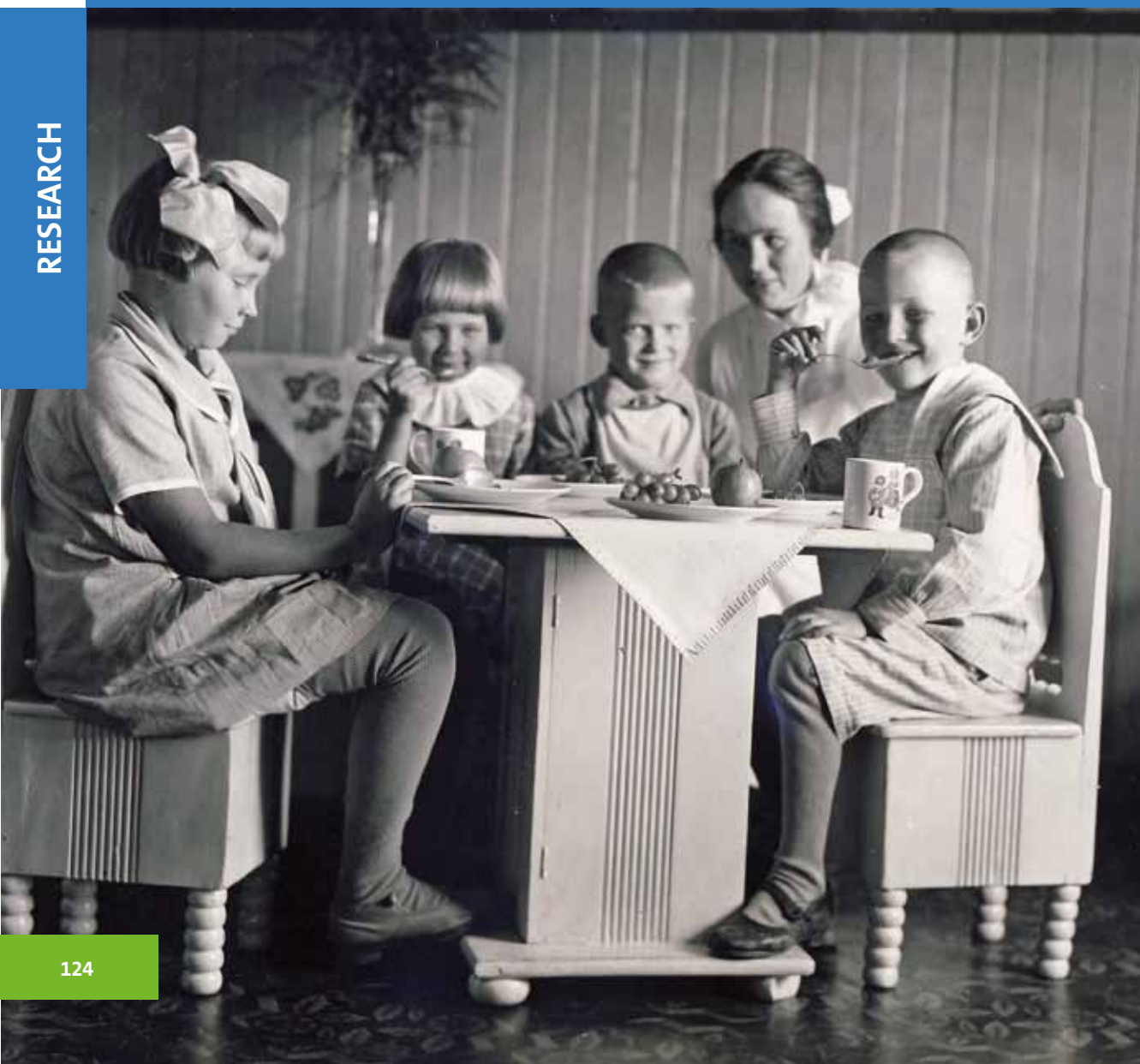
NATIONAL INSTITUTE FOR HEALTH AND WELFARE

Mia-Maria Perälä

Early Growth and Adult Health

Programming of postprandial responses, food intake and salt sensitivity

RESEARCH



124

RESEARCH 124

Mia-Maria Perälä

Early Growth and Adult Health

Programming of postprandial responses, food intake and salt sensitivity

ACADEMIC DISSERTATION

To be presented with the permission of the Faculty of Agriculture and Forestry of University of Helsinki for public examination in the Auditorium XV, University Main Building, on April 12th, 2014, at 12.

Department of Chronic Disease Prevention,
National Institute for Health and Welfare
and
Department of Food and Environmental Science,
Faculty of Agriculture and Forestry, University of Helsinki
and
Department of General Practice and Primary Health Care,
Faculty of Medicine, University of Helsinki

Helsinki, 2014

NATIONAL INSTITUTE
FOR HEALTH AND WELFARE

Cover photo: Lastenlinnan museo

ISBN 978-952-302-132-7 (printed)
ISSN 1798-0054 (printed)
ISBN 978-952-302-133-4 (pdf)
ISSN 1798-0062 (pdf)
http://urn.fi/URN:ISBN:978-952-302-133-4

JuvenesPrint – Tampereen Yliopistopaino Oy
Tampere, Finland, 2014

YMPÄRISTÖMERKKI
MILJÖMÄRKT
441 729
Painotuote

Supervised by
Professor Johan Eriksson, MD, DMSc
Department of General Practice and Primary Health Care
University of Helsinki
and
Department of Chronic Disease Prevention
National Institute for Health and Welfare
Helsinki, Finland

and

Adjunct Professor Liisa Valsta, PhD
Nutrition Unit
National Institute for Health and Welfare
Helsinki, Finland (on leave of absence)
and
Dietary and Chemical Monitoring
European Food Safety Authority (EFSA)
Parma, Italy

Reviewed by
Professor Jussi Pihlajamäki, MD, DMSc
Institute of Public Health and Clinical Nutrition
University of Eastern Finland
Kuopio, Finland

and

Adjunct Professor Harri Niinikoski, MD, DMSc
Department of Pediatrics
Turku University Hospital
Turku, Finland

Opponent
Associate Professor Kirsi Pietiläinen, MD, MSc, DMSc
Diabetes and Obesity Research Program
University of Helsinki
Helsinki, Finland

To my Family

Abstract

Mia-Maria Perälä. Early Growth and Adult Health. Programming of postprandial responses, food intake and salt sensitivity. National Institute for Health and Welfare (THL). Research 124. 132 pages. Helsinki, Finland 2014.
ISBN 978-952-302-132-7 (printed); ISBN 978-952-302-133-4 (pdf)

Background. Epidemiologic studies have shown that individuals who were born with small body size are at increased risk of metabolic diseases, including type 2 diabetes and cardiovascular disease, in adult life. Unhealthy dietary habits are also closely linked with these diseases. However, few results are available on whether dietary habits play a role in the association between birth size and disease risk in later life. Small body size at birth or infancy is also closely linked with cardiovascular disease risk factors, such as elevated fasting glucose and cholesterol levels. The association between small body size at birth and elevated fasting levels is surprisingly modest compared with the much stronger association between size at birth and disease risk. Postprandial levels of lipids and glucose have been proposed to be more important than fasting levels in disease process. However, only limited data is available on the long-term influences of early growth on postprandial responses.

Aims. The aim of this thesis was to determine whether body size at birth is associated with food and nutrient intake later in life and whether birth weight modifies the relationship between salt intake and blood pressure. In addition, the impact of early growth on postprandial metabolism was examined.

Subject and methods. The Helsinki Birth Cohort Study comprised 8760 individuals born during 1934–1944 in Helsinki. Of these, 2003 individuals participated in a clinical examination between the years 2001 and 2004. In the clinic, their weight, height and blood pressure were measured and they filled a validated food-frequency questionnaire. Of those who attended the clinical study, 12 obese individuals with a slow increase in body mass index (BMI) during the first year of life and 12 BMI- and age-matched controls were recruited to participate in the postprandial studies between the years 2009 and 2010. Each participant consumed six different test meals in random order. Blood samples were collected during the fasting state and 4-h postprandially. Glucose, insulin, lipids, incretins and appetite regulatory hormones were measured.

Results. Body size at birth was positively associated with consumption of fruits and berries and intake of carbohydrates, sugars and fibre. An inverse association between size at birth and fat intake was also observed. When participants were

divided into groups for the best obtained breakpoint to birth weight, it was observed that salt intake was related to systolic blood pressure among participants whose birth weight was ≤ 3050 g but not among participants whose birth weight was > 3050 g. Among low birth weight participants, a 1-g increase in salt intake was associated with a 2.48-mmHg higher systolic blood pressure. Salt intake was not significantly associated with diastolic blood pressure, either in the low birth weight or high birth weight groups. Early growth affected the postprandial responses and insulin and triglyceride responses were significantly higher in the group that grew slowly during early life than in the controls. Individuals with slow early growth also showed higher appetite regulatory hormone peptide YY responses than did the controls.

Conclusions. This study showed that individuals born with small body size may be programmed towards unhealthy dietary habits. In addition, they are sensitive to the blood pressure-raising effect of salt and therefore, may especially benefit from a reduction in salt intake. Slow growth during early life adversely affects postprandial insulin and triglyceride responses. Unhealthy dietary habits and elevated postprandial responses may be one underlying mechanism explaining the increased risk of metabolic diseases associated with nonoptimal early growth. Early growth may also alter appetite regulatory hormone secretion, which could be one explanation why individuals born small or who grow slowly during infancy are unlikely to become obese in later life.

Keywords: birth weight, early growth, DOHaD, food intake, salt intake, blood pressure, postprandial responses

Tiivistelmä

Mia-Maria Perälä. Varhainen kasvu ja aikuisiän terveys. Aterianjälkeisten vasteiden, ravinnonsaannin ja suolaherkkyyden ohjelmoituminen. Terveyden ja hyvinvoinnin laitos (THL). Tutkimus 124. 132 sivua. Helsinki 2014.
ISBN 978-952-302-132-7 (painettu); ISBN 978-952-302-133-4 (pdf)

Tausta. Sikiöaikainen ja varhaislapsuuden kasvu ovat yhteydessä riskiin sairastua kroonisiin tauteihin, kuten sydän- ja verisuonitauteihin ja tyypin 2 diabetekseen myöhemmällä iällä. Myös epäterveelliset ruokatottumukset ovat yhteydessä kyseisiin sairauksiin. Siitä, vaikuttavatko ruokatottumukset varhaiskasvun ja sairastumisriskin väliseen yhteyteen, on vain vähän tietoa. Varhaisen kasvun on todettu olevan yhteydessä myös sydän- ja verisuonitautien riskitekijöihin, kuten kohonneeseen veren glukoosi- ja kolesterolipitoisuuteen. Pienen syntymäkoon ja kohonneiden paastopitoisuuksien välinen yhteys on kuitenkin yllättävän vähäinen verrattuna paljon suurempaan syntymäkoon ja kroonisten tautien riskin väliseen yhteyteen. Monien riskitekijöiden, kuten glukoosin ja triglyseridien aterianjälkeiset vasteet voivat olla paastopitoisuuksia tärkeämmässä roolissa kroonisten tautien kehittymisessä. Siitä, vaikuttaako varhainen kasvu myös aterianjälkeisiin aineenvaihdunnan vasteisiin, on vain vähän tietoa.

Tavoitteet. Tämän väitöskirjatyön tarkoituksena oli tutkia syntymäkoon yhteyttä aikuisiän ravinnonsaantiin ja selvittää, selittääkö syntymäkoko suolan saannin ja verenpaineen välistä yhteyttä. Lisäksi tutkittiin varhaiskasvun vaikutusta aterianjälkeisiin aineenvaihdunnan vasteisiin ylipainoisilla aikuisilla.

Aineisto ja menetelmät. Helsingin syntymäkohorttitutkimukseen kuuluu 8760 vuosina 1934–44 Helsingissä syntynyttä miestä ja naista, joiden kasvumittoja sisältävät synnytyskertomukset ja neuvola- ja kouluterveydenhuollon tiedot ovat saatavilla. Heistä 2003 henkilöä osallistui yksityiskohtaisiin kliinisiin tutkimuksiin vuosina 2001–2004. Kliinisiin tutkimuksiin sisältyi pituuden, painon ja verenpaineen mittaukset. Lisäksi heidän ravinnonsaantiaan selvitettiin ruoankäytön frekvenssikyselyllä. Kliiniseen tutkimukseen osallistuneiden henkilöiden joukosta rekrytoitiin 12 ylipainoista henkilöä, jotka olivat kasvaneet hitaasti ensimmäisen elinvuoden aikana ja 12 vastaavan painoindeksin omaavaa samanikäistä kontrollihenkilöä osallistumaan ateriatestaukseen vuosina 2009–2010. Ateriatestauksessa henkilöt nauttivat kuusi erilaista testiateriaa satunnaistetussa järjestyksessä, minkä jälkeen verinäytteitä otettiin neljän tunnin ajan. Verinäytteistä määritettiin sokeri- ja rasva-aineenvaihdunnan vasteita sekä kylläisyyden säätelyyn osallistuvia hormoneita.

Tulokset. Syntymäkoko oli yhteydessä runsaampaan hedelmien ja marjojen kulutukseen. Lisäksi syntymäkoko oli yhteydessä pienempään rasvan saantiin ja suurempaan hiilihydraattien, sokerin ja kuidun saantiin. Kun tutkittavat jaettiin syntymäkoon perusteella ryhmiin parhaimman katkaisukohdan mukaan, havaittiin, että suolan saanti oli yhteydessä systoliseen verenpaineeseen ainoastaan henkilöillä, joiden syntymäpaino oli ≤ 3050 g. Heillä 1 g suurempi suolan saanti oli yhteydessä 2.48 mmHg korkeampaan systoliseen verenpaineeseen. Vastaavanlaista suolan saannin ja verenpaineen välistä yhteyttä ei havaittu suurempikokoisina syntyneillä (> 3050 g). Suolan saanti ei ollut yhteydessä diastoliseen verenpaineeseen pienipainoisina tai suurempikokoisina syntyneillä. Henkilöillä, jotka olivat kasvaneet hitaasti ensimmäisen elinvuoden aikana, oli kontrolliryhmään verrattuna suuremmat aterianjälkeiset triglyseridi- ja insuliinivasteet sekä kylläisyyttä säätelevän hormonin peptidi YY:n pitoisuudet.

Päätelmät. Tämä tutkimus osoitti, että pieni syntymäkoko voi olla yhteydessä epäterveellisempiin ruokatottumuksiin aikuisiällä. Pienempipainoisina syntyneillä myös suolansaanti on yhteydessä verenpaineeseen. Tämän vuoksi he voisivat erityisesti hyötyä suolan saannin vähentämisestä. Varhaislapsuuden hidas kasvu vaikuttaa epäsuotuisasti veren aterianjälkeisiin rasva- ja insuliinipitoisuuksiin. Nämä löydökset voivat olla yhtenä selityksenä sille, miksi sikiöaikainen ja varhaislapsuuden kasvu ovat yhteydessä riskiin sairastua sydän- ja verisuonitauteihin ja tyypin 2 diabetekseen. Varhainen kasvu voi myös vaikuttaa kylläisyyttä säätelevien hormonien erityksen, mikä voi osaltaan selittää, miksi pieni syntymäkoko tai hidas kasvu imeväisiässä on yhteydessä pienempään ylipainon riskiin.

Avainsanat: syntymäkoko, varhainen kasvu, elämänkaarinäkökulma, ravinnonsaanti, suola, verenpaine, aterianjälkeiset vasteet

Contents

List of original publications

This thesis is based on the following original articles referred to in the text by their Roman numerals. In addition, some unpublished material is presented.

I Perälä MM, Männistö S, Kaartinen NE, Kajantie E, Osmond C, Barker DJP, Valsta LM, Eriksson JG. Body size at birth is associated with food and nutrient intake in adulthood. PLoS ONE 2012; 7:e46139.

II Perälä MM, Moltchanova E, Kaartinen NE, Männistö S, Kajantie E, Osmond C, Barker DJP, Valsta LM, Eriksson JG. The association between salt intake and adult systolic blood pressure is modified by birth weight. American Journal of Clinical Nutrition 2011; 93:422-6.

III Perälä MM, Valsta LM, Kajantie E, Leiviskä J, Eriksson JG. Impact of early growth on postprandial responses in later life. PLoS ONE 2011; 6:e24070.

IV Perälä MM, Kajantie E, Valsta LM, Leiviskä J, Holst JJ, Eriksson JG. Early growth and postprandial appetite regulatory hormone responses. British Journal of Nutrition 2013; 110:1591-600.

Abbreviations

ANOVA	Analysis of variance
BMI	Body mass index
CCK	Cholecystokinin
CI	Confidence interval
CV	Coefficient of variation
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
DNA	Deoxyribonucleic acid
DOHaD	Developmental Origins of Health and Disease
DPP	Dipeptidyl peptidase
E%	Percentage of total energy intake
FF-meal	Fast-food meal
FFA	Free fatty acids
FFQ	Food-frequency questionnaire
GI	Glycaemic index
GIP	Glucose-dependent insulinotropic peptide
GL	Glycaemic load
GLP-1	Glucagon-like peptide 1
HBCS	Helsinki Birth Cohort Study
HPA-axis	Hypothalamus-pituitary-adrenal axis
IAOC	Incremental area over the curve

IAUC	Incremental area under the curve
MUFA	Monounsaturated fatty acid
OGTT	Oral glucose tolerance test
PI	Ponderal index
PP	Pancreatic polypeptide
PUFA	Polyunsaturated fatty acid
PYY	Peptide YY
REC-meal	Meal macronutrient composition according to dietary guidelines
SBP	Systolic blood pressure
SD	Standard deviation
SES	Socioeconomic status
SFA	Saturated fatty acid
SGI	Group with slow growth during infancy
TG	Triglycerides
totAUC	Total area under the curve
VAS	Visual analogue scale
WHO	World Health Organization

1 Introduction

Metabolic diseases, such as type 2 diabetes and cardiovascular disease (CVD), are common health problems, both in the developing as well as in developed countries, including Finland. Genetic and environmental factors, such as unhealthy dietary habits and physical inactivity, play key roles in the development of these disorders. There is strong epidemiological evidence that in addition to genetic and environmental factors, small body size at birth is also related to increased risk for the development of metabolic diseases (Barker 1995, Barker et al. 2005, Eriksson et al. 2007, Huxley et al. 2007, Mu et al. 2012, Osmond et al. 2007, van Abeelen et al. 2011).

The importance of prenatal growth on later health outcomes was demonstrated by David Barker and his colleagues almost 30 years ago (Barker and Osmond 1986). Based on animal findings as well as epidemiological observations, Barker formulated a theory that events occurring in early life could have long-term effects on health later in life. Since then, numerous epidemiological studies have been published, demonstrating that small body size at birth is associated with increased risk of chronic diseases later in life. The concept of long-term consequence of prenatal growth in later health is now widely accepted; e.g. the World Health Organization (WHO) acknowledged the importance of birth weight in preventing chronic diseases (World Health Organization 2011).

Even though dietary factors are well-known risk factors for metabolic diseases, few studies have focused on whether dietary factors interact with birth weight in predicting later health. Body size at birth has been found to modify the effect of some previously known risk factors for metabolic diseases, including lipid responses to dietary fat (Robinson et al. 2006) and the protective effect of dietary omega-3 fatty acids on carotid intima-media thickness (Skilton et al. 2013) as well as the protective effect of exercise on glucose tolerance (Eriksson et al. 2004).

Although epidemiological studies have shown that small body size at birth is closely linked with CVD risk factors, including elevated fasting glucose and cholesterol levels, the associations between small body size at birth and elevated fasting levels are surprisingly modest, compared with the association between size at birth and overall disease risk. With the exception of a few hours in the morning, we spend most of our waking hours in a postprandial state. Postprandial levels of lipids are also better predictors for the risk of development of CVD than fasting levels. Only a handful of studies (Byrne et al. 1997, Kensara et al. 2006, Schou et al. 2005) have examined postprandial responses in this context and, therefore, it is important to explore the long-term influences of early growth on postprandial responses.

The aim of this thesis was to focus on whether prenatal growth is associated with food intake and the relationship between salt intake and blood pressure and explore the effect of early growth on postprandial metabolism in adulthood.

2 Review of the literature

2.1 Developmental Origins of Health and Disease (DOHaD)

2.1.1 The DOHaD hypothesis

It was shown 80 years ago that death rates were more dependent on the decade of birth than on the decade of death (Kermack et al. 1934). Therefore, the authors proposed that living conditions during childhood explained mortality better than current circumstances. Forsdahl (1977) also observed in Norway that infant mortality rates were positively associated with mortality from CVD later in life. The association was so marked that he proposed that poor living conditions during early life followed by prosperity in adulthood are potential risk factors for CVD. In addition to mortality, Wadsworth and colleagues reported in 1985 that birth weight was inversely related to adult-life blood pressure (Wadsworth et al. 1985). Ravelli et al. (1976) observed that famine during the last trimester of pregnancy and the first months of life produced lower obesity rates, whereas famine during the first half of pregnancy resulted in higher obesity rates.

The importance of prenatal growth was also demonstrated by Barker and his colleagues in the 1980s who showed that there was a strong association between infant mortality rates and ischaemic heart disease, as well as an association between birth weight and rates of adult death from ischaemic heart disease (Barker and Osmond 1986, Barker et al. 1989). To explain these findings, they introduced a theory that fetal growth is associated with a number of chronic conditions later in life. The hypothesis is known as 'Barker's theory' and 'the Developmental Origins of Health and Disease (DOHaD) hypothesis'.

The theory was at first criticized by those who believed that recall bias, publication bias, socioeconomic conditions or lifestyles largely explained these findings (Huxley et al. 2002, Huxley 2006, Kramer and Joseph 1996). However, since the findings of Barker et al. (Barker and Osmond 1986, Barker et al. 1989), several epidemiological studies have been published and to date there is strong epidemiological evidence that low birth weight is related to an increased risk for the development of metabolic diseases, including type 2 diabetes (Johnson and Schoeni 2011, McNamara et al. 2012, Whincup et al. 2008), metabolic syndrome (Fall et al. 2008, Xiao et al. 2010) and CVD (Barker 1995, Barker et al. 2005, Eriksson et al. 2007, Huxley et al. 2007, Johnson and Schoeni 2011, Mu et al. 2012, Osmond et al. 2007, Stuart et al. 2013, van Abeelen et al. 2011). In addition to metabolic diseases, birth size is also linked with several other diseases, such as cancer (Xu et al. 2009),

osteoporosis (Martinez-Mesa et al. 2012), lung functioning (Lawlor et al. 2005) and asthma (Johnson and Schoeni 2011) in adulthood. The DOHaD field has also emerged into the mental health area, and associations between low birth weight and cognitive abilities (Räikkönen et al. 2009, Shenkin et al. 2004), personality (Lahti et al. 2008), temperament (Pesonen et al. 2006), disruptive behaviour disorders (Latimer et al. 2012) and psychiatric symptoms (Indredavik et al. 2004, Lund et al. 2012, Monfils Gustafsson et al. 2009) have been described.

The WHO defined low birth weight as that under 2500 g (World Health Organization Expert Commitee on Physical Status 1995). However, the above associations have also been observed within the normal birth weight range. In addition, associations of birth weight with disease risk in later life are not dependent on gestational age, even though the duration of gestation has a major impact on birth weight. Recent studies have proposed that not only low birth weight but also high birth weight are associated with some of these diseases, suggesting that the relationship between birth weight and later health is U-shaped (Dabelea et al. 1999, Eriksson et al. 2003, Harder et al. 2007).

In addition to prenatal life, early infancy is also a critical developmental period. Growth is rapid during infancy and development of tissues and organs, such as brain and liver, continue during this period. The importance of postnatal growth has been shown in a number of epidemiological studies which have shown that those who have experienced retarded growth in postnatal life have the highest risk of developing type 2 diabetes (Eriksson et al. 2003, Eriksson et al. 2006, Phillips et al. 2005), metabolic syndrome (Salonen et al. 2009a, Salonen et al. 2009b) and CVD in adulthood (Barker et al. 2005, Eriksson et al. 2007, Osmond et al. 2007). However, some studies have observed that accelerated growth during infancy is associated with increased risk of chronic disease in later life (Ibanez et al. 2006, Monasta et al. 2010, Salvi et al. 2012, Sonnenschein-van der Voort et al. 2012, Tzoulaki et al. 2010). Even though both retarded and accelerated growth during infancy is related to disease risk, there is no doubt that the first 1000 days after conception (gestation and first 2 postnatal years) is a critical time for programming of health in later life.

2.1.2 Factors influencing early growth

Several anthropometric measurements have been used to estimate prenatal growth. Birth weight is the most frequently used in epidemiological studies, because it is easy to measure and has been measured systematically for decades. It is, however, a crude indicator of prenatal growth. In addition to birth weight, birth length has also been used to measure prenatal growth. Length measurement contains a large amount of error which is partly explained by the activity level of the infants as well as difficulty in extending the infant's leg completely due to natural flexion (Johnson et

al. 1997). Therefore, birth length is a less reliable measure than birth weight (Johnson et al. 1997). In addition, the ponderal index (PI, kg/m^3) and body mass index (BMI, kg/m^2), both of which indicate thinness at birth, can be calculated from birth weight and length. Other commonly used measures of prenatal growth include head circumference and placental size.

