					
fP-gluk (mmol/l)	5.0 (1.08)	-0.2 (-3.3, 3.0)	5.1 (1.13)	1.1 (-1.0, 3.2)	5.0 (1.11)
fS-insulin (mU/l)	9.8 (1.46)	0.2 (-11.2, 13.1)	10.2 (1.53)	5.7 (-2.4, 14.1)	9.8 (1.49)
HOMA-IR	1.26 (1.52)	0.2 (-13.1, 15.6)	1.31 (1.52)	4.5 (-4.6, 14.4)	1.26 (1.49)
Boys					
fP-gluk (mmol/)	5.3 (1.09)	0.9 (-2.4, 4.3)	5.3 (1.08)	-0.7 (-2.4, 1.0)	5.3 (1.10)
fS-insulin (mU/l)	9.9 (1.46)	5.5 (-10.6, 24.5)	10.9 (1.70)	13.8 (4.7, 23.7)	9.6 (1.59)
HOMA-IR	1.37 (1.95)	14.1 (-8.0, 41.5)	1.42 (1.66)	13.2 (3.2, 24.3)	1.26 (1.58)

Abbreviations: fP-gluk; fastin plasma glucose; fS-insulin, fasting serum insulin; HOMA-IR, homeostasis model assessment for insulin resistance.

5.5.2 Glucose metabolism of young adults born preterm (III)

No statistically significant interaction between preterm birth and sex on glucose metabolism was found in young adults born preterm. Two subjects of the ESTER study born late preterm reported having type 2 diabetes, so we excluded them from the analyses of glucose metabolism. Adults born early preterm had 15.5% (-0.1, 33.6) higher 2-hour serum insulin levels, but the difference was not statistically significant

(Table 21). Otherwise, adults born early preterm showed no differences in glucose metabolism outcomes compared with controls born at term. Adults born late preterm had 10.1% (1.9, 19.0%) higher fasting and 16.5% (3.0, 31.7%) higher 2-hour insulin concentrations, and 9.8% (1.6, 18.6) higher HOMA-IR indices than the controls when adjusted for age, sex and cohort. These differences became statistically non-significant when controlled for parental and prenatal factors (parental educational attainment, maternal smoking during pregnancy, parental history of hypertension, diabetes, myocardial infarction or stroke), or intermediate factors (BMI, self-reported physical activity, daily smoking and birth weight SD score). Fasting and 2-hour glucose concentrations were similar in all groups. Eight (3.3%) of the late preterm subjects and 11 (3.2%) of the controls had impaired glucose tolerance (fasting glucose 6.0 to 6.9 mmol/l and/or 2-hour glucose 7.8 to 11.0 mmol/l) and one (0.4%) subject born late preterm was found to have diabetes (fasting glucose >7.0 and/or 2-hour glucose >11.0) in oral glucose tolerance tests (OGTTs). Adults born EPT-SGA had 71.3% (95% CI 16.3, 151.9) higher 2-hour insulin than adults born EPT-AGA. Otherwise, there was no statistically significant difference in glucose metabolism between EPT-SGA and EPT-AGA subjects or LPT-SGA and LPT-AGA subjects. We further reanalyzed the data by 1) excluding those born small for gestational age, 2) excluding those born in connection with a multiple pregnancy, and 3) further adjusting the analyses for maternal gestational diabetes. This did not alter any of the conclusions of the glucose metabolism.

Table 21. Geometric means (geometric SD) concerning glucose metabolism in young adults born early and late preterm and controls born at term, and mean percentage differences (95% CIs) between preterm groups and controls adjusted for age, sex and cohort (NFBC or FMBR).

Measurementt	Early preterm		Late preterm		Controls
	Geometric mean (SD)	Mean percentage difference (95% CI)	Geometric mean (SD)	Mean percentage difference (95% CI)	Geometric mean (SD)
fP-gluk	5.17 (1.09)	0.8 (-0.8, 2.4)	5.17 (1.10)	0.3 (-1.0, 1.6)	5.14 (1.09)
P-gluk 2h	4.90 (1.34)	-0.4 (-3.9, 3.2)	4.96 (1.29)	1.1 (-1.8, 4.0)	4.86 (1.27)
fS-insulin	7.27 (1.66)	8.8 (-1.0, 19.6)	7.40 (1.63)	10.1 (1.9, 19.0)	6.65 (1.51)
S-insulin 2h	24.89 (2.14)	15.5 (-0.1, 33.6)	25.08 (2.09)	16.5% (3.0, 31.7)	21.73 (2.04)
HOMA-IR	0.95 (1.66)	8.9 (-0.9, 19.7)	0.96 (1.63)	9.8 (1.6, 18.6)	0.87 (1.51)

Abbreviations: fP-gluk; fastin plasma glucose; fS-insulin, fasting serum insulin; HOMA-IR, homeostasis model assessment – insulin resistance; fP-gluk 2h, 2-hour plasma glucose; fS-insulin 2h, 2-hour serum insulin.

5.6 Other metabolic biomarkers (III)

In addition to conventional risk factors, we studied emerging risk factors that may reflect specific pathophysiological pathways, such as uric acid, markers of inflammation and markers of fatty liver (Table 22). In the ESTER study, subjects born preterm were 8- to 13-fold more likely to have an intermediate or high fatty liver index, a proxy of non-alcoholic fatty liver disease: 3.9% of subjects born early preterm, 2.5% of subjects born late preterm and 0.3% of the controls had an intermediate or high fatty liver index. However, the ORs were statistically significant in early preterm group only. Of the individual markers of fatty liver disease, plasma concentrations of alanine aminotransferase were 15.0% (95% CI 6.4, 24.2%) higher and those of aspartate transaminase were 11.7% (5.5, 18.2%) higher in those born late preterm, but the differences were not statistically significant.

Table 22. Geometric means (geometric SD) concerning cardiometabolic biomarkers in young adults born early and late preterm and controls born at term, and mean percentage differences (95% CIs) between preterm groups and controls adjusted for age, sex and cohort (NFBC or FMBR).