Both genetic and environmental factors affect prenatal growth (Kramer 1987, Ohlsson and Shah 2008). Therefore, not all babies who are small at birth have experienced growth retardation, but they may be genetically small. Some major factors associated with birth size are presented in **Table 1**. Genetic factors include sex of the fetus and genes that are passed on from the father and mother to the fetus. For example, maternal genes affect the size of the mother, as well as the mother's capability of carrying a pregnancy. Environmental factors include maternal nutrition (mostly energy and protein intake), socioeconomic status (SES), endocrine factors, parity, stress, smoking, infections and placental functioning. Body size at birth is also largely dependent on the duration of gestation. It has been estimated that the fetus' genes explain only 30–40% of birth weight and length, whereas environmental factors that are not related to the fetus' genes determine 60–70% of the resulting birth weight (Clausson et al. 2000, Lunde et al. 2007).

In addition to prenatal growth, several factors also influence postnatal growth (**Table 1**). Studies have shown that although parity and placental weight influence birth weight and prenatal growth, they have little effect on postnatal growth (Hindmarsh et al. 2008). Postnatal growth is predominantly influenced by nutrition. In addition, genes affect postnatal growth more than prenatal growth (Pietiläinen et al. 2002). Some other factors that also affect postnatal growth include gestational age, size at birth and parental SES (Hindmarsh et al. 2008, Regnault et al. 2010).

Table 1. Factors influencing prenatal growth and birth weight, as well as postnatal growth (Hindmarsh et al. 2008, Kramer 1987, Ohlsson and Shah 2008, Regnault et al. 2010).

Prenatal growth and birth weight	Postnatal growth
Genetic factors	Genetic factors
Maternal and paternal size	Maternal and paternal size
Infant sex	Infant sex
Gestational age	Birth weight
Demographic factors	Gestational age
Maternal age and stress	Demographic factors
Parental SES	Parental SES
Nutritional factors	Nutritional factors
Gestational weight gain	Gestational weight gain
Energy and nutrient intake	Energy and nutrient intake
Physical activity	Breastfeeding
Maternal morbidity	Infant morbidity
General morbidity	General morbidity
Infections	Infections
Gestational diabetes	Toxic exposure
Pre-eclampsia	Cigarette smoking in pregnancy
Obstetric factors	
Parity	
Maternal constraint	
Toxic exposure	
Cigarette smoking	
Alcohol consumption	
Placental abnormalities	
Reduced blood flow	

SES, socioeconomic status.

2.1.3 Mechanisms of programming

It has been proposed that during prenatal life and early postnatal life, a suboptimal environment could permanently influence organ development and functioning and thus has long-lasting influences on health. The process by which the early environment influences metabolic or endocrine changes in later life is called 'programming' (Lucas 1998). Changes in the early life environment may induce adaptations to ensure nutrient supply to the most vital organs, such as the brain, at the expense of other organs, such as liver, muscle and pancreas. These adaptations result in lifelong alterations in the structure and functioning of organs and may result in adverse health outcomes in adult life (**Figure 1**). For example, malnutrition during gestation may affect liver size (Winick and Noble 1966) and its microstructure (Burns et al. 1997) and functioning, such as changes in lipid metabolism (Cong et al. 2012, Lane et al. 2001, Liu et al. 2013) and liver damage (Fraser et al. 2008, Nobili et al. 2007). Growth retardation during prenatal or postnatal life also causes alterations in muscle mass (Eriksson et al. 2002) and muscle structure and functioning (Jensen et al. 2007, Jensen et al. 2008, Taylor et al. 1995), as well as alterations in adipose tissue by favouring abdominal fat accumulation and by changing its metabolic and hormonal functions (Boiko et al. 2005, Maiorana et al. 2007). In addition, suboptimal environments during early life may lead to structural changes in the brain (Coupe et al. 2010, Plagemann et al. 2000a) and lifelong changes in the functioning of different hormonal axes, including the hypothalamus-pituitary-adrenal axis (HPA-axis) and insulin-like growth factor system (Barker et al. 1993, Phillips et al. 1998, Reynolds 2013).

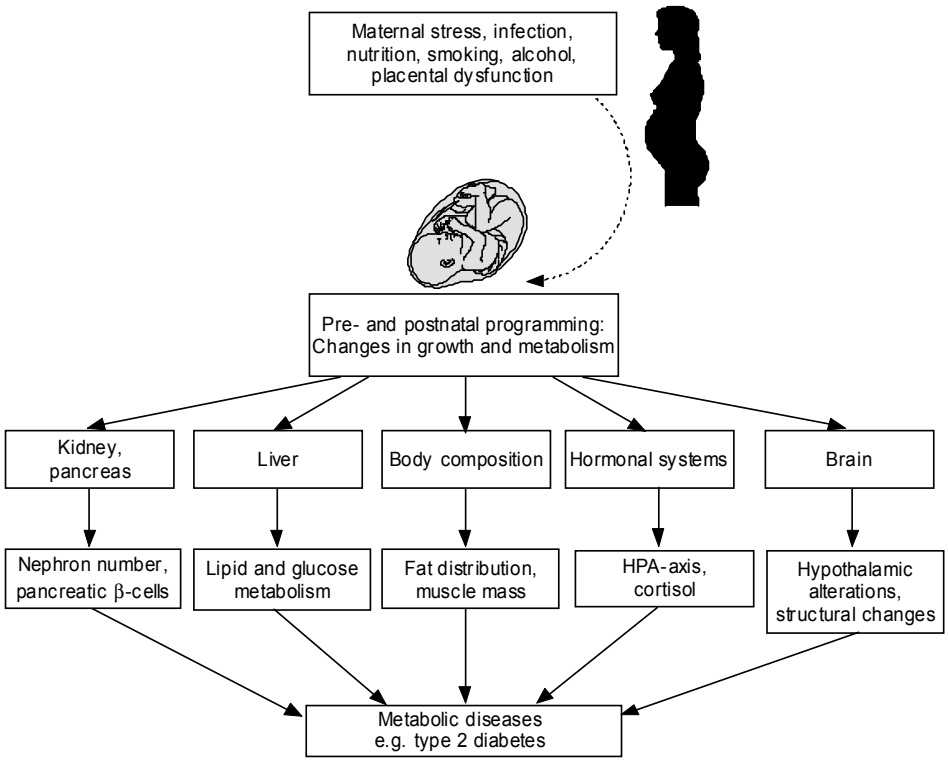


Figure 1. Figure illustrating the programming effects of a suboptimal prenatal or early postnatal environment, nutritional or otherwise, on early growth and subsequent development of metabolic diseases through altering of body and organ compositions and hormonal systems, such as the hypothalamus-pituitary-adrenal axis (HPA-axis). Modified from Perälä and Eriksson (2012).

Based on animal models, convincing evidence suggests that epigenetic events serve as a memory of exposure in early life and thus mediate developmental programming by causing alterations in tissue-specific gene expression, as reported in a review by Attig et al. (2010) and Portha et al. (2013). These changes may further cause structural and regulatory effects on many organ systems and thus lead to disease in later life (**Figure 1**). Epigenetic modifications do not alter the heritable deoxyribonucleic acid (DNA) sequence but do affect gene expression by causing alterations to DNA or chromatin (Callinan and Feinberg 2006). Epigenetic modification may involve DNA methylation, in particular promoter regions of specific genes, or histone modification, such as acetylation (reviewed in Callinan and Feinberg 2006). In general, methylated genes are silenced and hypomethylated genes are induced. For example, maternal protein restriction during gestation reduces DNA methylation of the glucocorticoid receptor and peroxisomal

proliferator-activated receptor alpha genes in the offspring, and thus increases the expression of these genes and further affects protein functioning (Lillycrop et al. 2005). It has also been proposed that one of the mechanisms by which prenatal or postnatal environments may affect developmental programming is mitochondrial DNA methylation (McConnell and Petrie 2004). However, further studies are still needed in this area to understand how the early life environment causes these epigenetic modifications.

Early programming may be beneficial for survival under poor nutritional conditions. The long-term consequences may, however, be especially harmful if the postnatal environment differs from that predicted by the prenatal conditions. This has been demonstrated in several studies that individuals who have experienced retarded growth during prenatal and postnatal life and accelerated childhood weight gain are at increased risk of CVD and other metabolic diseases in adult life (Barker et al. 2005, Eriksson et al. 2003, Eriksson et al. 2006, Eriksson et al. 2007, Osmond et al. 2007, Phillips et al. 2005, Salonen et al. 2009a, Salonen et al. 2009b). In contrast, individuals who have experienced both prenatal and postnatal growth retardation, not followed by high nutrient intake in later life, do not have increased risk of developing these diseases (Stanner and Yudkin 2001).

The timing of food or nutrient restriction in pregnancy may also be critical. Findings from Dutch famine studies have shown that individuals exposed to malnutrition during early gestation have increased risk of many chronic diseases later in life, whereas those exposed to malnutrition during late gestation had lower risk (de Rooij et al. 2006, Ravelli et al. 1998).

2.2 Programming of food intake and appetite

2.2.1 Factors affecting food choices and food intake

It is well known that diet plays an important role in the development of metabolic diseases. In addition to traditional nutrition recommendations that include recommendations for single nutrient intakes, food-based dietary guidelines describing how to choose food-items that both include the optimal amount of nutrients and are related to a decreased risk of metabolic diseases have been published (National Nutrition Council 2005, Nordic Council of Ministers 2013). These guidelines suggest that the diet should contain high amounts of vegetables, fruits and berries, nuts and wholegrain cereals. In addition, it is recommended to regularly eat fish and seafood and use vegetable oils, soft fats and low-fat dairy products. **Table 2** summarizes the recommendations for healthy food choices.

Table 2. Guidelines for healthy food choices and recommended macronutrient intake according to the Nordic Nutrition Recommendation 2012 (Nordic Council of Ministers 2013).

Increase consumption	Decrease consumption	Macronutrient intake
Vegetables	Red and processed meat	Carbohydrates 45–60 E%
Fruits and berries	Drinks with added sugar	Sucrose < 10 E%
Nuts and seeds	Food products with added sugar	Fibre 25–35 g/d
Wholegrain cereals	Food products with added fat	Protein 10–20 E%
Fish and seafood	Salt and food products with added salt	Total fat 25–40 E%
	Alcohol	SFA ≤ 10 E%
		PUFA 5–10 E%
		MUFA 10–20 E%
		Salt ≤ 6 g/d

E%, percentage of total energy intake; SFA, saturated fatty acids; PUFA, polyunsaturated fatty acids; MUFA, monounsaturated fatty acids.

Although there are guidelines for healthy food choices, knowledge of what people should eat does not always affect what individuals will eat. Food choices are influenced by many factors, most importantly food availability, as reported in a review by Blundell et al. (2010). **Figure 2** summarizes other important factors that influence food choices and food intakes. Briefly, physiologic factors, which include neural and hormonal signals, mostly affect how much people eat. Peripheral released physiologic factors may also affect the food reward system and thus food choices (Skibicka and Dickson 2011). Sensory factors, such as food taste, smell and texture, influence the liking of different foods and thus mostly affect what people eat but they also affect how much people eat. Environmental factors, including physiological state (e.g. thirst), psychological state (e.g. mood), social consequences and culture, as well as genes, interact with physiologic and sensory factors and thus affect food choices and food intakes (Mela 2001).

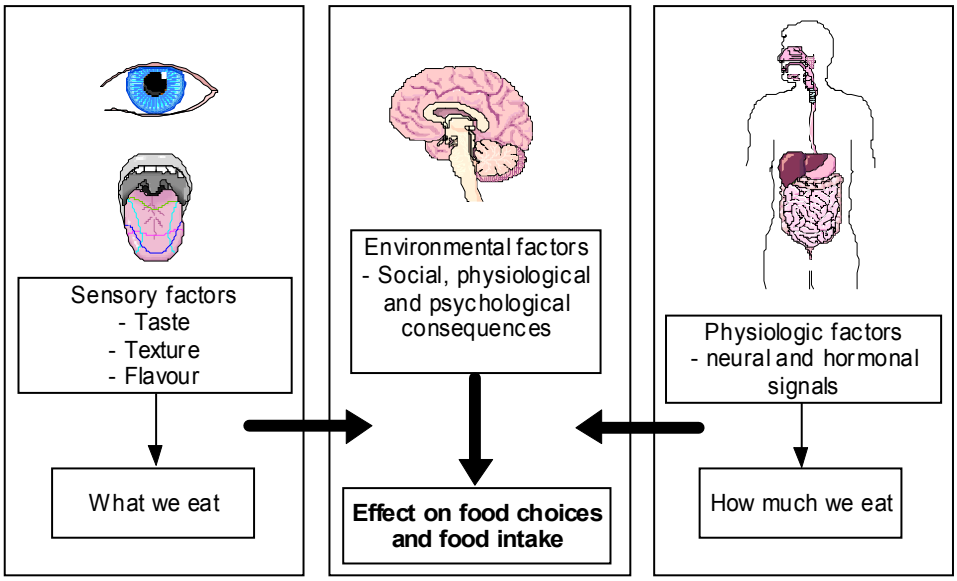


Figure 2. Simplified figure of how sensory and physiologic factors, together with environmental factors, influence food choices and feeding behaviour. Modified from Blundell et al. (2010).

2.2.2 Appetite regulatory hormones

Obesity is the result of an imbalance between energy intake and energy expenditure. The regulation of energy balance is very complex; both genetic and environmental factors affect it (Guyenet and Schwartz 2012). The regulation of energy intake is also a complex process involving environmental and behavioural factors, feelings of hunger and fullness, and physiologic factors such as appetite regulatory hormones (Blundell et al. 2010). Although physiologic factors regulate appetite and hunger and thus energy intake, meals are mostly initiated by factors that are not based on energy needs, such as food availability, habit, time of day and social conventions (Woods and D'Alessio 2008). Physiological factors mainly control how much is consumed once a meal begins (Blundell et al. 2010). It has, however, been proposed that appetite regulatory hormones play a role in the development of obesity. Several studies have supported this by showing alterations in appetite regulatory hormones in obese individuals, as reported in a review by Suzuki et al. (2010).

Many peripherally released appetite regulatory hormones have been identified. In this thesis, the focus is on peptide YY (PYY), glucagon-like peptide 1 (GLP-1) and ghrelin (**Table 3**). Both PYY and GLP-1 decrease appetite and thus food intake, whereas ghrelin stimulates appetite and food intake. PYY is produced by the endocrine L-cells in the ileum and colon in response to food intake (Suzuki et al.

2010). The PYY (1-36) released is rapidly metabolized by dipeptidyl peptidase 4 (DPP-4) to the active form, PYY (3-36). In addition to decreasing appetite, PYY has many other functions. For example, it inhibits insulin secretion and stimulates ileal break which means inhibition of upper gastrointestinal motility and gastric emptying by ingested food, thus restraining the rate of nutrient entry into the blood (Spiller et al. 1984).

Table 3. Summary of the characteristics of the appetite regulatory hormones.

Hormone	Primary site of production	Effect on appetite	Major target functions
Ghrelin	X/A -like cells, gastric mucosa	Increase	Growth hormone release ↑ Gastrointestinal motility ↑ Insulin ↓
GLP-1	L-cells, ileum and colon	Decrease	Insulin ↑ Glucagon release ↓ Gastrointestinal motility ↓ Ileal break ↑
PYY	L-cells, ileum and colon	Decrease	Insulin ↓ Ileal break ↑

GLP-1, glucagon-like peptide 1; PYY, peptide YY; ↓, decrease stimulation; ↑, increase stimulation.

Like PYY, GLP-1 is produced by the endocrine L-cells in the ileum and colon and delays gastric emptying, contributing to ileal break. DPP-4 rapidly inactivates secreted GLP-1. GLP-1 is an incretin hormone. Incretins stimulate insulin secretion in response to a meal or glucose ingestion. This so-called incretin effect accounts for approximately 50–70% of the total insulin secretion after a meal (Kazakos 2011). GLP-1 also inhibits glucagon secretion and increases β-cell growth (Cummings and Overduin 2007). Orexigenic ghrelin is released from the gastric mucosa. In addition to its short-term effect on appetite regulation and food intake, it also affects long-term body weight regulation (Cummings and Overduin 2007). In contrast to PYY and GLP-1, ghrelin increases gastrointestinal motility. It also decreases insulin secretion and stimulates the release of growth hormone (Hosoda et al. 2006). In addition to these peptides, other commonly measured appetite regulatory hormones include small intestine-released cholecystokinin (CCK) and pancreas-secreted pancreatic polypeptide (PP), both of which decrease food intake in short-term periods (Badman and Flier 2005).

Appetite regulatory hormones transmit information relating to energy stores or recent energy intake to the hypothalamus and the hindbrain (**Figure 3**). These peripheral released appetite regulatory hormones can transfer information to the central nervous system through the vagus nerve to the hindbrain or directly to the hypothalamus or hindbrain. In the arcuate nucleus of the hypothalamus, there are two particularly important categories of neurons: appetite-stimulating neurons,

which contain neuropeptide Y and agouti-related peptides and appetite-inhibiting neurons, which contain pro-opiomelanocortin peptide and cocaine- and amphetamine-stimulated transcript peptide. This area has been extensively studied and reviewed in the past decade (Badman and Flier 2005, Cummings and Overduin 2007, Suzuki et al. 2010, Vincent et al. 2008).

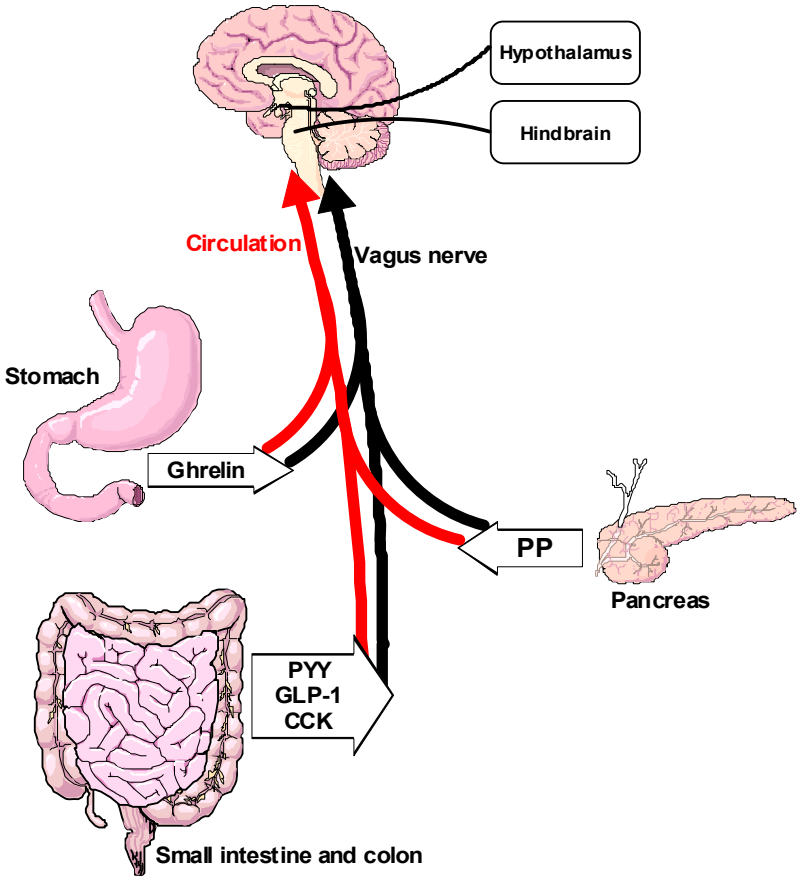


Figure 3. Simplified figure of physiologic factors affecting short-term appetite regulation. Ghrelin is released from the stomach preprandially and stimulates appetite through the central nervous system via circulation (to the hypothalamus) or vagus nerve. Peptide YY (PYY), glucagon-like peptide 1 (GLP-1) and cholecystokinin (CCK) are released the intestine postprandially and reduce appetite and food intake through signals to the hypothalamus, hindbrain and vagus nerve. Pancreatic polypeptide (PP) is released from the pancreas postprandially and reduces appetite and food intake through signals to the hindbrain or vagus nerve. Modified from Vincent et al. (2008).

2.2.3 Body size at birth and food intake

There is strong evidence that lifestyle factors such as unhealthy dietary habits and physical inactivity are independent and modifiable risk factors for CVD and type 2 diabetes (Ignarro et al. 2007, Rees et al. 2013, Schellenberg et al. 2013). Therefore, it has been proposed that one possible mechanism behind the association between small body size at birth and increased risk for development of chronic diseases could be by early programming of these lifestyle factors (Portella et al. 2012). Animal models (Bellinger et al. 2006, Vickers et al. 2003) and meta-analysis of adult individuals (Andersen et al. 2009) support this hypothesis by showing that low birth weight is related to physical inactivity. Thus, early growth may influence disease risk in later life through direct biological effects as well as modifying adult behaviour.

In addition, there is evidence from animal studies that the early environment may program dietary habits. One of these studies showed that rats whose mothers were fed a low-protein diet during gestation had a preference for a high-fat diet (Bellinger et al. 2004); however, not all studies support this finding (Bellinger and Langley-Evans 2005, Cambraia et al. 2001). Fat intake also increased with decreasing birth weight in young children (Shultis et al. 2005, Stafford and Lucas 1998). Similarly, two different Dutch study groups observed that famine during prenatal life was related to preference for a high-fat diet in adulthood (Lussana et al. 2008, Stein et al. 2009). However, only one of these studies examined the association between birth weight and macronutrient intake in adult life and found no relationships (Lussana et al. 2008). Contrasting results were reported by Barbieri et al. (2009), who showed that in young Brazilian women, severe intrauterine growth restriction was related to higher intake of carbohydrates. They also studied prenatal growth restriction and food intake and found no effect of intrauterine growth restriction on food consumption. A recently published study, in which birth weight and food intake in later life were also investigated, showed that young Finnish adults who were born preterm at below 1500 g had similar macronutrient intake compared with term controls although they consumed less fruits, berries, vegetables and milk products (Kaseva et al. 2013).

What are the underlying mechanisms explaining these altered food choices? It has been proposed that the early life environment may alter physiologic factors that are related to food choices. Animal models have shown that a low-protein diet during gestation may alter the size and neuronal density of hypothalamic structures and expression of neuropeptides that are involved in the regulation of food intake (Breton et al. 2009, Erhuma et al. 2007, Plagemann et al. 2000a). These peptides, such as neuropeptide Y, may also control macronutrient selection behaviour

(Primeaux et al. 2006, Smith et al. 1997, Tanaka and Kido 2008). However, since these results are based on animal models, it is still unknown whether these peptides play a role in macronutrient selection behaviour in humans as well. In addition, prenatal flavour experiences may enhance the acceptance and enjoyment of similarly flavoured foods during postnatal life. This was detected in an animal model (Bayol et al. 2007) and in a study of young children (Mennella et al. 2001) in which maternal diet during pregnancy influenced postnatal preference for the same diet.

Early growth may also affect sensory factors that are related to food choices. Subjects who have elevated leptin levels need higher concentrations of sweeteners, such as glucose, to detect the sweet stimulus, than subjects with lower leptin levels (Nakamura et al. 2008, Umabiki et al. 2010). It has been proposed that this type of alteration in detecting the sweet stimulus may lead to a reduced consumption of sweet food (Shigemura et al. 2004). Increased leptin secretion has been observed among participants who were born with low birth weight (Lissner et al. 1999, Phillips et al. 1999). Thus, altered leptin level could potentially be involved in food consumption. Early growth may also affect preference for salty foods as observed in one experimental study of young infants whose birth weight was inversely related to salty taste preference. The authors suggested that preference for salty foods among low birth weight individuals could lead to increased salt intake and subsequently elevated blood pressure (Stein et al. 2006). Another possible mechanism by which early growth could influence food choices later in life is programming of the sensitivity to the food reward, such as pleasure, that is associated with the consumption of palatable food. One recently published study supports this by showing that intrauterine growth retardation was associated with the consumption of palatable foods in preterm infants (Ayres et al. 2012).

2.2.4 Early growth and appetite regulation

Although low birth weight and small body size in infancy are related to increased risk for developing metabolic diseases in later life, large body size at birth and rapid growth during infancy are primarily associated with subsequent risk of obesity, as reported in systematic reviews and meta-analyses (Baird et al. 2005, Monasta et al. 2010, Monteiro and Victora 2005, Ong and Loos 2006, Schellong et al. 2012, Yu et al. 2011b, Zhao et al. 2012). Therefore, it has been suggested that growth retardation during the prenatal or postnatal periods may produce changes in the central control of appetite, such as altering appetite regulatory hormone secretions, and thus affect the risk for developing obesity. Consistent with this hypothesis, animal models have shown that both prenatal and postnatal growth retardation cause alterations in appetite regulation pathways, including alterations in hypothalamic nuclei structure and neuropeptide expression (Breton et al. 2009, Coupe et al. 2009, Desai et al.

2007, Ikenasio-Thorpe et al. 2007, Lopez et al. 2005, Lukaszewski et al. 2013, Plagemann et al. 1999, Plagemann et al. 2000a, Plagemann et al. 2000b, Remmers et al. 2008, Yousheng et al. 2008), and prevention of rapid catch-up growth in newborns may reduce the risk of obesity (Desai et al. 2005, Schellong et al. 2013).