Measurement	Early preterm		Late preterm		Controls
	Geometric mean (SD)	Mean difference [a] (95% CI)	Geometric mean (SD)	Mean difference [a] (95% CI)	Geometric mean (SD)
Fasting plasma uric acid (µmol/l)	314.3 (80.9)	20.1 (7.9, 32.2)	313.4 (74.5)	20.1 (10.7, 30.5)	291.7 (68.7)
High-sensitivity C-reactive protein, mg/l	1.19 (3.95)	-3.4% (-24.6, 23.7)	1.01 (3.59)	-9.4 (-25.9, 10.7)	1.15 (3.59)
Blood leukocytes, 10^9/l	6.06 (1.31)	5.5% (0.0, 11.2)	5.89 (1.29)	3.1% (-1.2, 7,7)	5.67 (1.29)
Plasma alanine aminotransferase, U/l	25.5 (1.63)	9.3% (-0.6, 20.1)	26.6 (1.69)	15.0% (6.4, 24.2)	23.2 (1.67)
Plasma aspartate transaminase, U/l	22.9 (1.34)	5.6% (-1.5, 13.2)	24.2 (1.43)	11.7% (5.5, 18.2)	21.7 (1.44)
Plasma albumin, g/l	47.1 (2.7)	0.6 (0.08, 1.0)	46.4 (2.4)	-0.1 (-0.5, 0.3)	46.5 (2.7)
Plasma gamma glutamate, U/l	19.1 (1.84)	3.5% (-6.7, 14.8)	19.4 (1.81)	5.7% (-2.8, 15.0)	18.4 (1.68)
Plasma urea, mmol/l	5.44 (1.8)	0.3 (0.0, 0.5)	5.13 (1.1)	0.0 (-0.2, 0.2)	5.1 (1.3)

[a]Mean differences are percentages except for fasting plasma uric acid, plasma albumin and plasma urea.

Concentrations of plasma uric acid, another marker of metabolic syndrome, were 20.1% (7.9, 32.2%) higher in the subjects born early preterm and 20.1% (10.7,

30.5%) higher in the late preterm group. In addition, plasma albumin concentrations were 0.6 g/l (0.08, 1.0) higher and plasma urea concentrations were 0.3 mmol/l (0.0, 0.5) higher in those born early preterm than in the controls, but the difference was not statistically significant when adjusted for the model used to assess the total effect of preterm birth (BMI, parental educational attainment, maternal smoking during pregnancy, parental history of hypertension, diabetes and myocardial infarction or stroke, self-reported physical activity, daily smoking and birth weight SD score). As for markers of inflammation, the levels of blood leukocytes were 5.5% (0.0, 11.2) higher in those born early preterm, but the difference was not statistically significant when adjusted for covariates. However, no difference in high-sensitivity C-reactive protein levels was found between adults born preterm and controls, except for 18.8% (0.4, 33.4) lower levels in the late preterm group when adjusted for the model used to assess the direct effect of preterm birth.

5.7 Metabolic syndrome (III)

Of the 711 subjects of the ESTER study who were included in the analysis, 46 (6.5%) fulfilled the criteria of metabolic syndrome. Of the controls, 12 (3.5%) had the syndrome (Fig. 16). Among those born early preterm, the number was 15 (11.5%), the odds ratio compared with controls being 3.97 (95% CI 1.76–8.62) adjusted for sex, age and cohort. Among those born late preterm, the number was 19 (7.9%), odds ratio 2.5 (95% CI 1.2–5.43). The results were similar when further adjusted for covariates.

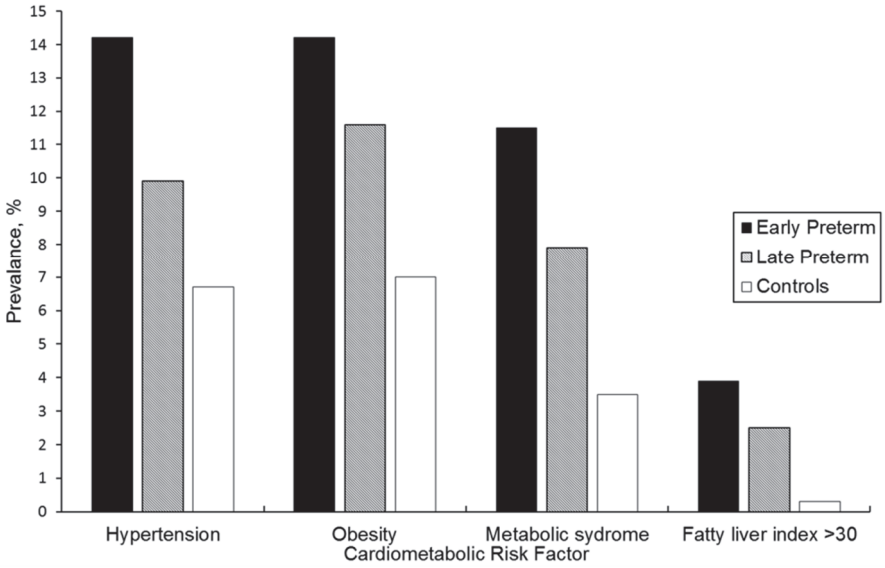

Fig. 16. Prevalence of hypertension, obesity, metabolic syndrome and fatty liver index >30 in adults born early and late preterm versus adults born at term (controls). Printed with permission; the same figure appears in Am J Epidemiol. 2015: In press.

6 Discussion

We found that adolescents and young adults born preterm show enhancement of cardiometabolic risk factors in several pathophysiological pathways (Fig. 17). While the results of previous studies have suggested that those born smallest and most immature have elevated levels of cardiometabolic risk factors, our study shows that some of these risk factors are also present in the much larger group of people born less preterm. Most of these risk factors were not explained by maternal pregnancy disorders, size at birth, socioeconomic status, current body size, or lifestyle. Although low birth weight is associated with later cardiometabolic risk factors, subjects born preterm and SGA did not have different cardiometabolic risk factors in adolescence or adulthood than subjects born preterm, except lower REE, lower SBP and DPB in adolescence, and higher 2-hour insulin than adults born preterm and AGA. However, the number of subjects born SGA is quite low for subgroup analysis.

6.1 Body size and composition (I–III)

Adolescents born preterm had similar body sizes and composition as their peers born at term (NFBC 1986, II). Nevertheless, young adults born early and late preterm have higher rates of obesity and higher waist circumferences than their peers born at term (the ESTER study, III). However, previous findings have shown that adults born severely preterm tend to be shorter compared with those born at term (Saigal *et al.* 2006, Indredavik Evensen *et al.* 2009) and tend to have a lower BMI as a result of lower lean body mass and similar fat percentages (Hovi *et al.* 2007, Parkinson *et al.* 2013). The early preterm group in our analysis included only 46 (34.3%) subjects born with VLBW (<1500 g), which may explain the difference between our study and previous ones. This is supported by the findings of other studies that have included subjects with all degrees of preterm birth and which have revealed higher BMI in adults born preterm compared with controls (Lewandowski *et al.* 2013, Mathai *et al.* 2013). The results of our study and others suggest that very preterm birth has a different effect on adult body size in comparison with late preterm birth.

Obesity, particularly abdominal obesity, is a key component underlying many characteristics of metabolic syndrome and is a major health problem throughout the world. The WHO defines obesity as abnormal or excessive fat accumulation that presents a risk to health and it is commonly classified according to BMI. The 2010 Global Burden of Disease Study ranked high BMI among the four leading risk factors for disability-adjusted life years in the Americas, Europe, the Middle East and

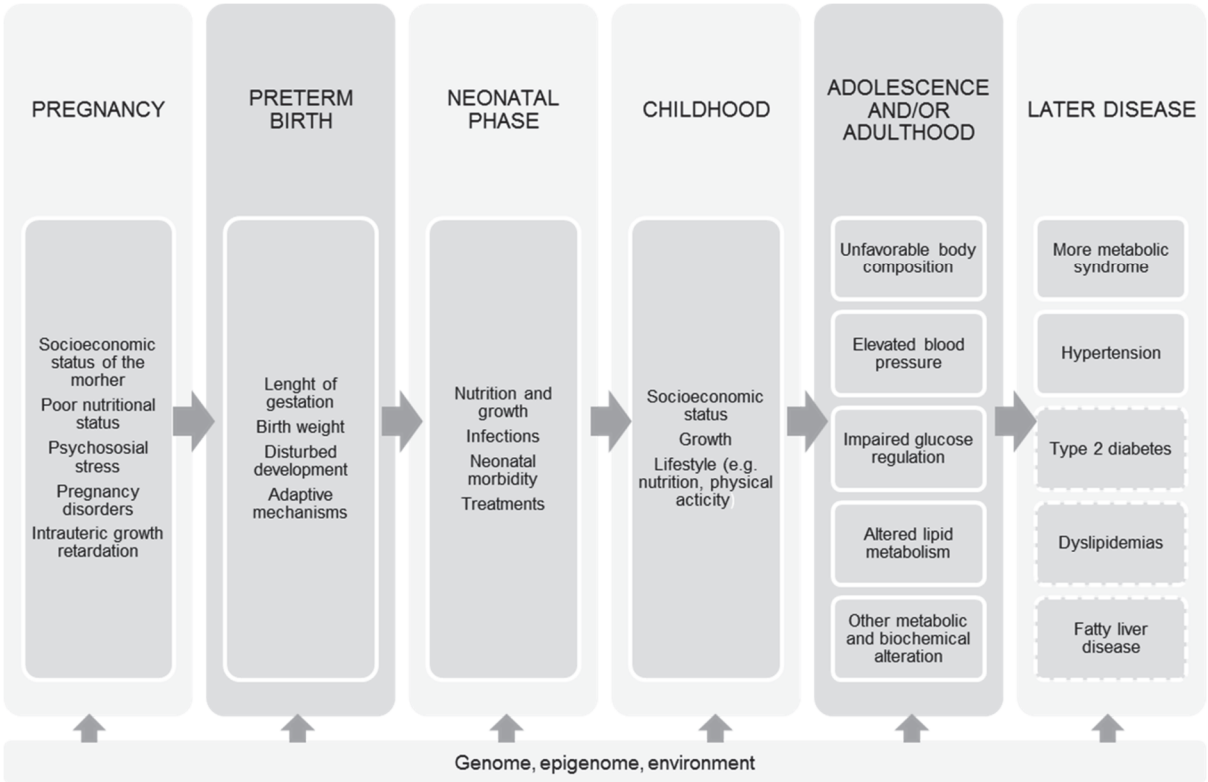

Fig. 17. Preterm birth and cardiometabolic risk factors in later life.

Australasia, and in recent decades it has increased the global disease burden by 81% (Lim *et al.* 2012). Much of this burden is associated with an increased risk of cardiometabolic conditions. Numerous studies have shown an association between obesity and various cardiovascular disease risk factors, such as diabetes, hypertension, and dyslipidemias (Kopelman 2000, Mokdad *et al.* 2003). An overweight condition in youth might have particularly long lasting impacts on future health: being overweight in youth is associated with increased risks of type 2 diabetes, hypertension, dyslipidemia and carotid-artery atherosclerosis in later life (Juonala *et al.* 2011, Koskinen *et al.* 2014).

BMI is a convenient marker of overweight conditions and obesity, but it is an imperfect indicator of body fat, explaining only 25% of its variation. BMI also reflects LBM, which has associations with a number of outcomes including all-cause mortality (Gallagher *et al.* 1996). Thus, we also assessed body composition by means of bioelectric impedance and showed that adults born preterm had a higher fat mass and a higher percentage of body fat, and the difference compared with controls was more pronounced in the late preterm group than in the early preterm group. The finding is consistent with the results of previous studies on body size and composition of former preterm infants. Studies with subjects born very preterm or with VLBW have revealed lower LBM, but no difference in fat mass (Peralta-Carcelen *et al.* 2000, Hovi *et al.* 2007), or no difference between preterm group and controls (Weiler *et al.* 2002, Rotteveel *et al.* 2008a), whereas those studies with subjects born less preterm have shown a more adipose body composition (Breukhoven *et al.* 2012, Lewandowski *et al.* 2013, Mathai *et al.* 2013). Additionally, in a recent meta-analysis it was determined that there were no differences in fat percentages; again, this is likely to reflect adults born severely preterm, as the mean gestational age of those born preterm was 30.6 weeks (Parkinson *et al.* 2013), whereas the mean GA in the subjects born early preterm was 31.8 weeks (SD 2.0) and in subjects born late preterm 35.8 weeks (SD 0.8).

Our findings were not explained by socioeconomic status, maternal smoking during pregnancy, birth weight SD score or antenatal disorders. However, we did not have the growth data to investigate the effects of early growth on adult body size and composition in the ESTER study. Catch-up growth in the first years of life is more pronounced in weight gain than in growth in length, and may lead to altered body composition. Epidemiological life-course studies have shown that a small body size at birth and suboptimal early growth have an effect on cardiovascular and cardiometabolic disorders in later life (Barker *et al.* 2005, Eriksson *et al.* 2006,

Huxley *et al.* 2007, Whincup *et al.* 2008). In addition to neonatal medical conditions, infant growth is usually determined by nutrition in infancy. In the Helsinki study of Very Low Birth Weight Adults, nutrient intake in the first three weeks of life, especially higher energy, protein and fat intake, predicted higher LBM in adulthood (Matinolli *et al.* 2014). The important role of early nutrition is supported by the results of many animal studies, in which alterations in early nutrient intake produce considerable life-long effects on risk factors of adult obesity and cardiometabolic conditions (Gluckman *et al.* 2007, Robinson & Fall 2012, Desai *et al.* 2013). Unfortunately, processing of the data on early nutrient intake in the NFBC 1986 and the ESTER study was unfinished, and we were not able to use the data in the analysis. Lifestyle factors, such as physical activity and daily smoking, did not clarify the picture as regards altered body composition in adults born preterm.