The evidence for early growth and appetite regulation systems in humans comes mostly from studies of young children. These studies indicate that infants who were born with low birth weight (Chen et al. 2012, Siahanidou et al. 2005) or born preterm (Berseth et al. 1992, Chen et al. 2012, Siahanidou et al. 2005, Siahanidou et al. 2007) have elevated levels of fasting PYY reflecting greater satiety. In addition, decreased fasting ghrelin concentrations have been reported in young children who were born with low birth weight (Siahanidou et al. 2005) and elevated ghrelin levels in young adolescents with rapid growth during infancy (Larnkjaer et al. 2010). However, not all studies support these findings (Chen et al. 2012, Darendeliler et al. 2009, Iniguez et al. 2002, Kyriakakou et al. 2009, Park 2010, Sahin et al. 2012). To date, the effect of early growth on postprandial responses of any appetite regulatory hormones has been investigated in only one previous study (Schou et al. 2005). In that study, GLP-1 responses were measured and no effect of birth weight on GLP-1 levels was observed. As mentioned above, GLP-1 affects appetite regulation by delaying food transit time from the stomach to the duodenum (Edholm et al. 2010), as well as through the central nervous system. Clearly, further studies are needed in this area.

2.3 Early growth and blood pressure

2.3.1 Blood pressure and salt intake

Elevated blood pressure (hypertension) is a common health problem in both the developing and developed countries. The WHO has estimated that the worldwide prevalence of elevated blood pressure among adults ≥ 25 years of age is 29.2% in men and 24.8% in women (World Health Organization 2011). Definitions for elevated blood pressure are presented in **Table 4**. Elevated blood pressure is also common in Finland; based on the FINRISK 2007 study, 52.1% of men and 33.6% of women have systolic blood pressure (SBP) over 120 mmHg and diastolic blood pressure (DBP) over 80 mmHg (Kastarinen et al. 2009). Elevated blood pressure is a major risk factor for CVD, including coronary heart disease and stroke (Mancia et al. 2007). It has been estimated that elevated blood pressure causes 7.5 million deaths globally, which is about 12.8% of all deaths (World Health Organization 2011).

Table 4. Definitions for elevated blood pressure according to the European Society of Hypertension and the European Society of Cardiology (Mancia et al. 2007) and the Finnish Current Care Guideline for Hypertension (Jula et al. 2009).

	SBP (mmHg)	DBP (mmHg)
Optimal	< 120	< 80
Normal	120–129	80–84
High-normal	130–139	85–89
Mild hypertension, grade 1	140–159	90–99
Moderate hypertension, grade 2	160–179	100–109
Severe hypertension, grade 3	≥ 180	≥ 110

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

Increased salt intake is one risk factor for elevated blood pressure (He and MacGregor 2002, Strazzullo et al. 2009). Other major lifestyle-related risk factors of elevated blood pressure include overweight, smoking, excessive alcohol intake and physical inactivity (Mancia et al. 2007). In addition, increased intake of saturated fatty acids (SFAs) and decreased intake of potassium, fruits and vegetables elevate blood pressure (Mancia et al. 2007).

Blood pressure reduction in response to decreasing salt intake varies among individuals. Both genetic factors and acquired factors affect blood pressure reactivity to salt, which is also known as salt sensitivity. For example, metabolic syndrome (Hoffmann and Cubeddu 2007), older age and African-American race (Luft et al. 1991, Richardson et al. 2013) have been linked with increased salt sensitivity. The aetiology of salt sensitivity is still unknown; however, it has been proposed that differences in blood pressure reactivity to salt may be the result of alterations in renal handling of salt and the renin-angiotensin-aldosteronesystem, as well as impaired microvascular functioning (Ando and Fujita 2012, Richardson et al. 2013, Weinberger 1996).

2.3.2 Early growth and blood pressure in later life

Several epidemiological studies have shown an inverse relationship between birth size and adult hypertension. A few systematic reviews and meta-analyses have also been published (Gamborg et al. 2007, Huxley et al. 2000, Law and Shiell 1996, Mu et al. 2012), summarizing data for over 80 studies and with over 400 000 participants. These systematic reviews and meta-analyses have demonstrated that each 1-kg higher birth weight is associated with 2–3-mmHg lower SBP. Similar results regarding birth weight and adult-life DBP have also been observed, although

the association is not as strong as it is with SBP (Mu et al. 2012). Studies have shown that the relationship between birth weight and blood pressure is stronger in older populations than in younger populations and thus the association is age-dependent (Gamborg et al. 2007).

Alterations of kidney structure and functioning may be the underlining mechanism by which prenatal growth is linked with blood pressure in later life. Growth retardation during prenatal life leads to permanently reduced nephron number (Hinchliffe et al. 1992, Hughson et al. 2008, Manalich et al. 2000, Zidar et al. 1998) and impaired kidney functioning (Hallan et al. 2008) in humans. This association also exists across normal birth weight ranges (Hughson et al. 2003). It has been suggested that reduction in the number of nephrons leads to increased glomerular filtration rates, thereby increasing the risk of glomerulosclerosis and further nephron deaths, decreased sodium excretion and subsequently elevated blood pressure (Brenner and Chertow 1994, Zandi-Nejad et al. 2006). Animal models also support the hypothesis that prenatal growth affects blood pressure by showing that maternal dietary protein restriction during pregnancy causes reduced nephron number and leads to hypertension in adult offspring (Langley and Jackson 1994, Manning and Vehaskari 2001, Woods et al. 2001, Woods et al. 2004).

2.3.3 Early growth and salt sensitivity

It has been proposed that individuals who were born with low birth weight could be particularly sensitive to the blood pressure-raising effect of salt, because they have alterations in kidney functioning. This hypothesis was tested in two studies of rodents in which pregnant rats consumed a low-protein diet. The offspring of these rats suffered from salt-sensitive hypertension during adult life (Augustyniak et al. 2010, Woods et al. 2004). Two independent animal studies also demonstrated that prenatal growth retardation caused alterations in both protein and gene expression of sodium transporters in the kidney and thus affected salt sensitivity (Alwasel and Ashton 2009, Manning et al. 2002).

There are only two small intervention studies in which the effect of birth weight on salt sensitivity has been investigated in humans. A study of young children demonstrated that renal mass is reduced in children born with low birth weight and is dependent on the degree of growth retardation (Simonetti et al. 2008). Growth retardation also lowered the glomerular filtration rate, increased salt sensitivity and elevated blood pressure. In addition, they found that the highest prevalence of salt sensitivity was observed among those children who had experienced the most severe growth retardation during gestation. Another study of adults confirmed this finding by showing that birth weight affects the salt sensitivity of blood pressure (de Boer et al. 2008). In this study, healthy adults consumed a high-salt diet for one week and

thereafter a low-salt diet for one week. The blood pressure was measured before and after both test periods. The salt sensitivity of blood pressure was defined as the difference in mean arterial blood pressure between the high- and low-salt periods. They showed that birth weight was inversely related to salt sensitivity of blood pressure; a 1-kg lower birth weight increased the salt sensitivity of blood pressure by 2.0 mmHg. Based on these studies, birth weight seems to modify the blood pressure-raising effect of salt. However, it remains to be determined whether these findings are also seen in larger study populations.

2.4 Early growth and postprandial responses

2.4.1 Importance of postprandial responses

The associations between metabolic abnormalities and CVD risk factors have been studied mostly in the fasting state. However, with the exception of the first few hours in the morning, individuals spend most of their daytime hours in a postprandial state. The important contribution of the postprandial state to the differing risk of diseases is increasingly being recognized, and to date there is strong evidence that elevated postprandial levels of glucose and lipids are independent risk factors for CVD and type 2 diabetes. In fact, they may even be better predictors of cardiovascular morbidity and mortality than fasting levels (Bansal et al. 2007, Mah and Bruno 2012, Nordestegaard et al. 2007, Rendell and Jovanovic 2006).

There are several possible mechanisms by which elevated postprandial responses of glucose, insulin and lipids may cause adverse health effects and be directly atherogenic. For example, triglyceride (TG) rich chylomicrons during the postprandial period are converted to remnants that could penetrate the arterial wall and deposit cholesterol. The remnants could also affect the atherosclerotic process by converting macrophages into foam cells (Goldberg et al. 2011, Jackson et al. 2012, Kolovou et al. 2011). In addition, postprandial hyperglycaemia may promote atherogenesis by several mechanisms, e.g. by increasing formation of free radicals and causing nonreversible glycosylation of proteins (Mah and Bruno 2012, O'Keefe and Bell 2007). Furthermore, postprandial hyperinsulinaemia leads to sodium retention and sympathetic nervous system activation, both of which have adverse health effects (Kopp 2006). Indeed, elevated postprandial levels of both glucose and TG even within the physiological range in healthy individuals, lead to increased production of proinflammatory cytokines and oxidative stress causing postprandial inflammation, which may further contribute to endothelial dysfunctioning (Klop et al. 2012). These postprandial changes, when repeated multiple times each day, can predispose to the development of CVD and type 2 diabetes.

2.4.2 Early growth and findings in postprandial studies

There is an increased interest in the field of early growth and metabolic disease risk factors, such as glucose and lipids, later in life. However, surprisingly little information is available on whether prenatal or postnatal growth affects postprandial metabolism. In one of the first postprandial studies within the DOHaD field, Byrne et al. (1997) tested postprandial TG and free fatty acid (FFA) responses in 57 men of known birth weight. The subjects consumed a test meal that contained 65 g of fat per m^2 of body surface area (14% was derived from carbohydrates, 3% from protein and 83% from fat). Blood samples were drawn in the fasting state and four times during an 8-h test period. The effect of birth weight on the postprandial responses of TG and FFA was examined by stratification of the group by birth weight (< 3.1 kg, 3.1–4.1 kg, > 4.1 kg). Participants born with low birth weight had higher postprandial TG and FFA responses than subjects who were born with medium birth size. In addition, participants who belonged to the highest birth weight group also had higher postprandial lipid responses than did the medium birth weight group. However, the birth weight groups did not differ significantly. The study included both nonsmokers and smokers. Several studies have reported significantly greater postprandial TG levels in smokers than in nonsmokers, without differences in fasting levels (Kabagambe et al. 2009, Lopez-Miranda et al. 2007). Therefore, excluding smokers is desirable when postprandial lipid responses are examined.

In another postprandial study, the effect of birth weight on macronutrient oxidative and nonoxidative metabolism was investigated in elderly healthy men (Kensara et al. 2006). Participants were born either below the 25th percentile of birth weight (under 3.23 kg, n = 16) or above the 75th percentile (over 3.89 kg, n = 13). In this study, participants consumed a meal containing 3720 kJ of energy of which 40% was derived from carbohydrates, 15% from protein and 45% from fat. Kensara et al. observed that the 6-h postprandial responses of glucose, TGs and FFAs did not differ significantly between groups. However, it is nevertheless challenging to investigate the effect of low birth weight if the controls are not born at medium birth weight, because high birth weight can also cause adverse effects on glucose and lipid metabolism (Dabelea et al 1999, Eriksson et al 2003, Harder et al 2007).

In the third study of this field, Schou and coworkers (2005) measured glucose and insulin responses in young normal weight men who were born either with low birth weight (< 3010 g, n = 24) or were matched normal birth weight controls (> 3390 g, n = 25). The participants consumed a standardized breakfast containing 2370 kJ of energy; the carbohydrate content was 47%, protein 19% and fat 34%. In this study, participants with low birth weight had higher fasting glucose but not insulin levels. Indeed, postprandial 195-min responses of both glucose and insulin were significantly increased in the group born with low birth weight. In this study,

incretins, glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 responses were also measured. However, although Schou et al. (2005) observed higher insulin levels after a meal, they did not demonstrate that low birth weight affects the secretion of incretins or β-cell stimulation by incretins.

Taken together, these results of postprandial studies demonstrate that early growth may affect insulin secretory responses. However, only a handful of postprandial studies have been published. In addition, the study protocols used have varied between studies, as have the exclusion criteria and characteristics of the controls. Therefore, far-going conclusions cannot be made based on the studies published.

2.4.3 Early growth and findings in fasting studies

In contrast to postprandial studies, several other studies have investigated the associations between body size at birth and fasting glucose, insulin and lipid concentrations in later life. In addition to fasting values, these results are also based on oral glucose tolerance tests (OGTTs). To date, there is strong epidemiological evidence that low birth weight is related to elevated fasting and 2-h glucose levels in adulthood, which indicate impaired glucose regulation (Newsome et al. 2003). Impaired glucose tolerance is usually the result of impaired insulin secretion and insulin resistance. There have been assumptions that early growth may affect β-cell functioning and thus alter insulin secretion. Animal models support this by showing decreased β-cell mass among offspring whose mothers were fed a low-protein diet during pregnancy (Dumortier et al. 2007). However, when insulin secretion has been measured in humans, using intravenous glucose tolerance tests or OGTTs, variable results have been observed. In a meta-analysis, Newsome and colleagues (2003) showed that size at birth was inversely associated with the measure of insulin secretion in 15 of 27 studies, not related in 5 and positively related only in 7 studies. These findings suggest that individuals who were born with small body size have no clear primary defect in insulin secretion. In contrast to insulin secretion, several studies have shown that low birth weight is linked with reduced insulin sensitivity, as reported in the same meta-analysis (Newsome et al. 2003). Insulin resistance in low birth weight individuals could be the cause of multiple abnormalities in their insulin-sensitive tissues, including muscles and adipose tissues (Boiko et al. 2005, Eriksson et al. 2002, Jensen et al. 2007, Jensen et al. 2008, Maiorana et al. 2007, Taylor et al. 1995).

The association between low birth weight and unfavourable lipid profiles, such as elevated fasting total cholesterol and TG levels, has also been widely studied. Several systematic reviews and meta-analyses have been published. Three of these reviews or meta-analyses have shown that a 1-kg increase in birth weight was

associated with about a 0.03–0.05-mmol/l decrease in total cholesterol in adult individuals (Huxley et al. 2004, Lawlor et al. 2006, Owen et al. 2003). These analyses comprised 28–58 studies and 20 000–70 000 individuals. However, one systematic review did not detect relationships between birth weight and total cholesterol. The authors did, however, find that there was a negative or U-shaped association between birth weight and fasting TG levels (Lauren et al. 2003). In addition to birth weight, some studies have also demonstrated that slow postnatal growth is associated with elevated fasting lipid levels (Kajantie et al. 2008, Skidmore et al. 2007, Tzoulaki et al. 2010). The associations between birth weight or postnatal growth and later-life fasting lipid concentrations are, however, surprisingly weak compared with the associations between birth weight and CVD risk.

The associations between low birth weight or slow postnatal growth and unfavourable lipid profiles could be due to altered liver functioning and metabolism (Burns et al. 1997, Lane et al. 2001, Winick and Noble 1966). In addition, alterations in lipid metabolism could be the result of excess lipid content in the liver (Kotronen and Yki-Järvinen 2008). Previous studies support this showing that low birth weight and small body size during infancy is associated with a higher likelihood of non-alcoholic fatty liver disease later in life (Fraser et al. 2008, Sandboge et al. 2013).

3 Aims of the study

The general aim of this study was to determine whether early growth is associated with dietary-related risk factors of metabolic diseases in later life. The specific aims were as follows:

1. To determine whether body size at birth is related to food consumption and nutrient intake in adulthood (I).

2. To investigate whether birth weight modifies the association between salt intake and blood pressure (II).

3. To examine the influences of early growth on postprandial glucose, insulin and lipid responses in later life (III, IV).

4. To explore whether early growth affects postprandial appetite regulatory hormone and incretin responses (IV).

4 Materials and methods

4.1 Helsinki Birth Cohort Study

The subjects in this thesis were all participants in the Helsinki Birth Cohort Study (HBCS), originally comprising 4630 men and 4130 women. They were born as singletons at the Helsinki University Central Hospital between 1934 and 1944, attended child welfare clinics in the city and lived in Finland in 1971, when a unique identification number was allocated to each member of the Finnish population (**Figure 4**).

Data on growth of the HBCS participants were obtained from hospital birth records and child welfare clinic records. Their birth records included date of birth, weight and length at birth and date of mother's last menstrual period, based on which gestational age was calculated. Child welfare records included serial measurements of weight and height in infancy and childhood. Individuals belonging to the original study cohort were traced, using personal identification numbers.

Those HBCS participants who were still alive and residing in Finland were sent a questionnaire in the year 2000 (n = 7078). The questionnaires gave information on their general background including weight and height, health and diseases, medication, lifestyles and social circumstances. A total of 4515 individuals answered the questionnaires.

To obtain a sample size of over 2000 individuals for the clinical examination, a random-number table was used to invite 2902 subjects living in the greater Helsinki area. Of these, 2003 men (n = 928) and women (n = 1075) participated in the clinical examination between August 2001 and March 2004.

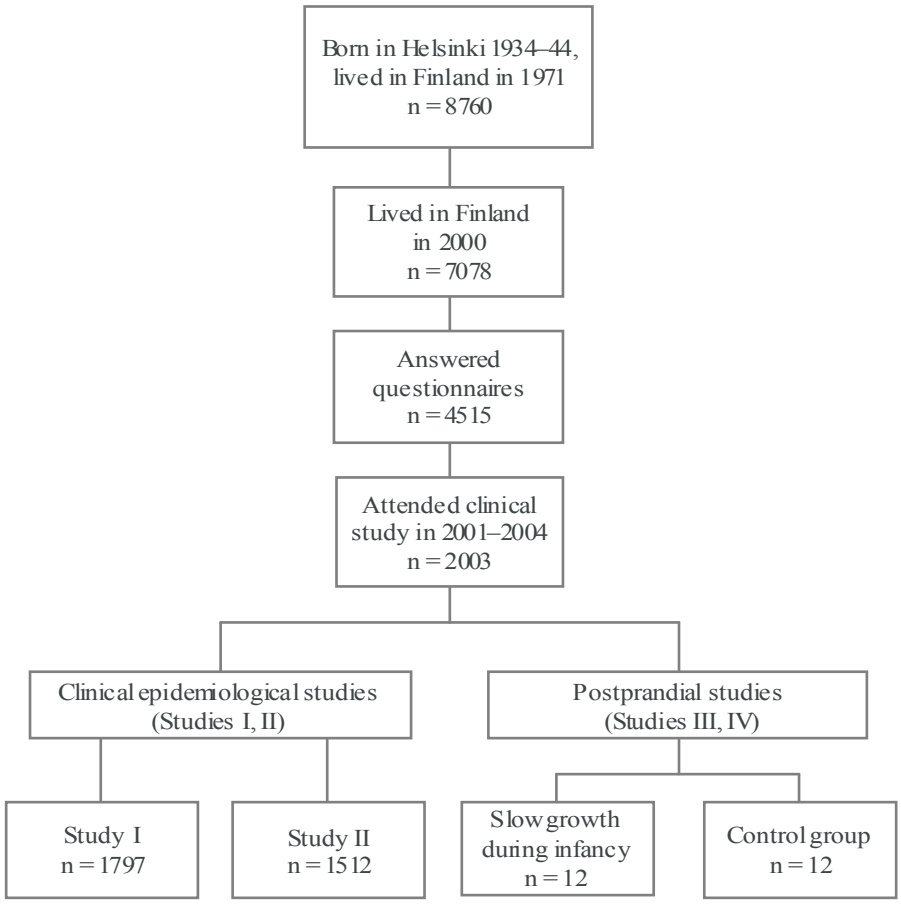


Figure 4. Flowchart of subgroups of the HBCS participants included in the studies in this thesis.

4.2 Clinical epidemiological studies (I, II)

4.2.1 Clinical examinations

The subjects attended the clinical examination after an overnight fast. Height was measured to the nearest 0.1 cm and weight to 0.1 kg in light clothing without shoes. The BMI was calculated as the weight in kilograms divided by the square of the height in metres. Blood pressure was measured from the right arm while the participant was in a sitting position and was recorded as the mean of two successive readings from a standard sphygmomanometer (Omron Matsusaka Europe, Hoofdorp, the Netherlands). A team of three trained research nurses performed all measurements. The participants were also asked about their medical history and current medication, using questionnaires at the clinic. In addition, educational attainment, smoking and exercise habits were obtained from a postal questionnaire before the clinical examination.

The Ethics Committee of Epidemiology and Public Health of the Hospital District of Helsinki and Uusimaa approved the clinical examination. Written informed consent was obtained from each subject.

4.2.2 Dietary assessments

The diet was assessed by a validated, self-administered, 128-item food-frequency questionnaire (FFQ) (Männistö et al. 1996, Paalanen et al. 2006). The FFQ was designed to assess the usual diet over the previous 12 months. The participants were asked to indicate the average intake frequency of each food-item and mixed dish, presented as 12 main food groups, e.g. dairy products and vegetables. The response options for nine possible frequency categories ranged from never or seldom to six or more times per day. The portion sizes for each food-item were specified in natural units (e.g. one banana, 190 g), common household measures (e.g. one glass of milk, 170 g) or portions (e.g. one portion of meat soup, 300 g). The portion sizes were based on the national FINDIET Survey and present the most commonly used portion sizes in Finland.

At the clinic, the participants completed the FFQ, which was then checked by a research nurse. The food intake data were entered and processed at the National Institute for Health and Welfare, Helsinki, Finland with the in-house calculation software Finessi, utilizing the National Food Composition Database FINELI ! (National Institute for Health and Welfare 2005). The daily food intake was calculated by multiplying the frequency of food consumption by fixed portion sizes

to obtain the weight of each listed food-item consumed as an average per day. The average daily intake of nutrients was calculated by multiplying the gram intake per day of each food by its nutrient content.

Salt (NaCl) intake included the natural sodium content of raw foods (sodium intake x 2.548), the salt added in cooking in average recipes and the salt used in manufactured foods. The dietary glycaemic index (GI) and glycaemic load (GL) were calculated, using the GI-database (Kaartinen et al. 2010). Dietary GI was calculated as the weighted mean of the GI values of the carbohydrate-containing foods in the diet, in which weighting was based on the proportion of the total carbohydrate content provided by each food. The dietary GL was calculated by multiplying the dietary GI value with the carbohydrate content of the diet and dividing by 100.

4.2.3 Statistical methods

The nutrients and foods were adjusted for energy intake by calculating the proportion of energy (E%) or by using the residual method (fibre, dietary GL, food groups, salt) (Willett and Stampfer 1986). Educational attainment was categorized into three groups, according to the number of years in school: basic (≤ 9 years of education); secondary (10–12 years) and higher (≥ 13 years of education). The participants were defined as current smokers if they smoked one or more cigarettes per day. Those who exercised at a level comparable to brisk walking three or more times per week were defined as physically active.

In Study I, the subjects were excluded if their FFQ had ≥ 10 blank food-items (n = 2) or if their calculated energy intake was under 2.7 MJ/d or over 25.5 MJ/d, corresponding to 0.5% at both ends of the self-reported daily energy intake distributions for men and women (n = 20). In all, 180 subjects were excluded, because their gestational age at birth was under 37 completed weeks, over 44 completed weeks or was not recorded. In addition, the BMI was not recorded for two subjects and for one it was considered too high to be included in the analysis (68.39 kg/m^2). In addition, one participant was excluded because his fruit and berry intake was over 5 kg/d. The final analysis of Study I comprised 1797 subjects.

In Study II, the subjects were excluded if their FFQ was incomplete (n = 22), their gestational age was missing (n = 122) or their BMI was missing (n = 2) or considered to be too high (n = 1) as in Study I. In addition, underreporters were also excluded. Underreporters were defined as subjects whose energy intake was below 1.27 * the basal metabolic rate, which is the minimum survival requirements used when habitual diet is measured (Goldberg et al. 1991). The basal metabolic rate was estimated, using WHO equations that take into account weight, age and sex (World Health Organization 1985). The final analysis of Study II comprised 1512 subjects.

Associations were also recalculated for this thesis by excluding those whose gestational age at birth was under 37 completed weeks or over 44 completed weeks (n = 44).

The relationship between body size at birth and food and macronutrient intake was examined by linear regression analysis (Study I). The models were adjusted for potential confounding variables, which included sex and current age (Model 1), while Model 2 was further adjusted for current BMI, smoking, education and gestational age. Additional analyses were also adjusted for physical activity (Model 3). Statistical analyses were done using the PASW Statistics version 18 for Windows® (SPSS Inc., Chicago, IL, USA). For this thesis summary, the associations between body size at birth and food and macronutrient intake were recalculated by adjusting Model 2 further for total energy intake (Model 4). Linear regression analyses of Models 2, 3 and 4 rendered similar results. Therefore, only the results of Models 1 and 2 will be presented below.

The SBP and DBP were adjusted for sex, current age and BMI, use of antihypertensive medication, gestational age and total energy intake (Study II). The relationship between the adjusted SBP and DBP and the energy-adjusted salt intake was examined visually and a piecewise multivariate regression with unknown breakpoints (Muggeo 2003) was fitted. The best breakpoints with respect to both birth weight and salt intake were determined simultaneously by fitting the linear regression and choosing the model with the best (i.e. lowest) value of the Akaike information criterion. In addition, a likelihood-ratio test was used to assess the need for the breakpoint. The breakpoints themselves were considered to be a parameter, and the final P-values were adjusted as described by Hunsberger et al. (2002). The linear piecewise regression models for the best fitting breakpoints were then finally estimated. Statistical analyses were done, using R-software (version 2.8.1, The R Foundation for Statistical Computing) and PASW Statistics version 18 for Windows® (SPSS Inc., Chicago, IL, USA).

4.3 Postprandial studies (III, IV)

4.3.1 Subjects

A total of 24 overweight or obese (BMI 25–32 kg/m^2) 65–75 year-old subjects, 12 with slow growth during infancy (SGI) and 12 age-, BMI- and sex-matched controls, participated in the postprandial studies between November 2009 and May 2010. The subjects belonged to the HBCS and had attended a clinical examination in 2001–2004. Growth during infancy was examined as gains in BMI between birth and 1 year of age. Each measurement of BMI for each individual was converted to a Z-

score, which represented the difference from the mean value for the entire study cohort (n = 2003) and was expressed as standard deviations (SDs). We examined how much the BMI at 1 year of age differed from that predicted by the BMI at birth, using the residual from linear regression; this measure was called 'conditional growth'. Participants who were born preterm (before 37 weeks of gestation) or whose gestational age was over 44 completed weeks or was not reported were excluded. Subjects in the SGI-group had a conditional growth of < -0.9 SD, and the conditional growth of the control group was > -0.9 SD. The conditional growth breakpoints were based on the previous study of the HBCS, in which it was observed that participants whose conditional growth was < -1 SD had significantly higher fasting level of cholesterol and TG in adulthood (Kajantie et al. 2008).

Glucose tolerance was assessed by a 75-g 2-h OGTT, and diabetics (fasting glucose ≥ 7.0 mmol/l and/or 2-h glucose ≥ 11.1 mmol/l) were excluded. Other exclusion criteria included smoking, milk allergy, regular medication that could have affected postprandial glucose or lipid metabolism (e.g. antidiabetic drugs, fibrates and asthma medicine), gastrointestinal disease influencing absorption, a first-degree family history of diabetes or blood donation less than 3 months before the study. Participants' diet, health and lifestyle data were assessed by questionnaires.

The postprandial study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving human subjects were approved by the Ethics Committee of the Hospital District of Helsinki and Uusimaa. Written informed consent was obtained from all the subjects.

4.3.2 Study design and test meals

The study used a crossover design. The subjects were recruited to participate in six 1-day studies separated by approximately 1 week. One participant in the control group was able to attend for only the first two study visits (Study III). Therefore, another subject was recruited to attend the last four visits (Study IV). The subjects were requested to follow their usual diet during the study period. In addition, they were not allowed to drink alcohol and were asked to avoid strenuous exercise and sauna for 24 h before each study day. Moreover, the subjects were advised not to take lipid-lowering medication (statins) preceding the study visit. The day before the study day, they were asked to consume an evening meal, in accordance with the instructions they had been given, which would provide 15% of the calculated daily energy requirement. The mean energy intake of the subjects was calculated, based on their calculated basal metabolic rate, taking into account the questionnaire data on daily physical activity (World Health Organization 2004). The carbohydrate content of the evening meals was 55 E%. The subjects were also asked to fast for

10–12 h after their standardized evening meal, to avoid exercise in the morning of the study and to arrive at the clinic by car or public transportation.

In the study clinic, body height and weight were measured and the BMI was calculated. Changes of up to 2 kg in weight were allowed during the study. The waist circumference was measured in a standing position, with the legs slightly apart, midway between the lowest ribs and the iliac crest. An intravenous cannula was inserted into an antecubital vein in the forearm and an intravenous blood sample was drawn. Thereafter, the subjects consumed the test meal within 10 min. After the start of the meal, venous blood samples were collected at 15, 30, 60, 90, 120, 180 and 240 min.

In Study III, all subjects consumed two different test meals, a fast-food meal (FF-meal) and a meal that followed the macronutrient composition of the dietary guidelines (REC-meal) in randomized order at 1-week intervals. Both test meals contained the same amount of energy. The foodstuffs and the nutrient composition of the test meals are shown in **Table 5**. In Study IV, all participants tested four test meals in random order: two high-protein meals and two high-fat meals (**Table 5**). Both high-protein meals contained the same amount of energy, carbohydrate, protein, and fat. Only the type of milk protein differed between meals: calcium caseinate (casein-meal) or whey protein isolate (whey-meal). Two high-fat meals also contained the same amount of energy, carbohydrates, protein and fat; only the type of fat (saturated [SFA-meal] or polyunsaturated [PUFA-meal] fat) differed between test meals.

Table 5. Foodstuffs and macronutrient content of the test meals.

Components, g	FF-meal	REC-meal	Casein-meal	Whey-meal	SFA-meal	PUFA-meal
Barley porridge [1]	-	215	-	-	-	-
Raspberry jam [2]	-	32	-	-	-	-
Orange juice [3]	-	260	-	-	-	-
Rye bread [4]	-	48	-	-	45	45
Margarine 70% [5]	-	10	-	-	-	11
Cheese 5% [6]	-	37	-	-	-	-
Milk (0% fat)	-	150	-	-	-	-
Cocoa powder [7]	-	15	27	27	26	26
Cucumber	-	40	40	40	40	40
Rapeseed oil	-	15	-	-	-	-
BigMac-hamburger [8]	210	-	-	-	-	-
French fries [8]	99	-	-	-	-	-
Light Cola [8]	380	-	-	-	-	-
Whey [9]	-	-	-	44	-	-
Casein [10]	-	-	44	-	-	-
Water	-	-	400	400	350	350
Milk powder [11]	-	-	-	-	23	23
Vanilla sugar	-	-	5	5	-	-
Sugar	-	-	15	15	-	-
White bread [12]	-	-	37	37	-	-
Butter [13]	-	-	25	25	60	-
Solid margarine [14]	-	-	-	-	-	51
Energy, kJ	3326	3359	2638	2638	2961	2961
Carbohydrate, g (E%)	76 (38)	102 (52)	59 (38)	59 (38)	51 (29)	51 (29)
Protein, g (E%)	31 (16)	29 (14)	45 (29)	45 (29)	12 (7)	12 (7)
Fat, g (E%)	40 (46)	30 (34)	23 (33)	23 (33)	50 (64)	50 (64)

E%, percentage of total energy; FF-meal, fast-food meal; PUFA-meal, polyunsaturated fatty acid meal; REC-meal, meal macronutrient composition followed dietary guidelines; SFA-meal, saturated fatty acid meal.

[1] Barley porridge prepared with low-fat (1.5% fat) milk.
[2] Raspberry jam, Menu Vadelmahillo; Roberts Ltd, Finland.
[3] Orange juice, Vip Appelsiini täysmehu; Vip-Juicemaker Ltd, Finland.
[4] Wholegrain rye bread, REAL-ruisleipä; Fazer Ltd, Finland.
[5] Keiju margarine 70%; Raisio Ltd, Finland.
[6] Aamu cheese 5%; Arla Ltd, Finland.
[7] Dumle cocoa powder; Fazer Ltd, Finland.
[8] McDonalds Ltd, Finland.
[9] Whey protein isolate (protein content 89 g/100 g); Glanbia Nutritionals, Ireland.
[10] Calcium caseinate I (protein content 90 g/100 g); DMW International, the Netherlands.
[11] Milk powder (fat-free, lactose-free); Valio Ltd, Finland.
[12] White bread, Vaasan Iso Paahto - vehnä; Vaasan&Vaasan Ltd, Finland.
[13] Butter, lactose-free; Arla Ltd, Finland.
[14] Solid margarine, Keiju Juokseva Rypsiöljyvalmiste; Raisio Ltd, Finland.

4.3.3 Laboratory analysis

Blood glucose was analysed by a glucose meter (HemoCue Glucose 201+ meter; HemoCue LtD, Espoo, Finland) which expresses concentrations as mmol/l of plasma glucose. The HemoCue Glucose system is based on a glucose dehydrogenase method. The mean interassay coefficient of variation (CV) was 0.8%. Blood for determination of plasma TGs, FFAs and insulin were collected in EDTA K2 tubes (Venosafe TM; Terumo Sweden AB, Västra Frölunda, Sweden). Blood for determination of plasma PYY, ghrelin, GLP-1 and GIP (Study IV) were collected in prechilled BD^{TM} P800 tubes (Becton, Dickenson and Company, Franklin Lakes, NJ, USA), containing DPP-4 and other protease inhibitor cocktails. The samples were centrifuged for 15 min at 4000 rpm (Rotofix 32; Hettich Zentrifugen, Tuttlingen, Germany) immediately after sample collection and the separated plasma was stored at –70 °C until analysed.

The plasma concentrations of TGs were measured by an enzymatic glycerol-3-phosphate oxidase method (Abbott Laboratories, Abbott Park, IL, USA), FFAs were measured by an enzymatic colorimetric method (NEFA-HR(2); Wako Chemicals GmbH, Neuss, Germany) and insulin was determined by a chemiluminescent microparticle immunoassay with Abbott reagents. Fasting total cholesterol at baseline was analysed, using an enzymatic method (Abbott Laboratories, Abbott Park, IL, USA). The TG, FFA, insulin and cholesterol laboratory analyses were done, using an Architect ci8200 analyser (Abbott Laboratories, Abbott Park, IL, USA). The interassay CV of TGs at the levels of 1.35 mmol/l and 4.93 mmol/l were 1.7% and 1.3%, and the intra-assay CV was 0.6%. The interassay CV of FFAs at the levels of 0.59 mmol/l and 1.11 mmol/l were 1.8% and 1.7%, and the intra-assay CV varied from 0.3% (low-level control) to 0.8% (high-level control). The CVs of insulin at the levels of 187 pmol/l and 1191 pmol/l were 1.6% and 2.5%, and the intra-assay CV was 1.7%.

PYY (total), ghrelin (active) and GIP (total) were measured with a MILLIPLEX MAP Human Metabolic Hormone Panel kit (HMH-34K), using a Luminex 200 System (Luminex Corporation, Austin, TX, USA). The plasma concentrations of GLP-1 were measured against standards of synthetic GLP-1 7-36-amide, using antiserum code no. 89390 (Orskov et al. 1994). The assay measures the sum of the intact, active hormones and the metabolites generated by DPP-4. The results therefore reflect the secretion of the GLP-1. The interassay CV of PYY was 4% and the intra-assay CV was 12%. The interassay and intra-assay CVs of ghrelin were 7% and 7%, respectively, and the interassay and intra-assay CVs of GIP were 7% and 5%, respectively. The interassay CV of GLP-1 was 6%.

4.3.4 Subjective satiety profile

The casein-meal and whey-meal subjective satiety profiles were measured, using a seven-point visual analogue scale (VAS) (Holt and Miller 1995). The participants rated their satiety immediately before each blood sample was drawn. The categories were scored from 0 'I am extremely hungry' through 3 'No particular feeling' to 6 'I am extremely full'. The participants were requested to mark a vertical line on the horizontal axis corresponding to their sensations that were the most appropriate at the time.

4.3.5 Statistical methods

The GLP-1 and subjective satiety profiles were measured only in the casein-meal and whey-meal. The 4-h incremental area under the glucose, insulin, TG, PYY, GIP and GLP-1 response curve (IAUC) and the 4-h incremental area over the FFA response curve (IAOC) were calculated, using a trapezoidal method for each test meal (World Health Organization 1998). In addition, the 2-h glucose, insulin, PYY, GIP and GLP-1 IAUC and the 4-h total area under the curve (totAUC) of the satiety profile and ghrelin were also calculated.

One subject's insulin IAUC results were excluded from the FF-meal analysis because his fasting insulin value was high and differed markedly from his previous study day fasting value as well as the fasting values of all other subjects.

The postprandial responses that were not normally distributed were log-transformed prior to the analyses. An independent sample t-test (Study III) and repeated-measures analysis of variance (ANOVA) (Study IV) were used for testing the differences in postprandial responses between the study groups. If the repeated-measures ANOVA was significant, an independent sample t-test was used to test whether the study groups differed in the different test meals (Study IV). An independent sample t-test was also used for testing the differences in baseline characteristics of the subjects between the study groups. All statistical analyses were carried out with the PASW Statistics version 18 for Windows® (SPSS Inc., Chicago, IL, USA); the level of significance was $P < 0.05$.

The sample size calculation for the postprandial studies was based on our previous study of elderly men and women who belonged to the HBCS (Perälä et al. 2011) and has been calculated for a sensitivity of 0.80 and a two-sided significance level of 0.05, indicating the 12 subjects were sufficient for both study groups. In addition, similar sample size has been used previous postprandial studies in the DOHaD field (Byrne et al. 1997, Kensara et al. 2006).

5 Results

5.1 Body size at birth and food intake (I)

There was no interaction between the effects of sex and PI at birth or birth weight or birth length on food and macronutrient intake, and therefore men and women were analysed together. **Table 6** shows the participants' characteristics at birth and adulthood.

Body size at birth was related to food intake in later life, such that each unit increase in PI at birth was associated with a 13.26-g higher intake of fruits and berries and a 1-kg increase in birth weight with an 83.16-g higher intake of fruits and berries (**Table 7**). Higher PI at birth also predicted higher intake of rye and rye products in adulthood. No other statistically significant associations were observed between PI at birth, birth weight or birth length (**Tables 7 and 9**) and adult-life food intake. Adding physical activity or total energy intake to Model 2 did not attenuate the results (data not shown).

A 1-kg/m^3 increase in PI at birth was associated with a 0.14-E% lower intake of total fat and a 0.06-E% lower intake of monounsaturated fatty acids (MUFAs) (**Table 8**). One unit increase in PI at birth was also associated with a 0.18-E% higher intake of carbohydrates as well as a 0.08-E% higher intake of sucrose, 0.05-E% higher fructose and 0.18-g higher fibre intake in adulthood. Similar associations were observed between birth weight and macronutrient intake (**Table 8**). Birth length was not significantly associated with macronutrient intake or dietary GI or GL in adulthood (**Table 9**). Adding physical activity to Model 2 did not attenuate the results (data not shown).

Table 6. Birth and adult data of the participants [1].

	Men	Women
N	836	961
Birth data		
Weight (g)	3514 (464)	3381 (438)
Gestational age (wk)	40.05 (1.42)	40.14 (1.44)
Length (cm)	50.8 (1.9)	50.1 (1.7)
Ponderal index (kg/m^3)	26.7 (2.3)	26.8 (2.2)
Adult data		
Age (y)	61.5 (2.8)	61.5 (3.1)
Weight (kg)	85.9 (13.6)	74.0 (13.8)
Height (cm)	176.8 (6.0)	163.3 (5.7)
BMI (kg/m^2)	27.5 (4.0)	27.8 (5.0)
Educational attainment [2]		
Basic (%)	39.5	43.7
Secondary (%)	24.0	22.9
Higher (%)	36.4	33.4
Smoker (%) [3]	21.9	15.9
Physically active (%) [4]	46.1	42.6
Dietary intake		
Energy intake (MJ)	10.3 (3.6)	8.6 (3.0)
Carbohydrate (E%)	45.5 (6.7)	47.7 (6.6)
Sucrose (E%)	9.0 (3.4)	9.8 (3.6)
Fat (E%)	33.7 (5.7)	33.1 (5.3)
SFA (E%)	12.2 (2.6)	12.1 (2.6)
MUFA (E%)	11.3 (2.2)	10.9 (2.1)
PUFA (E%)	5.3 (1.2)	5.3 (1.2)
Protein (E%)	16.6 (2.5)	17.4 (2.5)
Alcohol (E%)	4.4 (5.2)	1.9 (2.7)

BMI, body mass index; E%, percentage of total energy intake; MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids; SFA, saturated fatty acids.
[1] Results are expressed as mean (SD) or proportions.
[2] Educational attainment; three categories by approximate years studied (0–9 = basic, 10–12 = secondary, 13 or more = higher).
[3] Smoking one or more cigarettes per day.
[4] Proportion of people who exercised three or more times per week.

Table 7. Association between ponderal index at birth and birth weight and energy-adjusted food intake in adulthood. Mean difference (95% CI) in daily food intake is given to the increase of 1 kg/m^3 in ponderal index at birth or 1 kg in birth weight (n = 1797).

	Ponderal index (kg/m^3)				Birth weight (kg)			
Food group (g)	**Model 1 Regression coefficients (95% CI)**	***P***	**Model 2 Regression coefficients (95% CI)**	***P***	**Model 1 Regression coefficients (95% CI)**	***P***	**Model 2 Regression coefficients (95% CI)**	***P***
Cereals	1.44 (-1.10, 3.97)	0.27	1.77 (-0.80, 4.33)	0.18	5.62 (-6.78, 18.03)	0.37	6.51 (-6.70, 19.71)	0.33
Rye products	1.41 (0.06, 2.76)	0.041	1.54 (0.16, 2.91)	0.028	6.43 (-0.18, 13.03)	0.057	6.77 (-0.31, 13.84)	0.061
Wheat products	-0.09 (-1.80, 1.62)	0.92	-0.21 (-1.94, 1.53)	0.81	0.60 (-7.78, 8.98)	0.89	-0.22 (-9.18, 8.73)	0.96
Fruits and berries	10.90 (-1.93, 23.74)	0.096	13.26 (0.56, 25.96)	0.041	68.98 (6.18, 131.78)	0.031	83.16 (17.76, 148.56)	0.013
Vegetables and roots	2.75 (-4.86, 10.36)	0.48	2.62 (-5.10, 10.35)	0.51	2.45 (-34.80, 39.70)	0.90	-4.53 (-44.31, 35.24)	0.82
Potato products	-3.02 (-6.73, 0.69)	0.11	-3.49 (-7.17, 0.19)	0.063	-11.28 (-29.46, 6.90)	0.22	-16.53 (-35.51, 2.45)	0.088
Fish products	-1.27 (-3.19, 0.65)	0.19	-1.37 (-3.33, 0.60)	0.17	-2.28 (-11.90, 7.34)	0.64	-3.22 (-13.59, 7.15)	0.54
Total meat	0.09 (-3.81, 3.99)	0.96	-1.51 (-5.34, 2.32)	0.44	5.10 (-13.97, 24.16)	0.60	-8.14 (-27.84, 11.56)	0.42
Red meat	0.69 (-2.82, 4.19)	0.70	-1.01 (-4.45, 2.42)	0.56	-1.82 (-15.32, 18.96)	0.84	-9.93 (-27.60, 7.74)	0.27
Processed meat	-0.07 (-2.16, 2.02)	0.95	-1.13 (-3.03, 0.78)	0.25	-1.00 (-11.20, 9.20)	0.85	-8.30 (-18.11, 1.52)	0.097
Milk products	5.57 (-7.80, 18.95)	0.41	5.08 (-8.57, 18.72)	0.47	10.47 (-55.38, 76.32)	0.76	19.14 (-51.55, 89.83)	0.60
Fats	0.24 (-0.41, 0.90)	0.47	0.20 (-0.46, 0.86)	0.55	0.85 (-2.37, 4.07)	0.61	0.43 (-2.99, 3.86)	0.80
Butter	0.08 (-0.46, 0.61)	0.78	0.06 (-0.48, 0.60)	0.83	0.51 (-2.09, 3.11)	0.70	0.62 (-2.14, 3.38)	0.66
Margarine	0.21 (-0.15, 0.56)	0.25	0.20 (-0.17, 0.56)	0.29	0.01 (-1.73, 1.75)	0.99	0.12 (-1.75, 1.99)	0.90
Sugar and confectionery	0.12 (-0.97, 1.21)	0.83	0.27 (-0.84, 1.38)	0.63	3.29 (-2.03, 8.61)	0.23	4.89 (-0.81, 10.60)	0.093

95% CI; 95% confidence interval.
Model 1: Adjusted for sex and current age, tested by linear regression model.
Model 2: Adjusted for sex, current age and body mass index, education, smoking and gestational age, tested by linear regression model.

Table 8. Association between ponderal index at birth and birth weight and nutrient intake in adulthood. Mean difference (95% CI) in daily nutrient intake is given to the increase of 1 kg/m^3 in ponderal index at birth or 1 kg in birth weight (n = 1797).

	Ponderal index (kg/m^3)				Birth weight (kg)			
Nutrient intake	**Model 1 Regression coefficients (95% CI)**	***P***	**Model 2 Regression coefficients (95% CI)**	***P***	**Model 1 Regression coefficients (95% CI)**	***P***	**Model 2 Regression coefficients (95% CI)**	***P***
Energy (kJ)	27.9 (-41.1, 97.0)	0.43	22.0 (-48.2, 92.2)	0.54	247.7 (-90.7, 586.2)	0.15	221.0 (-140.6, 582.6)	0.23
Carbohydrates (E%)	0.14 (-0.01, 0.28)	0.055	0.18 (0.04, 0.32)	0.010	0.36 (-0.32, 1.04)	0.30	0.57 (-0.15, 1.29)	0.12
Fructose (E%)	0.04 (0.00, 0.09)	0.051	0.05 (0.01, 0.09)	0.019	0.24 (0.03, 0.45)	0.029	0.27 (0.05, 0.49)	0.017
Sucrose (E%)	0.05 (-0.02, 0.13)	0.18	0.08 (0.00, 0.15)	0.050	0.29 (-0.09, 0.66)	0.13	0.44 (0.04, 0.83)	0.030
Fibre (g) [1]	0.15 (-0.02, 0.32)	0.074	0.18 (0.02, 0.34)	0.031	0.65 (-0.16, 1.46)	0.12	0.78 (-0.06, 1.63)	0.070
Dietary GI	-0.08 (-0.18, 0.01)	0.093	-0.08 (-0.18, 0.02)	0.11	-0.51 (-0.99, -0.03)	0.036	-0.49 (-0.99, 0.02)	0.060
Dietary GL [1]	0.21 (-0.25, 0.67)	0.37	0.35 (-0.11, 0.81)	0.13	-0.22 (-2.45, 2.02)	0.85	0.41 (-1.95, 2.77)	0.73
Protein (E%)	-0.01 (-0.06, 0.04)	0.67	-0.03 (-0.08, 0.03)	0.30	-0.01 (-0.27, 0.25)	0.96	-0.14 (-0.41, 0.14)	0.33
Fat (E%)	-0.11 (-0.22, 0.01)	0.061	-0.14 (-0.26, -0.03)	0.013	-0.39 (-0.95, 0.17)	0.18	-0.62 (-1.21, -0.03)	0.039
SFA (E%)	-0.03 (-0.08, 0.03)	0.35	-0.04 (-0.09, 0.02)	0.20	-0.15 (-0.42, 0.12)	0.27	-0.15 (-0.43, 0.13)	0.30
MUFA (E%)	-0.04 (-0.09, 0.01)	0.076	-0.06 (-0.10, -0.01)	0.015	-0.11 (-0.33, 0.12)	0.35	-0.24 (-0.48, -0.01)	0.039
PUFA (E%)	-0.02 (-0.04, 0.01)	0.22	-0.02 (-0.05, 0.01)	0.11	-0.03 (-0.16, 0.10)	0.63	-0.09 (-0.22, 0.04)	0.19
Alcohol (E%)	-0.01 (-0.10, 0.07)	0.76	-0.01 (-0.09, 0.08)	0.85	0.02 (-0.39, 0.44)	0.91	0.17 (-0.27, 0.61)	0.46

95% CI; 95% confidence interval; E%, percentage of total energy intake; GI, glycaemic index; GL, glycaemic load; MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids; SFA, saturated fatty acids.

Model 1: Adjusted for sex and current age, tested by linear regression model.

Model 2: Adjusted for sex, current age and body mass index, education, smoking and gestational age, tested by linear regression model.

[1] Adjusted for energy by residual method.

Table 9. Association between birth length and food and nutrient intake in adulthood. Mean difference (95% CI) in daily food and nutrient intake is given to the increase of 1 cm in birth length (n = 1797).

	Birth length (cm)			
Foods and nutrients	**Model 1 Regression coefficients (95% CI)**	***P***	**Model 2 Regression coefficients (95% CI)**	***P***
Foods [1]				
Cereals (g)	0.29 (-2.85, 3.44)	0.86	0.14 (-3.20, 3.48)	0.94
Rye products (g)	0.60 (-1.08, 2.28)	0.49	0.49 (-1.31, 2.28)	0.59
Wheat products (g)	0.28 (-1.84, 2.40)	0.80	0.13 (-2.13, 2.39)	0.91
Fruits and berries (g)	9.83 (-6.12, 25.8)	0.23	10.7 (-5.86, 27.3)	0.21
Vegetables and roots (g)	-1.78 (-11.1, 7.54)	0.71	-3.75 (-13.69, 6.18)	0.46
Potato products (g)	-0.97 (-5.57, 3.64)	0.68	-1.47 (-6.28, 3.33)	0.55
Fish products (g)	-0.16 (-2.55, 2.23)	0.90	-0.35 (-2.91, 2.22)	0.79
Total meat (g)	0.99 (-3.85, 5.83)	0.69	-1.12 (-6.11, 3.88)	0.66
Red meat (g)	-0.47 (-4.81, 3.88)	0.83	-2.13 (-6.60, 2.35)	0.35
Processed meat (g)	-0.51 (-3.11, 2.08)	0.70	-1.46 (-3.95, 1.04)	0.25
Milk products (g)	-0.80 (-17.4, 15.8)	0.93	1.19 (-16.6, 19.0)	0.90
Fats (g)	0.05 (-0.77, 0.86)	0.92	-0.11 (-0.97, 0.76)	0.81
Butter (g)	0.09 (-0.57, 0.75)	0.78	-0.01 (-0.66, 0.65)	0.99
Margarine (g)	-0.26 (-0.76, 0.24)	0.31	-0.16 (-0.64, 0.31)	0.50
Nutrients				
Energy (kJ)	40.3 (-45.4, 126.0)	0.36	37.6 (-54.0, 129.1)	0.42
Carbohydrates (E%)	-0.02 (-0.20, 0.15)	0.81	-0.02 (-0.20, 0.16)	0.81
Fructose (E%)	0.03 (-0.02, 0.08)	0.28	0.03 (-0.03, 0.08)	0.35
Sucrose (E%)	0.04 (-0.06, 0.13)	0.45	0.05 (-0.05, 0.15)	0.36
Fibre (g) [1]	0.05 (-0.16, 0.25)	0.65	0.05 (-0.16, 0.27)	0.64
Dietary GI	-0.10 (-0.23, 0.02)	0.09	-0.09 (-0.21, 0.04)	0.19
Dietary GL [1]	-0.33 (-0.90, 0.24)	0.25	-0.30 (-0.90, 0.29)	0.32
Protein (E%)	0.01 (-0.06, 0.07)	0.81	-0.01 (-0.08, 0.06)	0.76
Fat (E%)	-0.01 (-0.15, 0.14)	0.94	-0.03 (-0.18, 0.12)	0.69
SFA (E%)	-0.01 (-0.08, 0.05)	0.68	-0.01 (-0.08, 0.07)	0.91
MUFA (E%)	0.01 (-0.05, 0.07)	0.75	-0.01 (-0.07, 0.05)	0.65
PUFA (E%)	0.01 (-0.03, 0.04)	0.68	-0.01 (-0.04, 0.03)	0.81
Alcohol (E%)	0.01 (-0.09, 0.12)	0.80	0.06 (-0.06, 0.17)	0.32

95% CI; 95% confidence interval; E%, percentage of total energy intake; GI, glycaemic index; GL, glycaemic load; MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids; SFA, saturated fatty acids.