6.2 Resting energy expenditure (I)

Body size and composition, especially lean body mass (LBM) have an influence on an individual's energy expenditure: LBM explains about 60% of the variation of REE between individuals (Johnstone *et al.* 2005). Low energy expenditure may lead to obesity (Ravussin *et al.* 1988, Astrup *et al.* 1999). We found that adults born preterm with VLBW had lower REE, but higher REE per unit lean body mass. The difference was not explained by differences in body fat percentage, smoking, childhood socioeconomic status or physical activity, and it seemed to be associated with VLBW birth *per se* rather than any related perinatal conditions. The association between preterm birth and later energy expenditure is not well studied. In accordance with the results of previous studies comparing those born with low versus normal birth weight (Eriksson *et al.* 2002, Kensara *et al.* 2006), we found that the lower REE in VLBW adults is largely attributable to their lower LBM. Although the higher REE/LBM ratio in VLBW adults implies that they may have more metabolically active tissue than the controls, previous studies of organ size have suggested that the metabolically most active organs are particularly small in VLBW adults, for example the kidneys (Keijzer-Veen *et al.* 2010a) and brain (Martinussen *et al.* 2009, Taylor *et al.* 2011). With DXA and calorimetry we were unable to distinguish whether differences in the REE/LBM ratio are due to higher metabolic rate of some specific organs or an overall increase in metabolic rate in adults born with VLBW.

Within the VLBW group, subjects born SGA had lower REE, but similar REE/LBM ratios as those born AGA when adjusted for age and sex. Our finding is consistent with that in a previous study in which children born preterm and SGA had

lower REE (Sepúlveda *et al.* 2013). Another study, however, showed that children born preterm and SGA had lower REE/LBM ratios (Mericq *et al.* 2009) than their peers born preterm and AGA. Within the VLBW group individuals born SGA and AGA differ in the conditions experienced before birth, although they have similar experiences after preterm birth. It is therefore possible that the long-term effects of adverse conditions during the period after preterm birth override those related to the conditions leading to preterm birth, such as intrauterine growth restriction. However, this should be interpreted with caution, since the study has limited power for subgroup analyses such as comparison of those born SGA and AGA. Nevertheless, the fact that an early growth pattern is important is also supported by our finding that the change in weight standard deviation score from preterm birth to term birth was not related to REE or the REE/LBM ratio, although a higher weight attained at 40 postmenstrual weeks (term) was related to higher REE through its association with LBM.

One possible factor affecting altered energy metabolism in adulthood might be early nutrition. After this study, data on early nutrient intake during the first nine weeks of life of subjects born with VLBW were collected from the hospital records and the association between early nutrient intake and adult REE and the REE/LBM ratio was evaluated. Nutrient intake in the first weeks of postnatal life was substantially below current recommendations. The lower energy, protein and fat intake was associated with lower REE but a higher REE/LBM ratio. This supports the view included in the DOHaD hypothesis that materno-fetal undernutrition influences the metabolic phenotype later in life so that undernutrition during early life increases metabolic activity, resulting in more active energy metabolism in adulthood (Matinolli *et al.* 2014). This might explain at least part of the difference in REE in adults born preterm with VLBW compared with their peers born at term. In addition, a higher REE/LBM ratio might protect adults born with VLBW from obesity, but this might not be the case in adults born less preterm. We were not able to measure REE in the ESTER study. To our knowledge, no investigators have measured or reported REE in adults born moderately or late preterm.

6.3 Blood pressure (II–IV)

We have shown that early preterm birth is associated with higher levels of blood pressure in adolescent girls and young adults. Findings in most previous studies are similar (Pharoah *et al.* 1998, Irving *et al.* 2000, Kistner *et al.* 2000, Doyle *et al.* 2003, Hovi *et al.* 2007, Rotteveel *et al.* 2008a, Indredavik Evensen *et al.* 2009, Keijzer-

Veen *et al.* 2010b, Vohr *et al.* 2010, Thomas *et al.* 2011). In contrast, we did not find any statistically significant association between late preterm birth and BP. The association has not been clear in studies that have included subjects born less preterm (Barros & Victora 1999, Singhal *et al.* 2001b, Järvelin *et al.* 2004a, Johansson *et al.* 2005, Dalziel *et al.* 2007, Cooper *et al.* 2009, Lazdam *et al.* 2010, Rossi *et al.* 2011, Skilton *et al.* 2011, Tauzin *et al.* 2014). However, we found an inverse linear association between GA and BP, which has been shown only in a few other studies (Siewert-Delle & Ljungman 1998, Leon *et al.* 2000, Järvelin *et al.* 2004b, Dalziel *et al.* 2007). Increased BP in children and adults born preterm has also been shown in two meta-analyses (de Jong *et al.* 2012, Parkinson *et al.* 2013).

6.3.1 Ambulatory blood pressure and variability of blood pressure

In connection with the ESTER study, we found that young adults born early preterm have higher mean BP in ABP measurements than their peers born at term. The difference was present when both awake and asleep, but it might be more pronounced when awake. In previous studies the difference has been smaller, for example 2.4–4.7 mmHg higher 24-hour SBP in children and adults born preterm (Doyle *et al.* 2003, Hovi *et al.* 2010, Keijzer-Veen *et al.* 2010b, Roberts *et al.* 2014). In contrast to previous studies (Doyle *et al.* 2003, Hovi *et al.* 2010) and the results of a meta-analysis (Parkinson *et al.* 2013) with gender-specific investigation, the difference was greater in men than in women in our study. Ambulatory measurement of BP is considered to be a more reliable approach to assessing blood pressure, because it is less affected by the anxiety response, but it also includes responses to environmental and lifestyle factors, such as physical activity (Verdecchia 2000, Kamarck *et al.* 2002, Clement *et al.* 2003).

We also found higher individual variability of ABP in early preterm adults than in their controls. There are only a few studies that have reported variability of ABP in former preterm individuals and the findings are parallel (Hovi *et al.* 2010, Gunay *et al.* 2014). Variability of BP is a key factor underlying the progression of organ damage (Parati 1987, Frattola 1993), and the triggering of vascular events (Clement *et al.* 2003). It also correlates with the development of hypertensive left ventricular hypertrophy (Parati & Valentini 2006).

6.3.2 Sex-specific analysis

We found higher blood pressure in adolescent girls, but not in boys compared with their peers born at term. In contrast, in ABP measurements in young adults the differences were larger among men born preterm. This was seen in particular for the adults born late preterm, in contrast to previous studies concentrating on those born at an earlier gestational age. A few studies have presented gender-specific analyses and most of them revealed a greater difference in women than in men (Doyle *et al.* 2003, Järvelin *et al.* 2004b, Hack *et al.* 2005, Cooper *et al.* 2009), but not all (Rotteveel *et al.* 2008a, Thomas *et al.* 2011). Statistically significant interaction between preterm birth and sex on blood pressure was seen in the Northern Finland Birth Cohort 1966 (Järvelin *et al.* 2004b) as well as in our NFBC 1986 study, but not in the ESTER study. Most previous studies have shown that masked hypertension is more common in men (Bobrie *et al.* 2008, Hänninen *et al.* 2011), while white-coat hypertension is more common in women (Ben-Dov *et al.* 2008). However, because of a lack of statistical power, we could not test this in our data. It is possible that the contradictory results in sex-specific BP analyses can be in part explained by men reacting differently to factors related to office measurement, such as psychosocial stress, and factors captured by the 24-h recording, such as subject's physical activity.

6.3.3 Hypertension

Adolescents born early preterm were more likely to have prehypertension and young adults born early preterm were more likely to have office-measured or daytime hypertension in ABP than adults born at term. However, the OR for hypertension was not statistically significant in adults born late preterm. Although an association between preterm birth and BP has been reported in several papers, only a few studies have reported more manifest hypertension in adults born preterm (Johansson *et al.* 2005, Dalziel *et al.* 2007, Crump *et al.* 2011b). Our subjects are relatively young, and the association between preterm birth and blood pressure could be clearer later in life. At least the association between low birth weight and blood pressure seems to increase with age (Law *et al.* 1993).

Hypertension is a major risk factor of ischemic heart disease and stroke. It is one of the most important causes of premature death worldwide (Mendis *et al.* 2011) and a leading risk factor as regards the global disease burden, accounting for 9.4 million deaths per year worldwide (Lim *et al.* 2012). A 3 to 5 mmHg increase in BP has been translated into an estimated increase in cardiovascular deaths of 25% and a 32%

increase in stroke (Yusuf *et al.* 2000, Law *et al.* 2003). The magnitude of increased BP in young adults born preterm is therefore notable.

6.3.4 Possible mechanisms

Hypertension has previously been attributed to an unfavorable genotype and lifestyle, for instance an unhealthy diet, physical inactivity, smoking and stress. However, there is strong evidence that early life factors such as preterm birth have an influence on increased blood pressure later in life. Our findings were not explained by socioeconomic status, lifestyle, body size or perinatal factors such as maternal pregnancy disorders, maternal smoking or IUGR. However, gender, parental educational attainment and maternal hypertension during pregnancy had the greatest and statistically significant influence on adult blood pressure in those born preterm. In our study maternal hypertension during pregnancy was associated with about 6 mmHg higher 24-hour ambulatory SBP in young adults born preterm, but it did not explain the whole difference in BP compared with controls born at term. It has been suggested that there is a common genetic background to preterm birth and hypertension that partially explains elevated BP levels in former preterm infants. However, a large twin study has shown that the twin with lower birth weight is more likely to have hypertension in later life (Bergvall *et al.* 2007), suggesting that body size at birth is related to later blood pressure.

Renal, vascular (e.g. arterial stiffness) and central regulatory (alteration of the hypothalamic-pituitary-adrenal axis) factors have been suggested to be involved in the developmental programming of BP (Nuyt 2008). At the time when preterm infants are born, nephrogenesis in the kidney is still ongoing, with the majority of nephrons normally formed from week 20 until 34 to 36 weeks of gestation (Hinchliffe *et al.* 1991), so it is possible that there are changes in the structural development of the kidney in preterm infants such as smaller kidney size (Keijzer-Veen *et al.* 2010a) and lower number of nephrons (Rodriguez *et al.* 2004). These changes may be related to higher BP levels in adolescents and adults born preterm.

Changes in vascular structure (Kistner *et al.* 2002, Lewandowski *et al.* 2013) and endothelial dysfunction or arterial stiffness in adolescents and adults born preterm (Bonamy *et al.* 2005, Bassareo *et al.* 2010, Hovi *et al.* 2011) have been suggested to be related to the higher BP levels as well as changes in the HPA axis (Kajantie & Raikkonen 2010). However, in the HeSVA, adults born preterm with VLBW had lower HPA-axis responses (Kaseva *et al.* 2014b) and similar or lower norepinephrine responses (Kaseva *et al.* 2014a) to psychosocial stress, arguing against a major role of

these systems in mediating BP levels or variability in adults born preterm (Kajantie & Raikkonen 2010). In addition, it has been shown that BP in adulthood is affected by maternal nutrition during pregnancy (Roseboom *et al.* 2001, Hult *et al.* 2010, Gubhaju *et al.* 2011), and postnatal nutrition might also have an effect on later BP in preterm infants (Singhal *et al.* 2001a). Catch-up growth, with rapid weight gain, may lead to higher BP (Rotteveel *et al.* 2008b, Vohr *et al.* 2010). However, the specific mechanism behind elevated BP still remains unclear.

6.4 Lipid metabolism (II, III)

Our findings concerning the association of preterm birth and lipid metabolism are inconsistent, as they have been in previous studies (Hovi *et al.* 2007, Lewandowski *et al.* 2013, Mathai *et al.* 2013, Parkinson *et al.* 2013). In adolescence, boys born early preterm had higher levels of serum TC, LDL-C and ApoB than boys born at term, and boys born late preterm had higher levels of TGs. However, we found no difference in girls born preterm compared with girls born at term. In contrast, women born early preterm had lower levels of HDL-C and its precursor ApoA1 than women born at term, but we found no difference in lipid levels in men.

Several investigators have reported no association between preterm birth and serum lipid levels in adolescence or adulthood (Irving *et al.* 2000, Kistner *et al.* 2004, Finken *et al.* 2006, Rotteveel *et al.* 2008a, Hovi *et al.* 2011, Skilton *et al.* 2011, Thomas *et al.* 2011). However, there are also studies that have shown more atherogenic lipid profiles in former preterm infants, such as higher LDL-C and TG levels than in their peers born at term (Lewandowski *et al.* 2013, Parkinson *et al.* 2013), lower HDL-C and higher total cholesterol concentrations, and differences in lipid levels after a meal (Rotteveel *et al.* 2008a) or as assessed in detailed lipid profiling by way of metabolomics (Hovi *et al.* 2013). Differences similar to those that we found in women born early preterm compared with women born at term have not been reported in previous studies. However, in a Finnish study, SGA subjects (mean age 20 years) had higher serum levels of LDL-C and higher LDL-C/HDL-C ratios, and lower HDL-C concentrations than AGA subjects. In the SGA group, total and LDL cholesterol levels correlated inversely with adult height SD score (Salonen *et al.* 2010).