Model 1: Adjusted for sex and current age, tested by linear regression model.

Model 2: Adjusted for sex, current age and body mass index, education, smoking and gestational age, tested by linear regression model.

[1] Adjusted for energy by residual method.

5.2 Early growth, salt intake and blood pressure (II)

Birth weight was inversely associated with unadjusted SBP throughout the study population (ρ = -0.058; P = 0.02) but not with unadjusted DBP (ρ = 0.010; P = 0.71). A positive association between unadjusted salt intake and unadjusted DBP was observed (ρ = 0.070; P = 0.006), but not between unadjusted salt intake and unadjusted SBP (ρ = 0.004; P = 0.89). The best-obtained breakpoint for birth weight was 3050 g and for salt intake 10.0 g (based on an energy intake of 10.5 MJ). The model with the breakpoints was significantly better than the one without breakpoints (adjusted P = 0.003).

Table 10. Birth measurements and adult clinical data [1].

	Men			Women		
	≤ 3050 g	**> 3050 g**	***P*** [2]	**≤ 3050 g**	**> 3050 g**	***P*** [2]
N	105	575		213	619	
Birth data						
Weight (g)	2780 (247)	3619 (374)	< 0.001	2831 (192)	3550 (343)	< 0.001
Gestational age (wk)	38.6 (1.4)	40.2 (1.4)	< 0.001	39.5 (1.7)	40.2 (1.5)	< 0.001
Length (cm)	48.2 (1.7)	51.2 (1.6)	< 0.001	48.5 (1.3)	50.7 (1.4)	< 0.001
Adult data						
Age (y)	62.0 (2.4)	61.5 (2.9)	0.11	61.8 (3.0)	61.6 (3.1)	0.57
Weight (kg)	81.8 (10.1)	84.9 (13.0)	< 0.01	71.4 (13.6)	73.5 (13.2)	0.05
Height (cm)	174.5 (5.1)	177.2 (5.9)	< 0.001	161.4 (5.9)	163.9 (5.5)	< 0.001
BMI (kg/m^2)	26.9 (3.4)	27.0 (3.7)	0.74	27.4 (5.1)	27.4 (4.8)	0.90
DBP (mmHg)	91.1 (9.9)	90.1 (10.6)	0.38	87.2 (10.4)	87.0 (9.9)	0.87
SBP (mmHg)	148.9 (19.7)	144.8 (19.2)	0.05	146.3 (20.6)	143.1 (20.4)	0.05
Antihypertensive medication (%)	38.7	33.7	0.38	41.3	30.5	< 0.01
Salt intake (g/d)	10.7 (3.8)	10.7 (3.4)	0.70	8.8 (3.1)	8.6 (3.0)	0.55

BMI, body mass index; DBP, diastolic blood pressure; SBP, systolic blood pressure.
[1] Results are expressed as mean (SD) or proportions.
[2] Differences between birth weight groups, tested by Student's t-test, except in the case of anti-hypertensive medication, for which Pearson's chi-square test for binomial proportions was applied.

Men and women who were born with low birth weight (≤ 3050 g) were lighter and smaller in adulthood; however, adulthood BMI was similar in low birth weight and higher birth weight groups (**Table 10**). Antihypertensive medication was more common in individuals with low birth weight than those with higher birth weight. Salt intake did not differ significantly between the birth weight groups.

The modifying effect of birth weight on the association between salt intake and SBP did not differ between men and women; therefore, men and women were analysed together. Among participants whose birth weight exceeded 3050 g, salt intake was not significantly related to SBP or DBP. However, among low birth weight subjects (≤ 3050 g), a 1-g higher daily salt intake was associated with a 2.48-mmHg (95% Confidence interval [CI]: 0.40, 4.52; P = 0.025) higher SBP until the saturation point of 10.0 g (**Figure 5**). After the saturation point (10.0 g), SBP was estimated to be 4.72 mmHg higher among the low birth weight group than among the higher birth weight group (95% CI: 1.96, 7.48; P < 0.001). After exclusion of participants taking antihypertensive medication from the analyses (data included 1000 participants), the modifying effect of birth weight on the association between salt intake and SBP became smaller and was not statistically significant (1.20 mmHg; P = 0.42). Among low birth weight subjects, salt intake was not significantly associated with DBP.

Excluding subjects whose gestational age at birth was under 37 completed weeks or over 44 completed weeks had only a minor effect on the results. In the low birth weight group, a 1-g increase in salt intake was associated with a 1.30-mmHg (95% CI: 0.01, 2.59; P = 0.048) higher SBP but not with DBP. Among the high birth weight group, salt intake was significantly associated with neither SBP nor DBP.

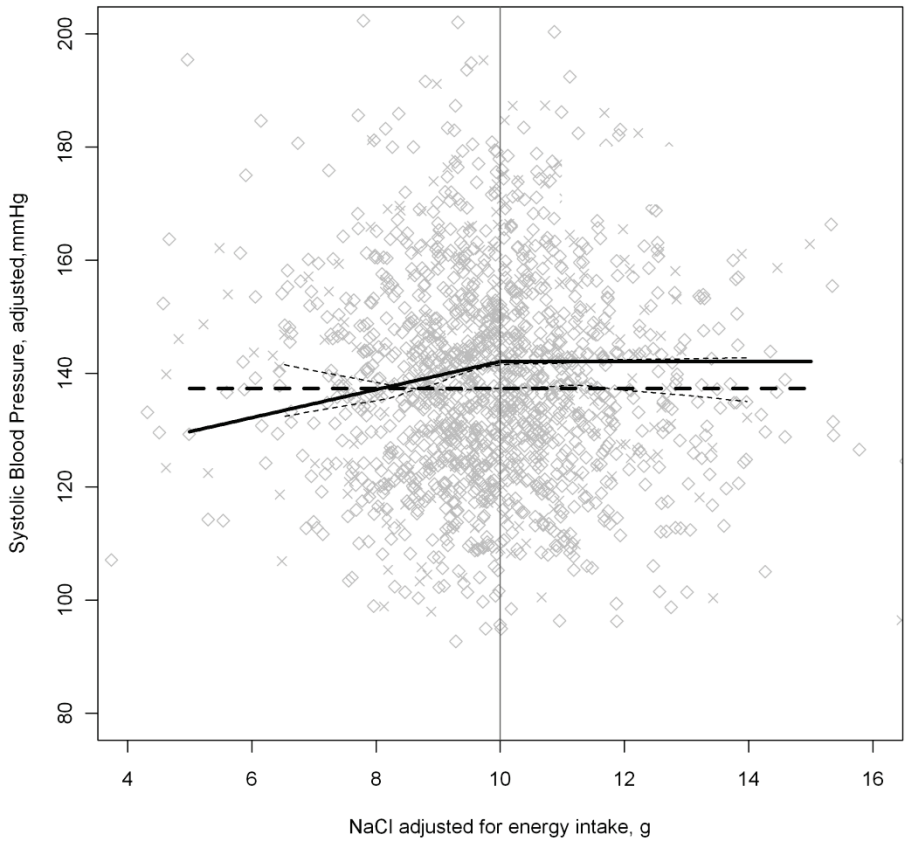


Figure 5. Association between energy-adjusted salt (NaCl) intake and systolic blood pressure among subjects with birth weight ≤ 3050 g (x = observed value, solid bold line = fitted model (linear regression with flexible breakpoint) and birth weight > 3050 g (o = observed value, dashed bold line = fitted model) (n = 1512). The thin dotted lines, obtained by locally weighted scatter plot smoothing (LOWESS method), are given for comparison. Reprinted from the American Journal of Clinical Nutrition 2011; 93:422–6, Perälä et al. "The association between salt intake and adult systolic blood pressure is modified by birth weight", with permission from the American Society for Nutrition.

5.3 Early growth and postprandial responses (III, IV)

5.3.1 Characteristics

The basic characteristics of the study participants are shown in **Table 11**. Five subjects in the SGI and four subjects in the control group used lipid-lowering medications (statins). Seven participants in the SGI and five participants in the control group had impaired glucose tolerance (2-h glucose ≥ 7.8 mmol/l).

Table 11. Characteristics of the postprandial studies participants [1].

	SGI (III, IV)	Control group (III)	Control group (IV)
N (men, women)	12 (6,6)	12 (7,5)	12 (6,6)
Birth and childhood data			
Birth weight (g)	3129 (360)	3648 (399) [2]	3597 (469) [2]
Birth length (cm)	49.6 (2.4)	51.3 (0.9)	51.0 (1.5)
Birth BMI (kg/m^2)	12.7 (1.0)	13.9 (1.3) [2]	13.8 (1.3) [2]
Gestational age (wk)	39.9 (1.3)	40.6 (1.0)	40.3 (1.9)
Z-score BMI at birth	-0.66 (0.85)	0.33 (1.0) [2]	0.26 (1.1) [2]
Weight at 1 y (kg)	8.9 (0.7)	10.9 (0.6) [3]	10.8 (0.7) [3]
Height at 1 y (cm)	74.7 (3.1)	77.1 (1.0) [2]	76.9 (1.4) [2]
BMI at 1 y (kg/m^2)	15.9 (0.5)	18.3 (0.7) [3]	18.3 (0.8) [3]
Z-score BMI at 1 y	-1.34 (0.34)	0.46 (0.47) [3]	0.44 (0.49) [3]
Conditional growth	-1.23 (0.28)	0.40 (0.32) [3]	0.40 (0.32) [3]
Adult data			
Age (y)	68.0 (2.13)	68.1(3.23)	68.2 (3.38)
Weight (kg)	75.5 (9.5)	80.5 (9.0)	80.5 (9.8)
Height (cm)	167.1 (10.0)	173.8 (7.5)	172.9 (8.6)
BMI (kg/m^2)	27.0 (2.78)	26.7 (2.94)	27.0 (3.08)
Waist circumference (cm)	90.1 (9.7)	92.2 (10.2)	91.6 (9.8)
OGTT fasting glucose (mmol/l)	5.39 (0.39)	5.68 (0.50)	5.63 (0.47)
OGTT glucose 2-h (mmol/l)	8.03 (1.43)	7.91 (1.20)	7.77 (1.03)
Fasting cholesterol (mmol/l)	5.06 (0.72)	4.70 (0.85)	4.72 (0.84)

BMI, body mass index; OGTT, oral glucose tolerance test; SGI, group with slow growth during infancy.
[1] Results are expressed as mean (SD).
[2] Differed significantly from the SGI, $P < 0.05$.
[3] Differed significantly from the SGI, $P < 0.001$.

5.3.2 Glucose and insulin responses

The 2-h and 4-h glucose responses did not differ significantly between the study groups. After ingestion of all the test meals, the concentration of plasma glucose increased for 30 min, declining thereafter and returning towards the fasting concentrations after 60–90 min (**Table 12, Figure 6**).

Growth during infancy affected the insulin postprandial responses and the groups differed significantly. The insulin 2-h and 4-h responses were significantly higher after the FF-meal (P = 0.082 and P = 0.036, respectively), the casein-meal (P = 0.031 and P = 0.023, respectively), the whey-meal (P = 0.066 and P = 0.037, respectively) and after the PUFA-meal (P = 0.008 and P = 0.002, respectively) for the SGI than for the control group. In addition, the insulin 2-h and 4-h responses were also higher after the REC-meal (P = 0.37 and P = 0.23) and the SFA-meal (P = 0.073 and P = 0.61) for the SGI than for the controls, although the differences were not statistically significant (**Table 12, Figure 6**). Excluding subjects who had impaired glucose tolerance from the analysis did not have major effect on the glucose or insulin results (data not shown).

Table 12. Glucose and insulin responses (IAUC) after test meals[1].

	FF-meal	REC-meal	Casein-meal	Whey-meal	SFA-meal	PUFA-meal
SGI Glucose 2-h	101 (18)	69 (16)	83 (22)	55 (16)	55 (13)	72 (17)
Controls Glucose 2-h	118 (26)	126 (31)	53 (13)	48 (11)	67 (13)	43 (9)
SGI Glucose 4-h	113 (17)	76 (12)	105 (24)	88 (23)	80 (20)	103 (16)
Controls Glucose 4-h	139 (31)	166 (41)	81 (19)	81 (14)	103 (24)	77 (12)
SGI Insulin 2-h	40 319 (6290)	50 492 (7792)	49 192 (6817)[2]	57 524 (9066)	27 083 (3644)	27 869 (5563)[2]
Controls Insulin 2-h	24 925 (4897)[3]	40 406(7669)	30 366 (5721)	38 115 (8200)	17 314 (2359)	13 508 (1485)
SGI Insulin 4-h	53 458 (8763)[2]	70 843 (10 699)	66 607(10 168)[2]	81 107 (13 418)[2]	33 469 (4824)	35 227 (6885)[2]
Controls Insulin 4-h	29 849 (5613)[3]	54 206 (10 711)	38 636 (6946)	52 570 (11 881)	21 608 (3150)	19 203 (3203)

FF-meal, fast-food meal; IAUC, incremental area under the curve; PUFA-meal, polyunsaturated fatty acid meal; REC-meal, meal macronutrient composition followed dietary guidelines; SFA-meal, saturated fatty acid meal; SGI, group with slow growth during infancy.

[1] Results are mean (standard error of the mean); Glucose responses are expressed as mmol·min/l and insulin responses are expressed as pmol·min/l; Glucose and insulin responses were log-transformed prior to the analyses.

[2] Differed significantly from the controls, $P < 0.05$, tested by an independent sample t-test.

[3] n = 11.

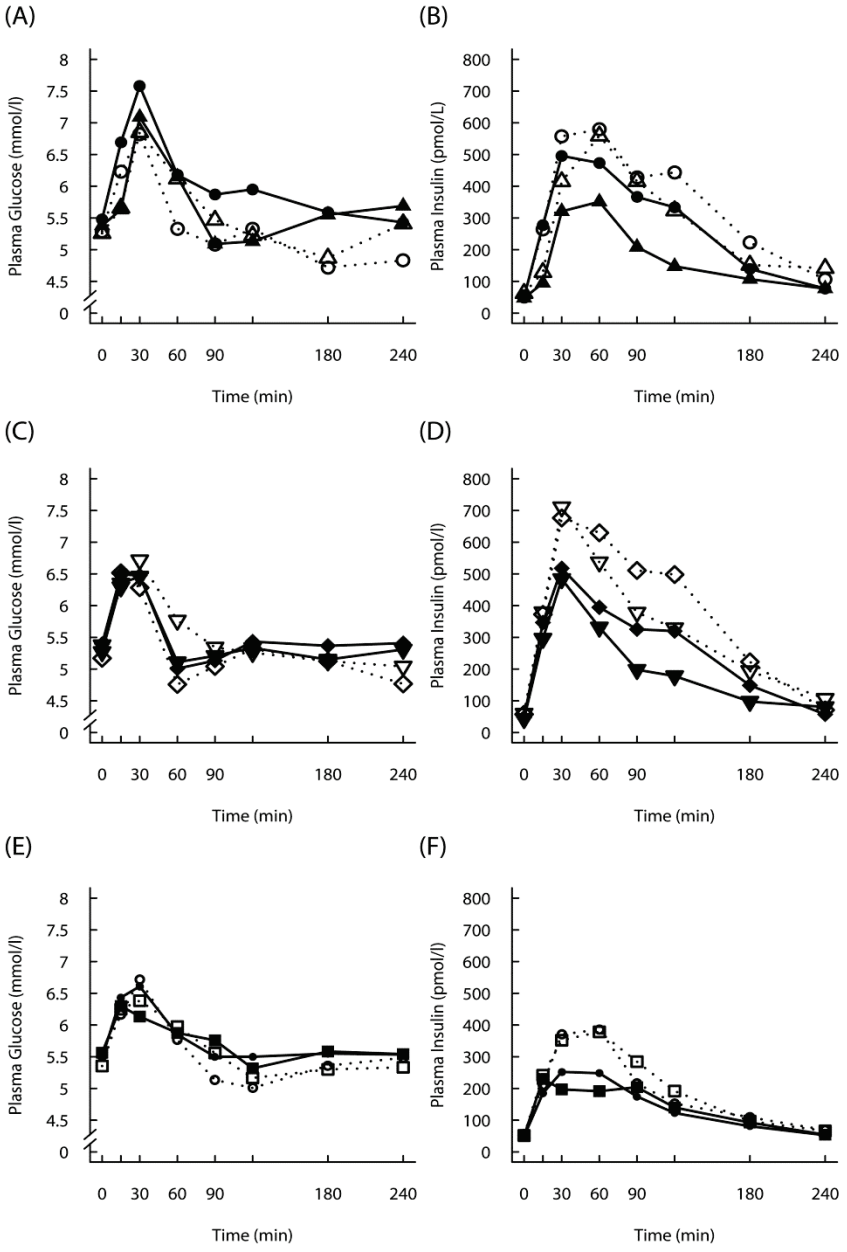


Figure 6. Mean responses of plasma A) glucose and B) insulin to a fast-food-meal (Δ ,▲) and a meal in which the macronutrient composition was according to dietary guidelines (○,●), C) glucose and D) insulin to a casein-meal (▽ ,▼)and whey-meal (◊,♦), and E) glucose and F) insulin to a saturated fatty acid meal (◦,•) and a polyunsaturated fatty acid meal (□,■) for subjects with slow growth during infancy (white marks) and for the control group (black marks).

5.3.3 Triglycerides and free fatty acids

After each test meal, the TG concentrations increased and were highest 3–4 hours after the start of the meal (**Figure 7**). Early growth affected the TG responses. The 4-h TG responses were significantly higher for the SGI than for the controls after the FF-meal (P = 0.047) and the PUFA-meal (P = 0.006) (**Table 13**). The TG responses of the REC-meal (P = 0.058), casein-meal (P = 0.158), whey-meal (P = 0.053) and SFA-meal (P = 0.074) were also higher for the SGI compared with the controls, although the differences were not statistically significant. Excluding subjects who used statins in the analysis did not have major effect on the results (data not shown).

Early growth did not significantly affect the postprandial FFA responses (**Table 13**). All the study meals suppressed the FFAs initially and reached nadir within 60–90 min.

Table 13. Postprandial triglyceride (TG) and free fatty acid (FFA) responses of the test meals[1].

	FF-meal	REC-meal	Casein-meal	Whey-meal	SFA-meal	PUFA-meal
SGI TG 4-h IAUC	101(15)[2]	107 (12)	59 (9)[3]	70 (11)[3]	132 (18)[3]	154 (21)[2, 3]
Controls TG 4-h IAUC	66 (8)	76 (10)	44 (8)[3]	45 (10)[3]	88 (12)[3]	91 (10)[3]
SGI FFA 4-h IAOC	67 (12)	64 (10)	71 (13)	59 (10)	31 (9)	36 (11)
Controls FFA 4-h IAOC	78 (14)	75 (9)	55 (9)	89 (12)	38 (7)	41 (9)

FF-meal, fast-food meal; IAOC, incremental area over the curve; IAUC, incremental area under the curve; PUFA-meal, polyunsaturated fatty acid meal; REC-meal, meal macronutrient composition followed dietary guidelines; SFA-meal, saturated fatty acid meal; SGI, group with slow growth during infancy.

[1] Results are mean (standard error of the mean), expressed as mmol·min/l.

[2] Differed significantly from the controls, $P < 0.05$, tested by an independent sample t-test.

[3] Postprandial responses were log-transformed prior to the analyses.

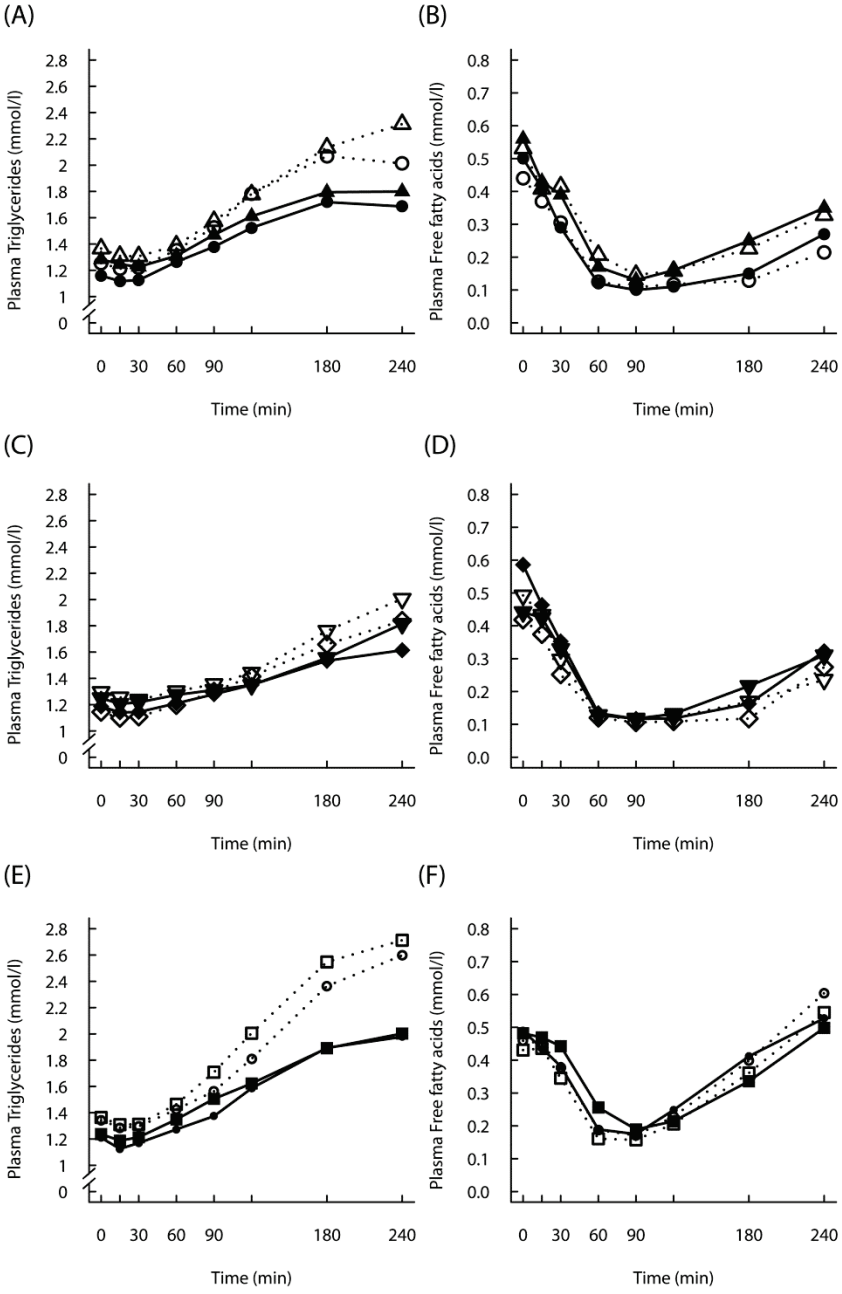


Figure 7. Mean responses of plasma A) triglycerides (TG) and B) free fatty acids (FFA) to a fast-food-meal (Δ,▲) and a meal in which the macronutrient composition was according to dietary guidelines (○,●), C) TG and D) FFA to a casein-meal (▽,▼) and whey-meal (◊,♦), and E) TG and F) FFA to a saturated fatty acid meal (○,●) and a polyunsaturated fatty acid meal (□,■) for subjects with slow growth during infancy (white marks) and for the control group (black marks).

5.3.4 Appetite-related outcomes (PYY, ghrelin, satiety profiles)

The postprandial concentration of PYY increased and ghrelin decreased after consumption of the test meals (**Figure 8, Table 14**). The PYY responses were slightly higher for the SGI than for the controls; however, only the 2-h responses differed significantly between the study groups after the casein-meal (P = 0.025) and the whey-meal (P = 0.046). Early growth had no effect on the postprandial ghrelin responses. Measures of subjective satiety (VAS) increased after ingestion of the high-protein test meals, reaching peak values by 30–60 min and declining thereafter. The 4-h VAS response curves were slightly, but not significantly, higher for the SGI than for the control group (**Table 14, Figure 9**).

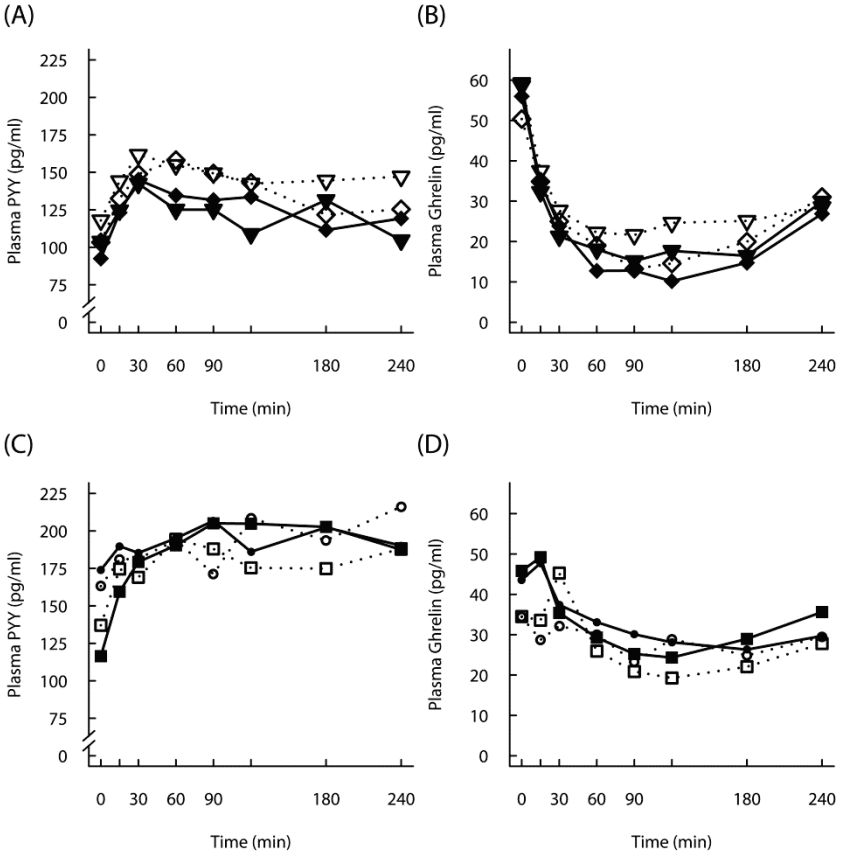


Figure 8. Mean responses of plasma A) peptide YY (PYY) and B) ghrelin to a casein-meal (▽,▼) and whey-meal (◊,♦) and C) PYY and D) ghrelin to a saturated fatty acid meal (○,●) and a polyunsaturated fatty acid meal (□,■) for subjects with slow growth during infancy (white marks) and for the control group (black marks).

5.3.5 GLP-1 and GIP responses

Neither the fasting concentrations nor the postprandial responses of GLP-1 or GIP differed significantly between the study groups. The postprandial concentration of GLP-1 peaked at 120 min and GIP at 60–90 min after the study meals (**Figure 9, Table 14**).

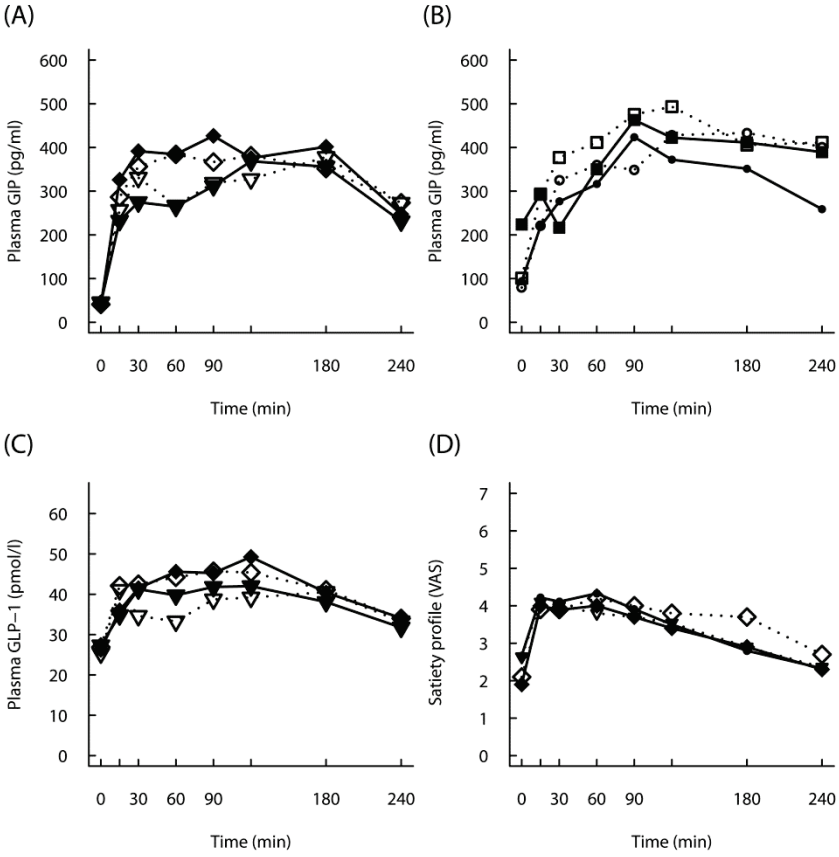


Figure 9. Mean responses of plasma glucose-dependent insulinotropic peptide (GIP) to A) a casein-meal (▽,▼) and whey-meal (◊,♦) and B) a saturated fatty acid meal (○,●) and a polyunsaturated fatty acid meal (□,■), and C) plasma glucagon-like peptide 1 (GLP-1) and D) satiety profile to a casein-meal (▽,▼) and whey-meal (◊,♦) for subjects with slow growth during infancy (white marks) and for the control group (black marks).

Table 14. Appetite regulatory hormone and incretin 2-h and 4-h postprandial responses after the test meals [1].

	Casein-meal		Whey-meal		SFA-meal		PUFA-meal		
	SGI	**Controls**	**SGI**	**Controls**	**SGI**	**Controls**	**SGI**	**Controls**	***P*** [2]
PYY 2-h IAUC (pg·min/l) [3]	6876 (1549) [4]	3196 (994)	6880 (830) [4]	4772 (977)	6218 (1428)	3229 (848)	7097 (1222)	8849 (1682)	0.005
PYY 4-h IAUC (pg·min/l) [3]	11 300 (2895)	6151 (1646)	11 010 (1898)	8042 (1536)	15 537 (5589)	8393 (1952)	15 955 (3373)	20 944 (4086)	0.15
Ghrelin 4-h totAUC (pg·min/l) [3]	6410 (1469)	5081 (1033)	5213 (1033)	4390 (746)	6673 (1104)	7515 (857)	6156 (1056)	7347 (576)	0.95
Satiety profile 4-h totAUC	803 (56)	777 (57)	882 (68)	781 (62)	-	-	-	-	0.35
GIP 2-h IAUC (pg·min/l)	26 990 (3218)	26 818 (4653)	35 222 (4519)	36 445 (7063)	31 376 (4682)	34 776 (9228)	35 848 (6324)	21 034 (5421)	0.78
GIP 4-h IAUC (pg·min/l)	63 734 (6139)	61 819 (9387)	71 880 (7896)	77 132 (12 001)	72 576 (9128)	72 323 (14 593)	81 344 (13 974)	56 530 (11 113)	0.70
GLP-1 2-h IAUC (pmol·min/l) [3]	2283 (925)	1466 (353)	1810 (400)	2058 (422)	-	-	-	-	0.86
GLP-1 4-h IAUC (pmol·min/l) [3]	4312 (1369)	2743 (619)	3587 (676)	3765 (671)	-	-	-	-	0.29

GIP, glucose-dependent insulinotropic peptide; GLP-1, glucagon-like peptide 1; IAUC, incremental area under the curve; PUFA-meal, polyunsaturated fatty acid meal; PYY, peptide YY; SFA-meal, saturated fatty acid meal; SGI, group with slow growth during infancy; totAUC, total area under the curve.

[1] Results are expressed as mean (standard error of the mean).

[2] Differences between the groups tested by repeated-measures ANOVA.

[3] Postprandial responses were log-transformed prior to the analyses.

[4] Differed significantly from the controls, $P < 0.05$. Tested an independent sample t-test if repeated-measures ANOVA were significant ($P < 0.05$).

6 Discussion

6.1 Birth size as a modifying factor

6.1.1 Food and macronutrient intakes

Diet plays an important and independent role in the development of several metabolic diseases. Although prenatal growth is strongly linked with these diseases, few studies have investigated whether prenatal growth is related to dietary habits.

We observed that body size at birth was positively related to consumption of fruits and berries, and rye and rye products in Finnish men and women aged 56 to 70. In addition, body size at birth was positively related to intake of carbohydrates, sugars, and fibre and inversely associated with intake of fat. Our findings indicate that prenatal growth may modify food intake in adult life, which may subsequently affect health outcomes in later life. The relationship between prenatal growth and food and nutrient intake later in life may be due to alterations of several physiologic and sensory factors (Ayres et al. 2012, Bayol et al. 2007, Beauchamp and Moran 1982, Breton et al. 2009, Erhuma et al. 2007, Mennella et al. 2001, Nakamura et al. 2008, Shigemura et al. 2004, Stein et al. 2006, Umabiki et al. 2010) that affect food choices.

Our findings are in agreement with previous studies in which low birth weight or famine during prenatal life was associated with higher intake of fat in children (Shultis et al. 2005, Stafford and Lucas 1998) and adults (Lussana et al. 2008, Stein et al. 2009). In contrast findings was observed Barbieri et al. (2009) who demonstrated that in Brazilian women severe intrauterine growth retardation was related to higher intake of carbohydrates. Differences in diet between study populations may, however, at least partly explain the inconsistent findings between the studies. Moreover, one study showed that Finnish adults who were born with very low birth weight consumed less fruits and vegetables than the controls (Kaseva et al. 2013). In that study, the difference between preterm and controls in the consumption of fruits and vegetables was about 60 g/d.

In our study population, carbohydrate intake was on average 2 E% lower than has been reported in Finnish adults in the FINDIET 2007 study (Paturi et al. 2008, Pietinen et al. 2010). In addition, women's fat intake and men's alcohol intake were higher in our study cohort than in the FINDIET 2007 study. However, the macronutrient intakes in our study population do meet the current Nordic Nutrition recommendations (Nordic Council of Ministers 2013), except for the SFA intake, which exceeded the recommended level.

In our study, a 1-kg increase in birth weight was associated with an about 80-g increase in daily intake of fruits and berries. Low consumption of fruits and berries reflects an unhealthy diet, which may increase the risk of CVD (Dauchet et al. 2009). Indeed, the importance of low fruit and berry intake as well as vegetable intake is highlighted by the WHO (Lopez et al. 2006), and is estimated to be the sixth major risk factor for death worldwide, thus causing a higher proportion of attributable deaths than overweight or physical inactivity. We suggest that low consumption of fruits and berries may be one explanation behind the association between small body size at birth and increased risk for metabolic diseases.

In addition to fruit and berries, low consumption of rye products has also been linked to an increased risk of CVD (Leinonen et al. 2000, Pietinen et al. 1996, Söderholm et al. 2012). In Finland, rye products are the major source of fibre. Based on the national FINDIET 2007 study, about half of the fibre intake in men and over a third in women were derived from rye bread (Paturi et al. 2008). Therefore, we propose that the positive association between body size at birth and fibre intake was mostly due to higher consumption of rye products.

6.1.2 Salt intake and blood pressure

The association between low birth weight and elevated blood pressure in later life has been well established (Gamborg et al. 2007). The association between birth weight and SBP, but not with DBP, was observed in our study as well. A previous report from the HBCS also demonstrated that those participants who had a diagnosis of hypertension in adulthood had a lower birth weight, were shorter in length and had a lower BMI at birth than did those with no diagnosis of hypertension (Eriksson et al. 2007).

We observed a relationship between salt intake and SBP in adult subjects with a birth weight of 3050 g or less, but not in subjects with higher birth weight. This finding supports two previously published intervention studies, in which low birth weight individuals had higher salt sensitivity to blood pressure in adulthood (de Boer et al. 2008) as well as in childhood (Simonetti et al. 2008). Increased salt sensitivity to blood pressure may well be explained by several alterations in kidney functioning that have been demonstrated in low birth weight individuals (Hallan et al. 2008, Hinchliffe et al. 1992, Hughson et al. 2003, Hughson et al. 2008, Manalich et al. 2000, Zidar et al. 1998). These results suggest that due to increased salt sensitivity, individuals with low birth weight may especially benefit from a reduction in dietary salt intake.

One previous study of young infants showed that birth weight was inversely related to salty taste preference, which could lead to increased salt intake (Stein et al. 2006). We did not observe differences in salt intake between birth weight groups.

Therefore, we do not believe that, at least in our study, elevated blood pressure of low birth weight individuals was due to their preference for salty foods.

We found that in those who were born with low birth weight, a 1-g higher daily salt intake resulted in a 2.48-mmHg increase in SBP. In any population, even small differences in blood pressure have a high impact. For example, it was shown that even a 2-mmHg reduction in SBP among adults could decrease stroke mortality by about 10% and ischaemic heart disease or other vascular causes of mortality by about 7% (Lewington et al. 2002). In addition, it has been estimated that decreasing daily salt intake by 1 g and replacing 1 E% of SFA by 1 E% PUFA could lead to 8000–13 000 preventable CVD cases in Finnish adults during the next 20 years (Martikainen et al. 2011). Therefore, even a small persistent reduction in salt intake and thus in blood pressure could have major implications for public health. In our study population, salt intake was 2–4 g higher than the daily recommended intake (National Nutrition Council 2005, Nordic Council of Ministers 2013). Therefore, if participants who were born with low birth weight were to decrease their salt intake to the recommended level, their SBP could, in theory, decrease by at least 5 mmHg, leading to a major impact in cardiovascular health.

6.2 Early growth and postprandial responses

6.2.1 Glucose, insulin and incretin responses

Strong epidemiological evidence is available that low birth weight or small body size in infancy is associated with elevated fasting glucose and lipid levels. Less has been reported on whether early growth affects postprandial responses as well.

We showed that birth size and growth during infancy have a major impact on adult postprandial insulin responses. In particular, both high-protein meals produced 1.5-fold greater insulin responses for the SGI-group than for the controls, despite similar adult anthropometric characteristics. Although insulin responses were significantly greater within the SGI-group, neither fasting levels nor postprandial responses of glucose differed between groups. It is, however, known that glucose homeostasis remains relatively normal for long periods of time, despite the development of hyperinsulinaemia or insulin resistance.

Our finding is in line with a previous study in which higher postprandial insulin responses were observed among low birth weight participants compared with the age- and sex-matched controls after a standardized breakfast (Schou et al. 2005). Elevated insulin responses indicate insulin resistance. Previous studies have also reported increased insulin responses and impaired insulin sensitivity among low birth weight participants after intravenous or oral glucose tolerance testing

(Newsome et al. 2003). Impaired insulin sensitivity could be the cause of multiple abnormalities in their insulin-sensitive tissues, including muscles and adipose tissues (Boiko et al. 2005, Eriksson et al. 2002, Jensen et al. 2007, Jensen et al. 2008, Maiorana et al. 2007, Taylor et al. 1995). We did not, however, find evidence to support the recent hypothesis that prenatal or postnatal growth reduces insulin secretion. However, the postprandial design used is not the optimal way for testing insulin secretions.

We detected no effect of early growth on fasting or postprandial incretin levels, although insulin responses were significantly greater in SGI. This finding is in line with a previous study by Schou et al. (2005), who found that subjects with low birth weight had higher insulin responses than did matched normal birth weight participants, whereas the GLP-1 and GIP responses did not differ between the groups. It has been observed that GLP-1 concentrations after a meal are reduced in type 2 diabetics, whereas individuals with impaired glucose tolerance have only slightly reduced incretin secretion (Nauck et al. 2011). In addition, recently published meta-analysis showed that type 2 diabetics do not display reduced GLP-1 secretion; only type 2 diabetics who have poorer glycaemic control may have reduced GLP-1 secretion (Calanna et al. 2013). Therefore, it is unlikely that growth retardation during early life alone affects incretin levels. Thus, even though individuals who grow slowly during prenatal life have an increased risk of developing type 2 diabetes (Whincup et al. 2008), incretins do not play a key role in disease risk.

Insulin resistance (Bansilal et al. 2007) as well as elevated fasting and nonfasting insulin levels (Kopp 2006, Sarwar et al. 2007) are associated with an increased risk of CVD. Studies have shown that elevated insulin levels can be directly atherogenic (Kopp 2006, Yu et al. 2011a). Insulin resistance may also cause elevated postprandial TG levels and thus cause atherosclerosis through dyslipidemia (Pansuria et al. 2012). We, therefore, propose that our findings of elevated postprandial insulin levels could be one mechanism underlying the increased risk of CVD in individuals who were small at birth and who grew slowly during infancy.

6.2.2 Triglycerides and free fatty acids responses

We observed that the postprandial TG responses were significantly greater, particularly, after high-fat meals, for the SGI-group than for the controls. No differences were seen between groups in either fasting TG concentrations or fasting FFA or FFA postprandial responses. Thus, elevated TG responses were not the result of increased adipose tissue lipolysis in the late postprandial state. Elevated TG responses indicate that individuals who grow slowly during early life have altered lipid metabolism. Restricted liver growth during early life may permanently alter

liver functioning and lipid metabolism, as detected and reported in animal studies (Burns et al. 1997, Lane et al. 2001, Winick and Noble 1966). Excess lipid content in the liver may also cause elevated postprandial lipid responses and insulin resistance. Studies have shown that non-alcoholic fatty liver disease is more common in adults who were born with small body size or were small at infancy (Fraser et al. 2008, Sandboge et al. 2013). Therefore, elevated TG responses could be the result of non-alcoholic fatty liver disease as well.

Our results differ from those of Byrne et al. (1997) and Kensara et al. (2006), who found no effect of birth weight on postprandial TG and FFA responses in elderly men and women. Unlike these two studies in which the effect of birth weight was investigated, we investigated the effect of early growth on postprandial responses and our participants were small at birth as well as at infancy. It was previously reported that prenatal growth has only a moderate effect on fasting TG levels (Huxley et al. 2004), whereas postnatal growth has a much greater effect (Kajantie et al. 2008). Therefore, we suggest that our observed elevated TG responses were mostly due to growth retardation during infancy.

It is well known that elevated postprandial lipid levels are closely related to a number of metabolic diseases, including CVD (Bansal et al. 2007, Nordestegaard et al. 2007). Small body size at birth as well as thinness during infancy are also associated with these diseases (Barker 1995, Barker et al. 2005, Eriksson et al. 2007, Huxley et al. 2007, Mu et al. 2012, Osmond et al. 2007, van Abeelen et al. 2011). The associations of birth weight with fasting lipid concentrations are quite modest, compared with the associations between birth weight and disease risk in later life. Since postprandial lipaemia occurs over 4–6 h in healthy individuals, most individuals spend the majority of their waking hours in a postprandial state. In addition, elevated postprandial TG levels are directly atherogenic (Goldberg et al. 2011, Jackson et al. 2012, Kolovou et al. 2011) and cause adverse health effects, such as increase oxidative stress and inflammation (Klop et al. 2012). Therefore, our findings of elevated postprandial TG levels are of significance for the understanding of increased metabolic disease risk among individuals who were born with small body size and who grew slowly during the first year of life.

6.2.3 Appetite regulatory hormones

Epidemiologic evidence is available that subjects who were born with small body size and grew slowly during infancy are less likely to become obese, whereas rapid growth during infancy has been associated with obesity later in life (Baird et al. 2005, Monasta et al. 2010, Monteiro and Victora 2005, Ong and Loos 2006, Schellong et al. 2012, Yu et al. 2011b, Zhao et al. 2012). It has been proposed that the relationship between early growth and obesity is due to alterations in the appetite

regulatory systems, as observed in several animal models (Breton et al. 2009, Coupe et al. 2009, Desai et al. 2007, Ikenasio-Thorpe et al. 2007, Lopez et al. 2005, Lukaszewski et al. 2013, Plagemann et al. 1999, Plagemann et al. 2000a, Plagemann et al. 2000b, Remmers et al. 2008, Schellong et al. 2013, Yousheng et al. 2008).

We showed that the postprandial responses of the appetite regulatory hormone PYY were significantly higher for the SGI-group than for the age-, sex- and BMI-matched controls. This finding may indicate greater satiety responses after a meal among subjects who grow slowly during early life. Greater satiety responses could potentially be one explanation why subjects who born with small body size and grow slowly during infancy are less likely to become obese.

Our results are in accordance with previous studies in young children that showed that infants who were born with low birth weight (Chen et al. 2012, Siahanidou et al. 2005) or born preterm (Berseth et al. 1992, Chen et al. 2012, Siahanidou et al. 2005, Siahanidou et al. 2007) had elevated levels of fasting PYY, reflecting greater satiety. Although early growth influenced the PYY responses in our study, we did not detect differences in ghrelin levels between the groups. Previous results from studies, in which the association between birth weight or weight gain during infancy and fasting levels of ghrelin have been investigated, have also been conflicting (Chen et al. 2012, Darendeliler et al. 2009, Iniguez et al. 2002, Kyriakakou et al. 2009, Larnkjaer et al. 2010, Park 2010, Sahin et al. 2012, Siahanidou et al. 2005).

To date, only one study has investigated the effect of birth weight on postprandial appetite regulatory hormone responses in adulthood (Schou et al. 2005). In that study, birth weight did not influence appetite regulation. However, in contrast to our study, they measured only GLP-1 levels, not other hormones that are involved in appetite regulation. We also saw that early growth did not influence the GLP-1 levels, even though it affected the PYY levels.

In addition to these gut-released appetite regulatory hormones, insulin is also an important satiety signal (Flint et al. 2007). Elevated postprandial insulin levels have found to reflect higher satiety feelings (Flint et al. 2007). Therefore, our observed elevated postprandial insulin responses in the SGI-group may thus also reflect greater satiety feelings in the postprandial state. However, it remains to be seen whether these alterations in PYY levels, as well as insulin levels, also reduce meal sizes in normal life and thus decrease the risk for developing obesity.

6.3 Strengths and limitations

6.3.1 Birth cohort and clinical epidemiological studies

The main strength of the clinical epidemiological studies of this thesis was the use of a large, well-characterized study cohort consisting of both men and women. In addition, birth data were obtained from reliable medical records and were not based on merely recalled values.

Our study cohort was restricted to people who were born in Helsinki University Central Hospital and who had attended child welfare clinics in Helsinki. The majority of children attended these clinics at that time. In addition, the participation rate of the clinical examination was 69% of those invited. However, the participants may not have represented the entire population living in Helsinki at that time. The social class distribution of the children in our study cohort, as defined by fathers' occupations, was similar to that in Helsinki as a whole. In addition, participants in the clinical examinations did not differ significantly from nonparticipants throughout the cohort regarding birth measures, socioeconomic status and educational attainment. Selection bias would be expected to affect the results only if the relationships were different in participants compared with nonparticipants. This is unlikely, but cannot be excluded.

In this study cohort, most individuals were born or grew up during World War II. Families might have suffered from food shortages in Finland at that time. In addition, intergenerational effects may also have impacted the results. Factors causing low birth weight may have differed from factors we have today; e.g. maternal smoking was rare in Finland in that time. Therefore, this must be considered in generalizing these results to current settings. On the other hand, small size at birth predicts premature death (Risnes et al. 2011) and several chronic diseases (Barker 1995, Barker et al. 2005, Eriksson et al. 2007, Huxley et al. 2007, Mu et al. 2012, Osmond et al. 2007, van Abeelen et al. 2011, Whincup et al. 2008, Xiao et al. 2010), which could cause individuals to drop out from the follow-ups of studies more frequently. Therefore, survivor bias might have caused some underestimation in terms of the results, because individuals who participated in the clinical examinations were about 60 years of age.

The cross-sectional design of the epidemiological part allows no conclusions regarding causality to be made. Nevertheless, epidemiological observations are invaluable for generating hypotheses on which associations can be confirmed in experimental studies. Finally, gestational age was based on the date of last menstrual period; thus it is prone to error.

6.3.2 Dietary assessments

FFQ

In the clinical epidemiological part of this thesis, dietary intake was measured by a validated semiquantitative FFQ. FFQ measures individuals' usual frequency of each food-item from a list of foods for a specific period (e.g. the past 12 months). Therefore, retrospective dietary assessment methods, such as diet history or FFQ, are widely used to assess the subjects' past long-term diet (Thompson and Byers 1994). Food records are, however, often regarded as the gold standards against other dietary assessment methods. Food records have been developed to assess the frequency of consumption and usual portion size of foods and mixed dishes. However, it is time-consuming and costly and, therefore, not suitable for large cohorts (Thompson and Byers 1994). Instead of food records, FFQ is widely used to estimate the usual dietary intake in large cohort studies, because the costs of data collection and processing as well as the respondent burden are much lower for FFQ methods than for food records. In epidemiological studies, FFQ is used to rank subjects according to food consumption or nutrient intakes for the purpose of assessing the relationships between dietary intake and disease risk (Thompson and Byers 1994).

When the diet is assessed by an FFQ, participants may, however, overestimate the consumption of food considered healthy and underreport the intake of food considered unhealthy (Paalanen et al. 2006). This is especially true for women who may overestimate their fruit and vegetable intake and for obese subjects who may underreport intakes of energy-dense foods (Paalanen et al. 2006). However, the FFQ used measured the entire diet and ranks subjects reasonably well according to their dietary intakes (Männistö et al. 1996, Paalanen et al. 2006).