The unfavorable lipid profile in boys born preterm was not explained by slow fetal growth or other antenatal factors. The difference was even stronger when boys born SGA were excluded, but was attenuated slightly when adjusted for birth weight SD score. This suggests that the higher rates of slow fetal growth among those born

preterm could in part underlie the higher plasma lipid concentrations in boys born preterm. In addition, slow fetal growth can have similar sex-specific associations as preterm birth as regards lipid profile later in life. Previous studies have shown male-specific association between low birth weight and serum LDL-C levels in adolescents (Kuzawa & Adair 2003) and TC in young adults (Mogren *et al.* 2001). In addition, among the general population, low birth weight is associated with elevated levels of TC among men, but not in women in meta-analysis (Lawlor *et al.* 2006b). The mechanisms behind these sex-specific differences are not known. A part of the difference could be explained by the differences in sex hormones and body composition between women and men. The unfavorable lipid profile in adolescent boys born preterm was not explained by socioeconomic status measured by parental education, lifestyle (smoking or physical activity) or pubertal stage.

The difference in HDL-C and ApoA1 levels between women born preterm and women born at term was not explained by perinatal factors, because it remained similar when controlled for these factors. Part of the difference, but not all, was explained by current body size and lifestyle, because it was attenuated when adjusted for BMI, physical activity and daily smoking.

ApoB is the primary apolipoprotein component of LDL-C and it is independently associated with increased risk of metabolic syndrome (Onat *et al.* 2007, Koskinen *et al.* 2012). In addition, elevated LDL-C levels in youth (at 12–18 years age) predicted coronary artery calcification in adulthood in the Young Finns Study (Hartiala *et al.* 2012). Decreased HDL-C levels are one of the key factors of metabolic syndrome. Dyslipidemias are major risk factors of ischemic heart disease and stroke, and high total cholesterol is one of the leading risk factors as regards death and disease (Lim *et al.* 2012). Our findings suggest that adolescents and adults born preterm may have altered lipid metabolism.

6.5 Glucose regulation (II, III)

Boys born late preterm had higher fasting insulin levels and HOMA-IR values than controls; otherwise we did not find any differences between adolescents born preterm and controls in outcomes used to assess glucose metabolism. In adults, late preterm birth was associated with elevated fasting and 2-hour insulin levels and HOMA-IR values, but not with glucose levels. Studies in prepubertal children (Hofman *et al.* 2004, Kistner *et al.* 2012) and young adults (Dalziel *et al.* 2007, Hovi *et al.* 2007, Pilgaard *et al.* 2010, Mathai *et al.* 2012) born preterm have shown lower insulin sensitivity, as clearly indicated by intravenous (Hofman *et al.* 2004) and oral glucose

tolerance tests, and also higher fasting insulin levels (Hovi *et al.* 2007). Although our subjects were born at grater gestational weeks, they had parallel adverse metabolic characteristics associated with impaired glucose regulation as those born severely preterm. However, the differences we found in adults were smaller than in the Helsinki Study of Very Low Birth Weight Adults (Hovi *et al.* 2007).

The DOHaD theory suggests that when a fetus is developing under suboptimal conditions, it adapts to guarantee immediate survival by preserving vital functions at the expense of other less immediately critical functions. For example, to preserve glucose for vital organs it induces peripheral insulin resistance, thus disturbing the development of other organs such as the kidneys and pancreas (Hales & Barker 2001). The differences in glucose metabolism in adolescents born late preterm versus their peers born at term was not explained by perinatal factors such as maternal pregnancy disorders. When adjusted only for birth weight SD score, the differences were even greater. However, the differences in glucose metabolism between adults born preterm and controls were not statistically significant when adjusted for parental, prenatal and lifestyle factors. A main contributing factor to impaired glucose regulation among adults born less preterm may be increased body fat with ectopic distribution. In contrast, in the smallest preterm individuals, a main contributing factor to impaired glucose regulation may be low muscle mass.

Abnormally low insulin sensitivity is called insulin resistance, which means that tissues resist the activity of insulin on a regular basis, disabling efforts to remove glucose from the circulation. The results of various prospective epidemiological studies across several population groups indicate that type 2 diabetes progresses over a continuum of worsening insulin action, beginning with peripheral insulin resistance and ending with a loss of insulin secretion (Saltiel 2000). Our subjects in both studies were young, and as expected, few of them fulfilled the criteria of type 2 diabetes or impaired glucose tolerance. Studies in older adults have suggested that higher rates of type 2 diabetes occur in those born preterm (Lawlor *et al.* 2006a, Indredavik Evensen *et al.* 2009, Kaijser *et al.* 2009, Kajantie *et al.* 2010a). In addition to type 2 diabetes, insulin resistance predicts atherosclerosis and cardiovascular events independently of other risk factors including fasting glucose and lipid levels (Hanley *et al.* 2002).

Our study shows that abnormal metabolic characteristics are already present in young adults. Our findings, together with the results of previous studies, are consistent with the hypothesis that preterm birth is associated with type 2 diabetes later in life.

6.6 Other metabolic biomarkers (IV)

Along with the conventional components of metabolic syndrome we found alterations in a wide range of biomarkers that reflect different underlying pathophysiological pathways. Uric acid concentrations were over 20% higher in both the early- and late-preterm groups than in the controls. Uric acid stimulates oxidative stress, endothelial dysfunction, inflammation and vasoconstriction and is a well-established strong predictor of type 2 diabetes and cardiovascular disease, independent of other metabolic syndrome components (Fang & Alderman 2000). We are unaware of any previous studies reporting uric acid concentrations in adults born preterm.