It is challenging to measure sodium or salt intake from food consumption data. However, the continually updated Finnish food composition database has included sodium content values since the 1980s (Pietinen 1982). In addition, our database was validated against 24-h urinary sodium excretion, and there is a correlation between dietary and urinary sodium measurements (Reinivuo et al. 2006). When salt intake is estimated by an FFQ, it is not possible to accurately measure the salt used in cooking and at the table. However, a validation study showed that sodium intake, as measured with our FFQ, was similar to that observed by diet records (Männistö et al. 1996). Furthermore, the average salt intake in our study was at the same level than in the national FINDIET 2007 study (Paturi et al. 2008, Pietinen et al. 2010). Therefore, we believe that the limitations of the FFQ in estimating salt intake did not affect the results.

Energy adjustments

Adjusting for nutrient or food intakes by applying the residual method (Willett and Stampfer 1986, Willett et al. 1997) is commonly used to control for confounding. Confounding can result if the total energy intake is related to disease risk, e.g. due to variation in body size or physical activity. The residual method may, however, introduce attenuation bias in the association, unless the total energy intake is also entered into the model (Palmgren and Kushi 1991). However, in Study I, the associations between body size at birth and food and nutrient intake in later life did not change, even though the total energy intake was included in the models.

6.3.3 Postprandial studies

Participants

The postprandial studies of this thesis included subjects who had either normal or impaired glucose tolerance. This may have increased the variation in the glucose responses and thus have affected the results. We, however, previously showed that impaired glucose tolerance affects only glucose responses, but not insulin, TG or FFA responses (Perälä et al. 2011).

The limitations of the postprandial studies may also have included the relatively small number of participants included in the studies. Therefore, the power of the postprandial studies may not have been sufficient to disclose all true differences between the study groups. Postprandial studies are extremely labour intensive and therefore the number of participants is limited. The sample size was based on power calculations and postprandial studies traditionally include 10–30 participants (Lairon et al. 2007). In addition, earlier postprandial studies in the DOHaD field have also contained similar amount of participants (Byrne et al. 1997, Kensara et al. 2006).

Another possible limitation related to the postprandial study populations was that participants who grew slowly during the first year of life were also born small. Therefore, we cannot distinguish between the effect of size at birth, growth during infancy or a combination of the two on postprandial responses. In addition, since all the subjects were overweight, our findings of early growth and postprandial responses may be limited only to overweight populations.

Meal size

It has been proposed that meal size in postprandial studies should be based on the participant's body weight or body surface area (Lairon et al. 2007). This approach takes into account the greater blood volume in larger subjects. However, fat mass also influences postprandial fat clearance (Lairon et al. 2007). Differences in fat mass cause the main variation in body weight in adults. Thus, meal sizes that have been estimated by body size may introduce bias into the results. In addition, most of

the studies in the field of postprandial research have used a fixed meal size (Lairon et al. 2007). Therefore, we do believe that meal size used in our studies was suitable.

Measurements

In the postprandial studies, PYY was measured using an assay that did not differentiate between PYY (1-36) and PYY (3-36); therefore, the total hormone concentrations may not have reflected the active hormone levels. The differing forms of PYY may also play different roles in food intake regulations (Sloth et al. 2007). Therefore, we do not know whether the active PYY responses would have varied among the study groups.

Participants' satiety profiles were assessed, using questionnaire that contained a scale of satiety feelings. These types of self-reported VAS questionnaires are widely used to measure several appetite-related subjective sensations (Blundell et al. 2010). In our study, each participant was instructed to use the satiety scale to increase the reliability of the method. The satiety feelings were also assessed immediately before blood drawing. Therefore, the experience of blood sampling did not affect the subjective evaluation of the satiety feelings. However, the most commonly used questionnaires typically contain multiple appetite sensation scales, such as hunger, satiety, fullness and desire to eat (Blundell et al. 2010). It is recommended that multiple appetite sensation scales should be used because the various sensations may sometimes be confused, e.g. satiety is often confused with fullness. Therefore, in future studies it would be desirable to use a VAS that measures different appetite feelings.

6.4 Implications for further research

To date, few studies have been performed within the DOHaD field that have focused on nutritional factors. Particularly, although numerous studies have investigated the role of prenatal or postnatal growth on glucose and insulin responses during an OGTT, only a handful of postprandial studies have been published. Postprandial assessment is, however, much more physiologic and describes better the normal life situation. Therefore, further studies that elucidate the effect of early growth on postprandial metabolism in large study groups are required. Upcoming postprandial studies should also put special emphasis on elucidating whether the size at birth, growth during infancy or the combination of the two is behind the elevated postprandial responses.

The findings of this thesis demonstrate that size at birth affects and modifies dietary related risk factors for metabolic disease, including unhealthy dietary habits and salt sensitivity. To see whether early growth modifies other associations

between diet and health conditions, for example physical functioning and body composition, further studies are needed. The results also suggest that PYY levels are elevated for participants who born with small body size and grow slowly during infancy. Although PYY and other physiologic factors regulate appetite, meals are mostly initiated by factors that are not based on energy needs, such as time of day. Therefore, more knowledge is needed whether elevated PYY responses could explain decreased risk of developing obesity among subjects with slow growth during early life.

The results of this thesis demonstrate that the responses to adult diet are conditioned by early growth. Therefore, longitudinal intervention studies, which include dietary counselling, are essential. A target group should be low birth weight individuals who have increased risk for developing chronic disease in later life and preferably, follow-up should cover the whole life span. These studies would shed important light within the DOHaD field.

7 Conclusions

The results presented in this thesis provide convincing evidence that diet plays a role in the association between early growth and disease risk in later life. These findings support the DOHaD hypothesis which suggests that early growth has long-term effects on health.

The main conclusions of this thesis can be summarized as follows:

1. Small body size at birth was associated with lower consumption of fruits and berries, decreased intake of carbohydrates and sugars and increased intake of fats, which suggest that adult dietary habits may be, in part, programmed during prenatal life. Therefore, dietary counselling would be particularly beneficial for those born with small body size, because they have increased risk of developing chronic disease in later life and may have unhealthy dietary habits.

2. Individuals who were born with low birth weight were especially sensitive to the blood pressure-raising effect of salt. Therefore, they would benefit from restricted salt intake.

3. Growth retardation during early life had adverse effects on postprandial insulin and TG responses. These elevated responses may partly explain the association between slow pre- and postnatal growth and increased risk for metabolic diseases in adulthood.

4. Those who grew slowly during early life had elevated appetite regulatory hormone PYY postprandial responses. This could potentially be one explanation why individuals born with small body size and who grow slowly during infancy are less likely to become obese later in life.

8 Acknowledgements

This study was carried out at the Department of Chronic Disease Prevention, Diabetes Prevention Unit, National Institute for Health and Welfare (THL), Finland. I would like to thank the director of THL Professor Pekka Puska and the head of the unit Adjunct Professor Jaana Lindström for providing excellent research facilities. This work was financially supported by the Academy of Finland and the Finnish Graduate School on Applied Bioscience: Bioengineering, Food & Nutrition, Environment.

My deepest gratitude goes to my supervisor, Professor Johan Eriksson, for his excellent guidance and encouragement during these years. Your positive attitude and invaluable scientific support carried me through the whole process. Despite your busy schedules, you always had time for me. I am also deeply grateful to my other supervisor, Adjunct Professor Liisa Valsta, for her generous support of this work and for introducing me to postprandial studies. I wish to thank my follow-up group Adjunct Professors Eero Kajantie and Satu Männistö, who contributed to my work by providing the best of scientific expertise. It has been a privilege to work under your impressive expertise.

I sincerely thank Professor Jussi Pihlajamäki and Adjunct Professor Harri Niinikoski for reviewing this thesis and for valuable advice and constructive criticism that improved the manuscript. I thank Associate Professor Kirsi Pietiläinen for accepting the role of opponent at my thesis defence.

I express my deep gratitude to all of my coauthors for contributing their valuable expertise, criticism and comments. I am sincerely grateful to Professors David Barker and Clive Osmond. I am proud to have had an opportunity to work with them. Special thanks go to Clive for giving statistical advice. I also want to thank study nurse Elina Rintala for her kindness and invaluable efforts in conducting the postprandial studies.

I extend my thanks to all my researcher colleagues involved in the IDEFIX-project both at the THL and psychologists at the University of Helsinki, as well as all the members of the Diabetes Prevention Unit, for inspiring and welcoming atmosphere with plenty of humour. I especially want to mention Anna-Maija Tiainen and Minna Salonen. Thank you for your kindness, friendship and good company.

I want to warmly thank my mother and father (you still live in my mind) who have taught me to believe in myself. I am also grateful that you have always let me choose my own path. I also thank my sister Anu and her wonderful family for being in my life. The supportive and always stimulating company of my friends has also

been invaluable. I am especially grateful to Susu and Niina for all the enjoyable moments during the past 20 years.

Finally, words fail to describe my gratitude for my dear husband Tommi, for loving me as I am, supporting me and being my best friend, and Emma, our daughter, for being the joy of my life!

Helsinki, February 2014

Mia-Maria Perälä

9 References

Alwasel SH, Ashton N (2009). Prenatal programming of renal sodium handling in the rat. *Clin Sci (Lond)* **117:** 75-84.

Andersen LG, Angquist L, Gamborg M, Byberg L, Bengtsson C, Canoy D, Eriksson JG, Eriksson M, Jarvelin MR, Lissner L, Nilsen TI, Osler M, Overvad K, Rasmussen F, Salonen MK, Schack-Nielsen L, Tammelin TH, Tuomainen TP, Sorensen TI, Baker JL (2009). Birth weight in relation to leisure time physical activity in adolescence and adulthood: meta-analysis of results from 13 nordic cohorts. *PLoS One* **4:** e8192.

Ando K, Fujita T (2012). Pathophysiology of salt sensitivity hypertension. *Ann Med* **44 Suppl 1:** S119-126.

Attig L, Gabory A, Junien C (2010). Early nutrition and epigenetic programming: chasing shadows. *Curr Opin Clin Nutr Metab Care* **13:** 284-293.

Augustyniak RA, Singh K, Zeldes D, Singh M, Rossi NF (2010). Maternal protein restriction leads to hyperresponsiveness to stress and salt-sensitive hypertension in male offspring. *Am J Physiol Regul Integr Comp Physiol* **298:** R1375-1382.

Ayres C, Agranonik M, Portella AK, Filion F, Johnston C, Silveira PP (2012). Intrauterine growth restriction and the fetal programming of the hedonic response to sweet taste in newborn infants. *Int J Pediatr* **2012:** 657379.

Badman MK, Flier JS (2005). The gut and energy balance: visceral allies in the obesity wars. *Science* **307:** 1909-1914.

Baird J, Fisher D, Lucas P, Kleijnen J, Roberts H, Law C (2005). Being big or growing fast: systematic review of size and growth in infancy and later obesity. *BMJ* **331:** 929.

Bansal S, Buring JE, Rifai N, Mora S, Sacks FM, Ridker PM (2007). Fasting compared with nonfasting triglycerides and risk of cardiovascular events in women. *JAMA* **298:** 309-316.

Bansilal S, Farkouh ME, Fuster V (2007). Role of insulin resistance and hyperglycemia in the development of atherosclerosis. *Am J Cardiol* **99 [suppl]:** 6B–14B.

Barbieri MA, Portella AK, Silveira PP, Bettiol H, Agranonik M, Silva AA, Goldani MZ (2009). Severe intrauterine growth restriction is associated with higher spontaneous carbohydrate intake in young women. *Pediatr Res* **65:** 215-220.

Barker DJ, Osmond C (1986). Infant mortality, childhood nutrition, and ischaemic heart disease in England and Wales. *Lancet* **1:** 1077-1081.

Barker DJ, Winter PD, Osmond C, Margetts B, Simmonds SJ (1989). Weight in infancy and death from ischaemic heart disease. *Lancet* **2:** 577-580.

Barker DJ, Gluckman PD, Godfrey KM, Harding JE, Owens JA, Robinson JS (1993). Fetal nutrition and cardiovascular disease in adult life. *Lancet* **341:** 938-941.

Barker DJ (1995). Fetal origins of coronary heart disease. *BMJ* **311:** 171-174.

Barker DJ, Osmond C, Forsén TJ, Kajantie E, Eriksson JG (2005). Trajectories of growth among children who have coronary events as adults. *N Engl J Med* **353:** 1802-1809.

Bayol SA, Farrington SJ, Stickland NC (2007). A maternal 'junk food' diet in pregnancy and lactation promotes an exacerbated taste for 'junk food' and a greater propensity for obesity in rat offspring. *Br J Nutr* **98:** 843-851.

Beauchamp GK, Moran M (1982). Dietary experience and sweet taste preference in human infants. *Appetite* **3:** 139-152.

Bellinger L, Lilley C, Langley-Evans SC (2004). Prenatal exposure to a maternal low-protein diet programmes a preference for high-fat foods in the young adult rat. *Br J Nutr* **92:** 513-520.

Bellinger L, Langley-Evans SC (2005). Fetal programming of appetite by exposure to a

maternal low-protein diet in the rat. *Clin Sci (Lond)* **109:** 413-420.

Bellinger L, Sculley DV, Langley-Evans SC (2006). Exposure to undernutrition in fetal life determines fat distribution, locomotor activity and food intake in ageing rats. *Int J Obes (Lond)* **30:** 729-738.

Berseth CL, Nordyke CK, Valdes MG, Furlow BL, Go VL (1992). Responses of gastrointestinal peptides and motor activity to milk and water feedings in preterm and term infants. *Pediatr Res* **31:** 587-590.

Blundell J, de Graaf C, Hulshof T, Jebb S, Livingstone B, Lluch A, Mela D, Salah S, Schuring E, van der Knaap H, Westerterp M (2010). Appetite control: methodological aspects of the evaluation of foods. *Obes Rev* **11:** 251-270.

Boiko J, Jaquet D, Chevenne D, Rigal O, Czernichow P, Levy-Marchal C (2005). In situ lipolytic regulation in subjects born small for gestational age. *Int J Obes (Lond)* **29:** 565-570.

Brenner BM, Chertow GM (1994). Congenital oligonephropathy and the etiology of adult hypertension and progressive renal injury. *Am J Kidney Dis* **23:** 171-175.

Breton C, Lukaszewski MA, Risold PY, Enache M, Guillemot J, Riviere G, Delahaye F, Lesage J, Dutriez-Casteloot I, Laborie C, Vieau D (2009). Maternal prenatal undernutrition alters the response of POMC neurons to energy status variation in adult male rat offspring. *Am J Physiol Endocrinol Metab* **296:** E462-472.

Burns SP, Desai M, Cohen RD, Hales CN, Iles RA, Germain JP, Going TC, Bailey RA (1997). Gluconeogenesis, glucose handling, and structural changes in livers of the adult offspring of rats partially deprived of protein during pregnancy and lactation. *J Clin Invest* **100:** 1768-1774.

Byrne CD, Wareham NJ, Phillips DI, Hales CN, Martensz ND (1997). Is an exaggerated postprandial triglyceride response associated with the component features of the insulin resistance syndrome? *Diabet Med* **14:** 942-950.

Calanna S, Christensen M, Holst JJ, Laferrere B, Gluud LL, Vilsboll T, Knop FK (2013). Secretion of glucagon-like peptide-1 in patients with type 2 diabetes mellitus: systematic review and meta-analyses of clinical studies. *Diabetologia* **56:** 965-972.

Callinan PA, Feinberg AP (2006). The emerging science of epigenomics. *Hum Mol Genet* **15 Spec No 1:** R95-101.

Cambraia RP, Vannucchi H, Almeida SS, De-Oliveira LM (2001). Effects of malnutrition during early lactation on development and feeding behavior under the self-selection paradigm. *Nutrition* **17:** 455-461.

Chen X, Du X, Zhu J, Xie L, Zhang Y, He Z (2012). Correlations of circulating peptide YY and ghrelin with body weight, rate of weight gain, and time required to achieve the recommended daily intake in preterm infants. *Braz J Med Biol Res* **45:** 656-664.

Clausson B, Lichtenstein P, Cnattingius S (2000). Genetic influence on birthweight and gestational length determined by studies in offspring of twins. *BJOG* **107:** 375-381.

Cong R, Jia Y, Li R, Ni Y, Yang X, Sun Q, Parvizi N, Zhao R (2012). Maternal low-protein diet causes epigenetic deregulation of HMGCR and CYP7alpha1 in the liver of weaning piglets. *J Nutr Biochem* **23:** 1647-1654.

Coupe B, Grit I, Darmaun D, Parnet P (2009). The timing of "catch-up growth" affects metabolism and appetite regulation in male rats born with intrauterine growth restriction. *Am J Physiol Regul Integr Comp Physiol* **297:** R813-824.

Coupe B, Amarger V, Grit I, Benani A, Parnet P (2010). Nutritional programming affects hypothalamic organization and early response to leptin. *Endocrinology* **151:** 702-713.

Cummings DE, Overduin J (2007). Gastrointestinal regulation of food intake. *J Clin Invest* **117:** 13-23.

Dabelea D, Pettitt DJ, Hanson RL, Imperatore G, Bennett PH, Knowler WC (1999). Birth weight, type 2 diabetes, and insulin resistance in Pima Indian children and young adults. *Diabetes Care* **22:** 944-950.

Darendeliler F, Poyrazoglu S, Bas F, Sancakli O, Gokcay G (2009). Ghrelin levels are decreased in non-obese prepubertal children born large for

gestational age. *Eur J Endocrinol* **160:** 951-956.

Dauchet L, Amouyel P, Dallongeville J (2009). Fruits, vegetables and coronary heart disease. *Nat Rev Cardiol* **6:** 599-608.

de Boer MP, IJzerman RG, de Jongh RT, Eringa EC, Stehouwer CD, Smulders YM, Serné EH (2008). Birth weight relates to salt sensitivity of blood pressure in healthy adults. *Hypertension* **51:** 928-932.

de Rooij SR, Painter RC, Phillips DI, Osmond C, Michels RP, Godsland IF, Bossuyt PM, Bleker OP, Roseboom TJ (2006). Impaired insulin secretion after prenatal exposure to the Dutch famine. *Diabetes Care* **29:** 1897-1901.

Desai M, Gayle D, Babu J, Ross MG (2005). Programmed obesity in intrauterine growth-restricted newborns: modulation by newborn nutrition. *Am J Physiol Regul Integr Comp Physiol* **288:** R91-96.

Desai M, Gayle D, Han G, Ross MG (2007). Programmed hyperphagia due to reduced anorexigenic mechanisms in intrauterine growth-restricted offspring. *Reprod Sci* **14:** 329-337.

Dumortier O, Blondeau B, Duvillie B, Reusens B, Breant B, Remacle C (2007). Different mechanisms operating during different critical time-windows reduce rat fetal beta cell mass due to a maternal low-protein or low-energy diet. *Diabetologia* **50:** 2495-2503.

Edholm T, Degerblad M, Gryback P, Hilsted L, Holst JJ, Jacobsson H, Efendic S, Schmidt PT, Hellstrom PM (2010). Differential incretin effects of GIP and GLP-1 on gastric emptying, appetite, and insulin-glucose homeostasis. *Neurogastroenterol Motil* **22:** 1191-1200, e1315.

Erhuma A, Bellinger L, Langley-Evans SC, Bennett AJ (2007). Prenatal exposure to undernutrition and programming of responses to high-fat feeding in the rat. *Br J Nutr* **98:** 517-524.

Eriksson J, Forsen T, Tuomilehto J, Osmond C, Barker D (2002). Size at birth, fat-free mass and resting metabolic rate in adult life. *Horm Metab Res* **34:** 72-76.

Eriksson JG, Forsén TJ, Osmond C, Barker DJ (2003). Pathways of infant and childhood growth that lead to type 2 diabetes. *Diabetes Care* **26:** 3006-3010.

Eriksson JG, Ylihärsilä H, Forsén T, Osmond C, Barker DJ (2004). Exercise protects against glucose intolerance in individuals with a small body size at birth. *Prev Med* **39:** 164-167.

Eriksson JG, Osmond C, Kajantie E, Forsén TJ, Barker DJ (2006). Patterns of growth among children who later develop type 2 diabetes or its risk factors. *Diabetologia* **49:** 2853-2858.

Eriksson JG, Forsén TJ, Kajantie E, Osmond C, Barker DJ (2007). Childhood growth and hypertension in later life. *Hypertension* **49:** 1415-1421.

Fall CH, Sachdev HS, Osmond C, Lakshmy R, Biswas SD, Prabhakaran D, Tandon N, Ramji S, Reddy KS, Barker DJ, Bhargava SK (2008). Adult metabolic syndrome and impaired glucose tolerance are associated with different patterns of BMI gain during infancy: Data from the New Delhi Birth Cohort. *Diabetes Care* **31:** 2349-2356.

Flint A, Gregersen NT, Gluud LL, Moller BK, Raben A, Tetens I, Verdich C, Astrup A (2007). Associations between postprandial insulin and blood glucose responses, appetite sensations and energy intake in normal weight and overweight individuals: a meta-analysis of test meal studies. *Br J Nutr* **98:** 17-25.

Forsdahl A (1977). Are poor living conditions in childhood and adolescence an important risk factor for arteriosclerotic heart disease? *Br J Prev Soc Med* **31:** 91-95.

Fraser A, Ebrahim S, Smith GD, Lawlor DA (2008). The associations between birthweight and adult markers of liver damage and function. *Paediatr Perinat Epidemiol* **22:** 12-21.

Gamborg M, Byberg L, Rasmussen F, Andersen PK, Baker JL, Bengtsson C, Canoy D, Droyvold W, Eriksson JG, Forsen T, Gunnarsdottir I, Jarvelin MR, Koupil I, Lapidus L, Nilsen TI, Olsen SF, Schack-Nielsen L, Thorsdottir I, Tuomainen TP, Sorensen TI (2007). Birth weight and systolic blood pressure in adolescence and adulthood: meta-regression

analysis of sex- and age-specific results from 20 Nordic studies. *Am J Epidemiol* **166:** 634-645.

Goldberg GR, Black AE, Jebb SA, Cole TJ, Murgatroyd PR, Coward WA, Prentice AM (1991). Critical evaluation of energy intake data using fundamental principles of energy physiology: 1. Derivation of cut-off limits to identify under-recording. *Eur J Clin Nutr* **45:** 569-581.

Goldberg IJ, Eckel RH, McPherson R (2011). Triglycerides and heart disease: still a hypothesis? *Arterioscler Thromb Vasc Biol* **31:** 1716-1725.

Guyenet SJ, Schwartz MW (2012). Clinical review: Regulation of food intake, energy balance, and body fat mass: implications for the pathogenesis and treatment of obesity. *J Clin Endocrinol Metab* **97:** 745-755.

Hallan S, Euser AM, Irgens LM, Finken MJ, Holmen J, Dekker FW (2008). Effect of intrauterine growth restriction on kidney function at young adult age: the Nord Trondelag Health (HUNT 2) Study. *Am J Kidney Dis* **51:** 10-20.

Harder T, Rodekamp E, Schellong K, Dudenhausen JW, Plagemann A (2007). Birth weight and subsequent risk of type 2 diabetes: a meta-analysis. *Am J Epidemiol* **165:** 849-857.

He FJ, MacGregor GA (2002). Effect of modest salt reduction on blood pressure: a meta-analysis of randomized trials. Implications for public health. *J Hum Hypertens* **16:** 761-770.

Hinchliffe SA, Lynch MR, Sargent PH, Howard CV, Van Velzen D (1992). The effect of intrauterine growth retardation on the development of renal nephrons. *Br J Obstet Gynaecol* **99:** 296-301.

Hindmarsh PC, Geary MP, Rodeck CH, Kingdom JC, Cole TJ (2008). Factors predicting ante- and postnatal growth. *Pediatr Res* **63:** 99-102.

Hoffmann IS, Cubeddu LX (2007). Increased blood pressure reactivity to dietary salt in patients with the metabolic syndrome. *J Hum Hypertens* **21:** 438-444.

Holt SH, Miller JB (1995). Increased insulin responses to ingested foods are associated with lessened satiety. *Appetite* **24:** 43-54.

Hosoda H, Kojima M, Kangawa K (2006). Biological, physiological, and pharmacological aspects of ghrelin. *J Pharmacol Sci* **100:** 398-410.

Hughson M, Farris AB, 3rd, Douglas-Denton R, Hoy WE, Bertram JF (2003). Glomerular number and size in autopsy kidneys: the relationship to birth weight. *Kidney Int* **63:** 2113-2122.

Hughson MD, Gobe GC, Hoy WE, Manning RD, Jr., Douglas-Denton R, Bertram JF (2008). Associations of glomerular number and birth weight with clinicopathological features of African Americans and whites. *Am J Kidney Dis* **52:** 18-28.

Hunsberger S, Albert PS, Follmann DA, Suh E (2002). Parametric and semiparametric approaches to testing for seasonal trend in serial count data. *Biostatistics* **3:** 289-298.

Huxley R, Neil A, Collins R (2002). Unravelling the fetal origins hypothesis: is there really an inverse association between birthweight and subsequent blood pressure? *Lancet* **360:** 659-665.

Huxley R, Owen CG, Whincup PH, Cook DG, Colman S, Collins R (2004). Birth weight and subsequent cholesterol levels: exploration of the "fetal origins" hypothesis. *JAMA* **292:** 2755-2764.

Huxley R (2006). Fatal flaw in the fetal argument. *Br J Nutr* **95:** 441-442.

Huxley R, Owen CG, Whincup PH, Cook DG, Rich-Edwards J, Smith GD, Collins R (2007). Is birth weight a risk factor for ischemic heart disease in later life? *Am J Clin Nutr* **85:** 1244-1250.

Huxley RR, Shiell AW, Law CM (2000). The role of size at birth and postnatal catch-up growth in determining systolic blood pressure: a systematic review of the literature. *J Hypertens* **18:** 815-831.