Levels of liver transaminases were also higher in adults born preterm, and the participants with a moderate or high fatty liver index, which is a proposed marker of non-alcoholic fatty liver disease (NAFLD) (Bedogni *et al.* 2006), were almost all born preterm. Previous studies have not reported liver transaminases in adults born preterm. NAFLD is one cause of a fatty liver, occurring when triacylglycerol-rich lipid droplets are deposited (steatosis) in the hepatocytes without excessive alcohol use. However, NAFLD is usually diagnosed by ultrasonographic imaging and the fatty liver index is an estimated value used to predict NAFLD, and based on BMI, waist circumference, triglycerides and gamma glutamate: an FLI <30 rules out and an FLI ≥60 rules in hepatic steatosis as detected by ultrasonographic imaging (Bedogni *et al.* 2006). It may not reveal all cases of non-alcoholic fatty liver disease, because the prevalence of NAFLD in our study was relatively low, being 20–30% in Western European countries (subjects aged 20–83 years) (Targher *et al.* 2010) and 18.5% in Finnish adults (34–49 years of age) (Suomela *et al.* 2014), and the prevalence is higher in obese versus normal-weight adults. However, the subjects in these studies were older, which may explain the difference in prevalence. Liver transaminases and non-alcoholic fatty liver disease also predict cardiometabolic disorders, although the literature is less consistent, as they are better independent indicators of pathology rather than general markers of metabolic syndrome (Sniderman *et al.* 2011, Lv *et al.* 2013) and strong risk factors of type 2 diabetes (Fan *et al.* 2007, Yun *et al.* 2009).

Chronic subclinical inflammation is part of metabolic syndrome (Festa *et al.* 2000). As for markers of inflammation, levels of blood leukocytes were higher in those born early preterm, but the difference was not statistically significant when adjusted for covariates. In contrast, adults born late preterm had lower levels of high-sensitivity C-reactive protein when adjusted for parental, prenatal and lifestyle factors and BMI. In addition, adults born early preterm had higher plasma albumin and urea

concentrations, but the difference was not statistically significant when adjusted for parental and prenatal factors. Previous studies have shown a positive association between serum albumin and blood pressure levels (Hostmark *et al.* 2005) and metabolic syndrome (Ishizaka *et al.* 2007, Cho *et al.* 2012). However, an inverse relationship between serum albumin concentrations and cardiovascular disease mortality has also been reported (Phillips *et al.* 1989). In addition to kidney function, the plasma urea level can be an indicator of liver function, nutrition, and plasma volume.

6.7 Metabolic syndrome (II, III)

In addition to elevated cardiometabolic risk factors in several pathophysiological pathways, adults born preterm were 8- to 13-fold more likely to fulfill the criteria of metabolic syndrome. This has not been reported in other studies before. The overall prevalence of metabolic syndrome in our study population was 6.4%; as it was 1.7–2.4% in 16-year old adolescents in Northern Finland in 2001–2002 (Pirkola *et al.* 2008), and it was 10–15% in Finnish adults aged 24–39 years in 2001 and it increases with age (Mattsson *et al.* 2007). As mentioned before, metabolic syndrome is a combination of factors that multiply a person's risk of heart disease, diabetes and stroke (Lakka *et al.* 2002, Onat *et al.* 2002). It has been suggested that as the number of cardiovascular risk factors increases, so does the severity of asymptomatic coronary and aortic atherosclerosis in young people (Lewandowski *et al.* 2014).

6.8 Limitations and strengths of the studies

The present work is based on data from three different studies (HeSVA, NFBC 1986, the ESTER study) with a wide spectrum of outcome measurements. An important strength of the HeSVA study population is the prospective cohort with controls matched by age, sex and birth hospital. However, the sample size of subjects born with VLBW or early preterm is relatively small, but still the same size or larger than in most previous studies. The main strength of the NFBC 1986 and the ESTER studies is the study populations, which were chosen to include the whole range of preterm births in a specific geographic area. The participation rate in the ESTER study was relatively low, and selection bias cannot be excluded in either of the studies. For example, adolescents born preterm were less likely to participate in the NFBC 1986 clinical examination at 16 years of age, and it is possible that subjects with impairments associated with preterm birth are underrepresented. In the ESTER

study, there was some difference in the proportion of the late preterm and control groups recruited through the NFBC or the FMBR, for which reason we adjusted for the recruitment cohort. Nevertheless, detailed non-participant analysis did not raise any major concerns as regards selection bias in any of the studies. Moreover, while we had sufficient power for most outcomes, power was limited for more rare outcomes, such as moderate or high fatty-liver index. In addition, the number of subjects born early preterm was too small for detailed subgroup analysis of maternal pregnancy disorders or other SGA vs. AGA comparisons.

The subjects of the studies were born in the 1970s and 1980s, and they are the first generation whose gestational age at birth has been increasingly confirmed with ultrasonographic imaging. We paid particular effort in the NFBC 1986 and ESTER studies to determine the lengths of gestation as accurately as possible. However, the treatment of prematurely born infants in neonatal intensive care was different in the 1970s and 1980s than it is nowadays. Nevertheless, they represent a big population group of today's adults that have been exposed to deviant circumstances in the perinatal period and are now at a higher risk of developing disease. Today's prematurely born infants have lower rates of morbidity and mortality in childhood, and it is possible that they have lower rates of cardiometabolic risk factors in adulthood. However, the associations between preterm birth and later cardiometabolic risk factors were not explained by the medical conditions and treatment in the neonatal period. Therefore, some of these cardiometabolic risk factors might exist in today's infants born preterm. On the other hand, our subjects are still too young to allow study of the association between preterm birth and manifest cardiovascular disease, and our findings are limited to early markers of cardiovascular disease. Nevertheless, we have shown that young adults born early preterm have more hypertension and metabolic syndrome than their peers born at term.

Another strength of the study is the comprehensive measurement of conventional and emerging cardiometabolic risk factors. However, not all participants underwent calorimetry and DXA; in HeSVa the availability of ABP monitoring was limited, and not all subjects were willing to wear the equipment in the ESTER study. Therefore, indirect calorimetry and ABP measurement were performed in subgroups of the original cohorts. It is possible that these subgroups were not representative of the original cohort. Furthermore, some subjects did not wear an accelerometer, and we could not objectively determine their awake and sleep periods. This factor may increase inaccuracy and lead to a more conservative estimate. Moreover, some of the confounders and intermediate factors, such as parental history of disease, medication,

physical activity, smoking and pubertal stage were self-reported and some missing values exist, which may further introduce inaccuracy.

Although we adjusted for several key confounders, there is a possibility of residual confounding. For example, we had no data to distinguish between spontaneous and medically-indicated preterm birth. Instead, we relied on proxy measures, such as SGA or maternal hypertension in pregnancy, that, nevertheless, are likely to cover a major proportion of indicated preterm deliveries. These things may have resulted in less precise estimates. In addition, we did not have data on early or current nutrition or growth, so we were unable to assess the effect of these factors on cardiometabolic risk in adolescence or in adulthood. Further, collider stratification bias is possible when intermediate factors, such as BMI, physical activity and smoking are adjusted for in regression models; this is unlikely to have had any significant effect, as these adjustments had a negligible effect on the results.

6.9 Significance of the findings and future perspectives

Adolescents and adults born preterm, including those born late preterm, have elevated cardiometabolic risk factors in several pathophysiological pathways, including hypertension and metabolic syndrome, compared with their peers born at term. Together with the results of numerous previous studies, this may indicate a later risk of cardiometabolic disorders such as type 2 diabetes and coronary artery disease in adults born preterm. To date, previous studies have not revealed higher prevalence of metabolic syndrome, resting energy expenditure or elevated levels of liver transaminases in adults born preterm. Only a handful of previous studies have concerned ABP in adults born preterm, and those studies have focused on subjects born preterm with VLBW, or born very or extremely preterm, and even fewer have reported variability of blood pressure. In particular, the cardiometabolic health of adolescents and adults born late preterm has not been well studied. Many of the risks have dose-response relationships and these risks are increased in those born late preterm – in the group representing the majority of individuals born preterm. Timing of the interruption of development is important as regards later outcome. Some of the risk factors seem to be different in adolescents and adults born late preterm versus those born in early gestational weeks, for example a more adipose body composition and related factors. However, more studies on the cardiometabolic health of adults born late preterm are needed.

Despite the large amount of evidence concerning elevated cardiometabolic risk factors in adults born preterm, most previous studies have failed to show an

association between preterm birth and coronary artery disease or cerebrovascular disease, although the risks of these diseases increase throughout life. The results of studies on elderly people cannot be easily translated to infants born in recent decades, because of the improvements in NICUs and, for example, the nutrition of preterm infants. In addition, preterm infants born several decades ago were less likely to survive to adulthood – survival was more selective than it is today. Therefore, longer follow up is needed to investigate whether or not adults born preterm and treated in modern NICUs have more cardiometabolic diseases.

In spite of the significant number of studies in humans and animals, the mechanisms linking preterm birth and adult diseases are still incompletely understood, probably because the pattern is so intricate. Theory of DOHaD proposes that circumstances *in utero* (e.g. mother's nutrition, psychosocial stress, pregnancy disorders) or during infancy (e.g. disturbed development of organs, nutrition, growth, neonatal morbidity and treatments) may induce changes in body size and structure, metabolism, hormone secretion and gene expression. Those experiences during critical periods of early development may have consequences on cardiometabolic health through a lifespan. In addition to early life factors, there are several intermediated factors in childhood and youth that may influence to cardiometabolic risk factors in later life such as socioeconomic status including education, physical activity, and nutrition. The limited number of subjects in the cohorts has not allowed investigation of the mechanisms behind the risk and protective factors. For example, collaboration of investigators and pooled data sets might illustrate these mechanisms and throw light on the impact of all potential confounders. It has been suggested that some genetic determinants are associated with preterm birth as well as with cardiovascular diseases: Women with a history of premature labor have an elevated risk of cardiovascular disease (Robbins *et al.* 2014). Sibling studies may give more information as to whether or not there is a genetic background to these elevated risk levels (D'Onofrio *et al.* 2013). It would also be interesting to investigate the impact of early nutrition and growth on our findings, and whether they can be explained by epigenetic mechanisms (Hanson *et al.* 2011Hanson *et al.* 2011, Wehkalampi *et al.* 2013). Although the mechanisms are unclear, the present data support the DOHaD theory that developmental influences have lifelong effects on cardiovascular and metabolic function.

Most of the cardiometabolic risk factors related to preterm birth are modifiable. Favorable early life circumstances of premature infants, such as optimal nutrition and reduction of stress in neonatal intensive care units, might reduce the risk of later cardiometabolic disorders. In addition, children and adults born preterm might

particularly benefit from primary prevention such as screening of risk factors and promotion of a healthy lifestyle.

7 Conclusions

1. Adults born preterm show enhancement of cardiometabolic risk factors concerning several aspects such as body size and composition, energy metabolism, blood pressure, glucose and lipid metabolism, and some emerging cardiometabolic risk factors. They also have a 2.5- to 4-fold greater risk of full-blown metabolic syndrome than those born at term.
2. Some of the risk factors are already elevated in adolescence, for example blood pressure in girls and LDL cholesterol and apolipoprotein B levels in boys born before 34 weeks of gestation.
3. These risks are also present in the large group of young adults born late preterm, which is consistent with a dose-response relationship between the degree of prematurity and metabolic syndrome. However, some of the risk factors might be different in those born late preterm, such as adipose body composition, and lower insulin sensitivity.
4. Preterm birth may have a different effect as regards cardiometabolic risk factors in females and males, for example in blood pressure and lipid metabolism.
5. Most of these elevated levels of risk factors are not attributable to lower socioeconomic status, parental history of cardiovascular disease, maternal pregnancy disorders, birth weight SD score, current body size, or life style.
6. In conclusion, adolescents and adults born preterm may be at a greater risk of developing cardiometabolic disorders in later life. Adolescents and adults born preterm benefit from a healthy lifestyle, especially because the cardiometabolic risk factor baseline seems to be higher than in those born at term.

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Original articles

This thesis is based on the following publications, which are referred throughout the text by their Roman numerals:

I Sipola-Leppänen M, Hovi P, Andersson S, Wehkalampi K, Vääräsmäki M, Strang-Karlsson S, Järvenpää AL, Mäkitie O, Eriksson JG & Kajantie E. Resting energy expenditure in young adults born preterm ─ the Helsinki study of very low birth weight adults. PLoS One.6(3):e17700.

II Sipola-Leppänen M, Vääräsmäki M, Tikanmäki M, Hovi P, Miettola S, Ruokonen A, Pouta A, Järvelin M & Kajantie E (2014) Cardiovascular risk factors in adolescents born preterm. Pediatrics 2014: 134(4): 1072-1081.

III Sipola-Leppänen M, Vääräsmäki M, Tikanmäki M, Matinolli H, Miettola S, Hovi P, Wehkalampi K, Ruokonen A, Sundvall J, Pouta A, Eriksson JG, Järvelin M, Kajantie E. Cardiometabolic risk factors in adults born preterm. Am J Epidemol. 2015: In press.

IV Sipola-Leppänen M, Karvonen R, Tikanmäki M, Matinolli H, Martikainen S, Pesonen A, Räikkönen K, Järvelin M, Hovi P, Eriksson JG, Vääräsmäki M, Kajantie E. Ambulatory blood pressure and its variability in adults born preterm. Hypertension 2015;65: 615-621.

Original publications are not included in the electronic version of the dissertation.

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