Ibanez L, Ong K, Dunger DB, de Zegher F (2006). Early development of adiposity and insulin resistance after catch-up weight gain in small-for-gestational-age children. *J Clin Endocrinol Metab* **91:** 2153-2158.

Ignarro LJ, Balestrieri ML, Napoli C (2007). Nutrition, physical activity, and cardiovascular disease: an update. *Cardiovasc Res* **73:** 326-340.

Ikenasio-Thorpe BA, Breier BH, Vickers MH, Fraser M (2007). Prenatal influences on susceptibility to diet-induced obesity are mediated by altered neuroendocrine gene expression. *J Endocrinol* **193:** 31-37.

Indredavik MS, Vik T, Heyerdahl S, Kulseng S, Fayers P, Brubakk AM (2004). Psychiatric symptoms and disorders in adolescents with low birth weight. *Arch Dis Child Fetal Neonatal Ed* **89:** F445-450.

Iniguez G, Ong K, Pena V, Avila A, Dunger D, Mericq V (2002). Fasting and post-glucose ghrelin levels in SGA infants: relationships with size and weight gain at one year of age. *J Clin Endocrinol Metab* **87:** 5830-5833.

Jackson KG, Poppitt SD, Minihane AM (2012). Postprandial lipemia and cardiovascular disease risk: Interrelationships between dietary, physiological and genetic determinants. *Atherosclerosis* **220:** 22-33.

Jensen CB, Storgaard H, Madsbad S, Richter EA, Vaag AA (2007). Altered skeletal muscle fiber composition and size precede whole-body insulin resistance in young men with low birth weight. *J Clin Endocrinol Metab* **92:** 1530-1534.

Jensen CB, Martin-Gronert MS, Storgaard H, Madsbad S, Vaag A, Ozanne SE (2008). Altered PI3-kinase/Akt signalling in skeletal muscle of young men with low birth weight. *PLoS ONE* **3:** e3738.

Johnson RC, Schoeni RF (2011). Early-life origins of adult disease: national longitudinal population-based study of the United States. *Am J Public Health* **101:** 2317-2324.

Johnson TS, Engstrom JL, Gelhar DK (1997). Intra- and interexaminer reliability of anthropometric measurements of term infants. *J Pediatr Gastroenterol Nutr* **24:** 497-505.

Jula A, Kantola I, Lehto S, Mervaala E, Metsärinne K, Pörsti I, Strandberg T, Tikkanen I, Tikkanen T, Kukkonen-Harjula K (2009). National Current Care Guideline for Hypertension. Working group appointed by the Finnish Medical Society Duodecim and the Finnish Hypertension Society: Helsinki.

Kaartinen NE, Similä ME, Pakkala H, Korhonen T, Männistö S, Valsta LM (2010). Glycaemic index values in the Finnish food composition database: an approach to standardised value documentation. *Eur J Clin Nutr* **64 Suppl 3:** S68-72.

Kabagambe EK, Ordovas JM, Tsai MY, Borecki IB, Hopkins PN, Glasser SP, Arnett DK (2009). Smoking, inflammatory patterns and postprandial hypertriglyceridemia. *Atherosclerosis* **203:** 633-639.

Kajantie E, Barker DJ, Osmond C, Forsen T, Eriksson JG (2008). Growth before 2 years of age and serum lipids 60 years later: the Helsinki Birth Cohort study. *Int J Epidemiol* **37:** 280-289.

Kaseva N, Wehkalampi K, Hemiö K, Hovi P, Järvenpää AL, Andersson S, Eriksson JG, Lindström J, Kajantie E (2013). Diet and Nutrient Intake in Young Adults Born Preterm at Very Low Birth Weight. *J Pediatr* **163:** 43-48.

Kastarinen M, Antikainen R, Peltonen M, Laatikainen T, Barengo NC, Jula A, Salomaa V, Jousilahti P, Nissinen A, Vartiainen E, Tuomilehto J (2009). Prevalence, awareness and treatment of hypertension in Finland during 1982-2007. *J Hypertens* **27:** 1552-1559.

Kazakos K (2011). Incretin effect: GLP-1, GIP, DPP4. *Diabet Res Clin Pract* **93:** S32-S36.

Kensara OA, Wooton SA, Phillips DI, Patel M, Hoffman DJ, Jackson AA, Elia M (2006). Substrate-energy metabolism and metabolic risk factors for cardiovascular disease in relation to fetal growth and adult body composition. *Am J Physiol Endocrinol Metab* **291:** E365-371.

Kermack WO, McKendrick AG, McKinlay PL (1934). Death-rates in Great Britain and Sweden. Some general regularities and their significance. *Lancet* **223:** 698-703.

Klop B, Proctor SD, Mamo JC, Botham KM, Castro Cabezas M (2012). Understanding postprandial inflammation and its relationship to lifestyle

behaviour and metabolic diseases. *Int J Vasc Med* **2012:** 947417.

Kolovou GD, Mikhailidis DP, Kovar J, Lairon D, Nordestgaard BG, Ooi TC, Perez-Martinez P, Bilianou H, Anagnostopoulou K, Panotopoulos G (2011). Assessment and clinical relevance of non-fasting and postprandial triglycerides: an expert panel statement. *Curr Vasc Pharmacol* **9:** 258-270.

Kopp W (2006). The atherogenic potential of dietary carbohydrate. *Prev Med* **42:** 336-342.

Kotronen A, Yki-Järvinen H (2008). Fatty liver: a novel component of the metabolic syndrome. *Arterioscler Thromb Vasc Biol* **28:** 27-38.

Kramer MS (1987). Determinants of low birth weight: methodological assessment and meta-analysis. *Bull World Health Organ* **65:** 663-737.

Kramer MS, Joseph KS (1996). Enigma of fetal/infant-origins hypothesis. *Lancet* **348:** 1254-1255.

Kyriakakou M, Malamitsi-Puchner A, Mastorakos G, Boutsikou T, Hassiakos D, Papassotiriou I, Kanaka-Gantenbein C (2009). The role of IGF-1 and ghrelin in the compensation of intrauterine growth restriction. *Reprod Sci* **16:** 1193-1200.

Lahti J, Räikkönen K, Heinonen K, Pesonen AK, Kajantie E, Forsén T, Osmond C, Barker DJ, Eriksson JG (2008). Body size at birth and socio-economic status in childhood: implications for Cloninger's psychobiological model of temperament at age 60. *Psychiatry Res* **160:** 167-174.

Lairon D, Lopez-Miranda J, Williams C (2007). Methodology for studying postprandial lipid metabolism. *Eur J Clin Nutr* **61:** 1145-1161.

Lane RH, Kelley DE, Gruetzmacher EM, Devaskar SU (2001). Uteroplacental insufficiency alters hepatic fatty acid-metabolizing enzymes in juvenile and adult rats. *Am J Physiol Regul Integr Comp Physiol* **280:** R183-190.

Langley SC, Jackson AA (1994). Increased systolic blood pressure in adult rats induced by fetal exposure to maternal low protein diets. *Clin Sci* **86:** 217-222.

Larnkjær A, Schack-Nielsen L, Molgaard C, Ingstrup HK, Holst JJ, Michaelsen KF (2010). Effect of growth in infancy on body composition, insulin resistance, and concentration of appetite hormones in adolescence. *Am J Clin Nutr* **91:** 1675-1683.

Latimer K, Wilson P, Kemp J, Thompson L, Sim F, Gillberg C, Puckering C, Minnis H (2012). Disruptive behaviour disorders: a systematic review of environmental antenatal and early years risk factors. *Child Care Health Dev* **38:** 611-628.

Lauren L, Jarvelin MR, Elliott P, Sovio U, Spellman A, McCarthy M, Emmett P, Rogers I, Hartikainen AL, Pouta A, Hardy R, Wadsworth M, Helmsdal G, Olsen S, Bakoula C, Lekea V, Millwood I (2003). Relationship between birthweight and blood lipid concentrations in later life: evidence from the existing literature. *Int J Epidemiol* **32:** 862-876.

Law CM, Shiell AW (1996). Is blood pressure inversely related to birth weight? The strength of evidence from a systematic review of the literature. *J Hypertens* **14:** 935-941.

Lawlor DA, Ebrahim S, Davey Smith G (2005). Association of birth weight with adult lung function: findings from the British Women's Heart and Health Study and a meta-analysis. *Thorax* **60:** 851-858.

Lawlor DA, Owen CG, Davies AA, Whincup PH, Ebrahim S, Cook DG, Davey Smith G (2006). Sex differences in the association between birth weight and total cholesterol. A meta-analysis. *Ann Epidemiol* **16:** 19-25.

Leinonen KS, Poutanen KS, Mykkänen HM (2000). Rye bread decreases serum total and LDL cholesterol in men with moderately elevated serum cholesterol. *J Nutr* **130:** 164-170.

Lewington S, Clarke R, Qizilbash N, Peto R, Collins R (2002). Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* **360:** 1903-1913.

Lillycrop KA, Phillips ES, Jackson AA, Hanson MA, Burdge GC (2005). Dietary protein restriction of pregnant rats induces and folic

acid supplementation prevents epigenetic modification of hepatic gene expression in the offspring. *J Nutr* **135:** 1382-1386.

Lissner L, Karlsson C, Lindroos AK, Sjostrom L, Carlsson B, Carlsson L, Bengtsson C (1999). Birth weight, adulthood BMI, and subsequent weight gain in relation to leptin levels in Swedish women. *Obes Res* **7:** 150-154.

Liu C, Lin G, Wang X, Wang T, Wu G, Li D, Wang J (2013). Intrauterine growth restriction alters the hepatic proteome in fetal pigs. *J Nutr Biochem* **24:** 954-959.

Lopez-Miranda J, Williams C, Lairon D (2007). Dietary, physiological, genetic and pathological influences on postprandial lipid metabolism. *Br J Nutr* **98:** 458-473.

Lopez AD, Mathers CD, Ezzati M, Jamison DT, Murray CJ (2006). Global and regional burden of disease and risk factors, 2001: systematic analysis of population health data. *Lancet* **367:** 1747-1757.

Lopez M, Seoane LM, Tovar S, Garcia MC, Nogueiras R, Dieguez C, Senaris RM (2005). A possible role of neuropeptide Y, agouti-related protein and leptin receptor isoforms in hypothalamic programming by perinatal feeding in the rat. *Diabetologia* **48:** 140-148.

Lucas A (1998). Programming by early nutrition: an experimental approach. *J Nutr* **128:** 401S-406S.

Luft FC, Miller JZ, Grim CE, Fineberg NS, Christian JC, Daugherty SA, Weinberger MH (1991). Salt sensitivity and resistance of blood pressure. Age and race as factors in physiological responses. *Hypertension* **17:** I102-108.

Lukaszewski MA, Butruille L, Moitrot E, Montel V, Dickes-Coopman A, Lesage J, Laborie C, Vieau D, Breton C (2013). The hypothalamic POMC mRNA expression is upregulated in prenatally undernourished male rat offspring under high-fat diet. *Peptides* **43:** 146-154.

Lund LK, Vik T, Skranes J, Lydersen S, Brubakk AM, Indredavik MS (2012). Low birth weight and psychiatric morbidity; stability and change between adolescence and young adulthood. *Early Hum Dev* **88:** 623-629.

Lunde A, Melve KK, Gjessing HK, Skjaerven R, Irgens LM (2007). Genetic and environmental influences on birth weight, birth length, head circumference, and gestational age by use of population-based parent-offspring data. *Am J Epidemiol* **165:** 734-741.

Lussana F, Painter RC, Ocke MC, Buller HR, Bossuyt PM, Roseboom TJ (2008). Prenatal exposure to the Dutch famine is associated with a preference for fatty foods and a more atherogenic lipid profile. *Am J Clin Nutr* **88:** 1648-1652.

Mah E, Bruno RS (2012). Postprandial hyperglycemia on vascular endothelial function: mechanisms and consequences. *Nutr Res* **32:** 727-740.

Maiorana A, Del Bianco C, Cianfarani S (2007). Adipose Tissue: A metabolic regulator. Potential implications for the metabolic outcome of subjects born small for gestational age (SGA). *Rev Diabet Stud* **4:** 134-146.

Manalich R, Reyes L, Herrera M, Melendi C, Fundora I (2000). Relationship between weight at birth and the number and size of renal glomeruli in humans: a histomorphometric study. *Kidney Int* **58:** 770-773.

Mancia G, De Backer G, Dominiczak A, Cifkova R, Fagard R, Germano G, Grassi G, Heagerty AM, Kjeldsen SE, Laurent S, Narkiewicz K, Ruilope L, Rynkiewicz A, Schmieder RE, Struijker Boudier HA, Zanchetti A, Vahanian A, Camm J, De Caterina R, Dean V, Dickstein K, Filippatos G, Funck-Brentano C, Hellemans I, Kristensen SD, McGregor K, Sechtem U, Silber S, Tendera M, Widimsky P, Zamorano JL, Erdine S, Kiowski W, Agabiti-Rosei E, Ambrosioni E, Lindholm LH, Manolis A, Nilsson PM, Redon J, Struijker-Boudier HA, Viigimaa M, Adamopoulos S, Bertomeu V, Clement D, Farsang C, Gaita D, Lip G, Mallion JM, Manolis AJ, O'Brien E, Ponikowski P, Ruschitzka F, Tamargo J, van Zwieten P, Waeber B, Williams B, The task force for the management of arterial hypertension of the European Society of H, The task force for the management of arterial hypertension of the European Society of C (2007). 2007 Guidelines

for the management of arterial hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur Heart J* **28:** 1462-1536.

Manning J, Vehaskari VM (2001). Low birth weight-associated adult hypertension in the rat. *Pediatr Nephrol* **16:** 417-422.

Manning J, Beutler K, Knepper MA, Vehaskari VM (2002). Upregulation of renal BSC1 and TSC in prenatally programmed hypertension. *Am J Physiol Renal Physiol* **283:** F202-206.

Martikainen JA, Soini EJ, Laaksonen DE, Niskanen L (2011). Health economic consequences of reducing salt intake and replacing saturated fat with polyunsaturated fat in the adult Finnish population: estimates based on the FINRISK and FINDIET studies. *Eur J Clin Nutr* **65:** 1148-1155.

Martinez-Mesa J, Restrepo-Mendez MC, Gonzalez DA, Wehrmeister FC, Horta BL, Domingues MR, Menezes AM (2012). Life-course evidence of birth weight effects on bone mass: systematic review and meta-analysis. *Osteoporos Int* **24:** 7-18.

McConnell JM, Petrie L (2004). Mitochondrial DNA turnover occurs during preimplantation development and can be modulated by environmental factors. *Reprod Biomed Online* **9:** 418-424.

McNamara BJ, Gubhaju L, Chamberlain C, Stanley F, Eades SJ (2012). Early life influences on cardio-metabolic disease risk in aboriginal populations--what is the evidence? A systematic review of longitudinal and case-control studies. *Int J Epidemiol* **41:** 1661-1682.

Mela DJ (2001). Determinants of food choice: relationships with obesity and weight control. *Obes Res* **9 Suppl 4:** 249S-255S.

Mennella JA, Jagnow CP, Beauchamp GK (2001). Prenatal and postnatal flavor learning by human infants. *Pediatrics* **107:** E88.

Monasta L, Batty GD, Cattaneo A, Lutje V, Ronfani L, Van Lenthe FJ, Brug J (2010). Early-life determinants of overweight and obesity: a review of systematic reviews. *Obes Rev* **11:** 695-708.

Monfils Gustafsson W, Josefsson A, Ekholm Selling K, Sydsjo G (2009). Preterm birth or foetal growth impairment and psychiatric hospitalization in adolescence and early adulthood in a Swedish population-based birth cohort. *Acta Psychiatr Scand* **119:** 54-61.

Monteiro PO, Victora CG (2005). Rapid growth in infancy and childhood and obesity in later life--a systematic review. *Obes Rev* **6:** 143-154.

Mu M, Wang SF, Sheng J, Zhao Y, Li HZ, Hu CL, Tao FB (2012). Birth weight and subsequent blood pressure: a meta-analysis. *Arch Cardiovasc Dis* **105:** 99-113.

Muggeo VM (2003). Estimating regression models with unknown break-points. *Stat Med* **22:** 3055-3071.

Männistö S, Virtanen M, Mikkonen T, Pietinen P (1996). Reproducibility and validity of a food frequency questionnaire in a case-control study on breast cancer. *J Clin Epidemiol* **49:** 401-409.

Nakamura Y, Sanematsu K, Ohta R, Shirosaki S, Koyano K, Nonaka K, Shigemura N, Ninomiya Y (2008). Diurnal variation of human sweet taste recognition thresholds is correlated with plasma leptin levels. *Diabetes* **57:** 2661-2665.

National Institute for Health and Welfare (2005). Finnish food composition database Release 5. National Institute for Health and Welfare, Helsinki, Finland.

National Nutrition Council (2005). Suomalaiset ravitsemussuositukset - ravinto ja liikunta tasapainoon (In Finnish, title in English: Finnish Nutrition Recommendations – Diet and physical activity in balance). In: Edita Publishing Oy. Available at http://www.ravitsemusneuvottelukunta.fi/portal/fi/julkaisut/. Accessed January 15, 2014.

Nauck MA, Vardarli I, Deacon CF, Holst JJ, Meier JJ (2011). Secretion of glucagon-like peptide-1 (GLP-1) in type 2 diabetes: what is up, what is down? *Diabetologia* **54:** 10-18.

Newsome CA, Shiell AW, Fall CH, Phillips DI, Shier R, Law CM (2003). Is birth weight related to later glucose and insulin

metabolism?--A systematic review. *Diabet Med* **20:** 339-348.

Nobili V, Marcellini M, Marchesini G, Vanni E, Manco M, Villani A, Bugianesi E (2007). Intrauterine growth retardation, insulin resistance, and nonalcoholic fatty liver disease in children. *Diabetes Care* **30:** 2638-2640.

Nordestegaard BG, Benn M, Sehnohr P, Tybjærg-Hansen A (2007). Nonfasting triglycerides and risk of myocardial infraction, ischemic heart disease, and death in men and women. *JAMA* **298:** 299-308.

Nordic Council of Ministers (2013). Nordic Nutrition Recommendations 2012. *Part 1. Summary, principles and use*. Available at: http://www.slv.se/en-gb/Startpage-NNR/Public-consultation/. Accessed January 15, 2014.

O'Keefe JH, Bell DS (2007). Postprandial hyperglycemia/hyperlipidemia (postprandial dysmetabolism) is a cardiovascular risk factor. *Am J Cardiol* **100:** 899-904.

Ohlsson A, Shah P (2008). Determinants and prevention of low birth weight: A synopsis of the evidence. Institute of Health Economics: Alberta, Canada.

Ong KK, Loos RJ (2006). Rapid infancy weight gain and subsequent obesity: systematic reviews and hopeful suggestions. *Acta Paediatr* **95:** 904-908.

Orskov C, Rabenhoj L, Wettergren A, Kofod H, Holst JJ (1994). Tissue and plasma concentrations of amidated and glycine-extended glucagon-like peptide I in humans. *Diabetes* **43:** 535-539.

Osmond C, Kajantie E, Forsen TJ, Eriksson JG, Barker DJ (2007). Infant growth and stroke in adult life: the Helsinki birth cohort study. *Stroke* **38:** 264-270.

Owen CG, Whincup PH, Odoki K, Gilg JA, Cook DG (2003). Birth weight and blood cholesterol level: a study in adolescents and systematic review. *Pediatrics* **111:** 1081-1089.

Paalanen L, Männistö S, Virtanen MJ, Knekt P, Räsänen L, Montonen J, Pietinen P (2006). Validity of a food frequency questionnaire varied by age and body mass index. *J Clin Epidemiol* **59:** 994-1001.

Palmgren J, Kushi LH (1991). Re: "Total energy intake: implications for epidemiologic analyses". *Am J Epidemiol* **133:** 1291-1293.

Pansuria M, Xi H, Li L, Yang XF, Wang H (2012). Insulin resistance, metabolic stress, and atherosclerosis. *Front Biosci (Schol Ed)* **4:** 916-931.

Park E (2010). Birth weight was negatively correlated with plasma ghrelin, insulin resistance, and coenzyme Q10 levels in overweight children. *Nutr Res Pract* **4:** 311-316.

Paturi M, Tapanainen H, Reinivuo H, Pietinen P, eds. (2008). The National FINDIET 2007 Survey. *National Public Health Institute: Helsinki, Report No: B23*.

Perälä MM, Hätönen KA, Virtamo J, Eriksson JG, Sinkko HK, Sundvall J, Valsta LM (2011). Impact of overweight and glucose tolerance on postprandial responses to high- and low-glycaemic index meals. *Br J Nutr* **105:** 1627-1634.

Perälä MM, Eriksson JG (2012). Early growth and postprandial glucose, insulin, lipid and inflammatory responses in adulthood. *Curr Opin Lipidol* **23:** 327-333.

Pesonen AK, Räikkönen K, Kajantie E, Heinonen K, Strandberg TE, Järvenpää AL (2006). Fetal programming of temperamental negative affectivity among children born healthy at term. *Dev Psychobiol* **48:** 633-643.

Phillips DI, Barker DJ, Fall CH, Seckl JR, Whorwood CB, Wood PJ, Walker BR (1998). Elevated plasma cortisol concentrations: a link between low birth weight and the insulin resistance syndrome? *J Clin Endocrinol Metab* **83:** 757-760.

Phillips DI, Fall CH, Cooper C, Norman RJ, Robinson JS, Owens PC (1999). Size at birth and plasma leptin concentrations in adult life. *Int J Obes Relat Metab Disord* **23:** 1025-1029.

Phillips DI, Goulden P, Syddall HE, Sayer A, Dennison EM, Martin H, Cooper C, Group. HCS (2005). Fetal and infant growth and glucose tolerance in the Hertfordshire Cohort Study: a study of men and women born

between 1931 and 1939. *Diabetes* **54:** S145-150.

Pietiläinen KH, Kaprio J, Räsänen M, Rissanen A, Rose RJ (2002). Genetic and environmental influences on the tracking of body size from birth to early adulthood. *Obes Res* **10:** 875-884.

Pietinen P (1982). Estimating sodium intake from food consumption data. *Ann Nutr Metab* **26:** 90-99.

Pietinen P, Rimm EB, Korhonen P, Hartman AM, Willett WC, Albanes D, Virtamo J (1996). Intake of dietary fiber and risk of coronary heart disease in a cohort of Finnish men. The Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study. *Circulation* **94:** 2720-2727.

Pietinen P, Paturi M, Reinivuo H, Tapanainen H, Valsta LM (2010). FINDIET 2007 Survey: energy and nutrient intakes. *Public Health Nutr* **13:** 920-924.

Plagemann A, Harder T, Rake A, Waas T, Melchior K, Ziska T, Rohde W, Dorner G (1999). Observations on the orexigenic hypothalamic neuropeptide Y-system in neonatally overfed weanling rats. *J Neuroendocrinol* **11:** 541-546.

Plagemann A, Harder T, Rake A, Melchior K, Rohde W, Dorner G (2000a). Hypothalamic nuclei are malformed in weanling offspring of low protein malnourished rat dams. *J Nutr* **130:** 2582-2589.

Plagemann A, Waas T, Harder T, Rittel F, Ziska T, Rohde W (2000b). Hypothalamic neuropeptide Y levels in weaning offspring of low-protein malnourished mother rats. *Neuropeptides* **34:** 1-6.

Portella AK, Kajantie E, Hovi P, Desai M, Ross MG, Goldani MZ, Roseboom TJ, Silveira PP (2012). Effects of *in utero* conditions on adult feeding preferences. *J DOHaD* **3:** 140-152.

Portha B, Fournier A, Ah Kioon MD, Mezger V, Movassat J (2014). Early environmental factors, alteration of epigenetic marks and metabolic disease susceptibility. *Biochimie* **97:** 1-15.

Primeaux SD, York DA, Bray GA (2006). Neuropeptide Y administration into the amygdala alters high fat food intake. *Peptides* **27:** 1644-1651.

Ravelli AC, van der Meulen JH, Michels RP, Osmond C, Barker DJ, Hales CN, Bleker OP (1998). Glucose tolerance in adults after prenatal exposure to famine. *Lancet* **351:** 173-177.

Ravelli GP, Stein ZA, Susser MW (1976). Obesity in young men after famine exposure in utero and early infancy. *N Engl J Med* **295:** 349-353.

Rees K, Dyakova M, Ward K, Thorogood M, Brunner E (2013). Dietary advice for reducing cardiovascular risk. *Cochrane Database Syst Rev* **3:** CD002128.

Regnault N, Botton J, Forhan A, Hankard R, Thiebaugeorges O, Hillier TA, Kaminski M, Heude B, Charles MA (2010). Determinants of early ponderal and statural growth in full-term infants in the EDEN mother-child cohort study. *Am J Clin Nutr* **92:** 594-602.

Reinivuo H, Valsta LM, Laatikainen T, Tuomilehto J, Pietinen P (2006). Sodium in the Finnish diet: II trends in dietary sodium intake and comparison between intake and 24-h excretion of sodium. *Eur J Clin Nutr* **60:** 1160-1167.

Remmers F, Verhagen LA, Adan RA, Delemarre-van de Waal HA (2008). Hypothalamic neuropeptide expression of juvenile and middle-aged rats after early postnatal food restriction. *Endocrinology* **149:** 3617-3625.

Rendell MS, Jovanovic L (2006). Targeting postprandial hyperglycemia. *Metabolism Clinical and Experimental* **55:** 1263– 1281.

Reynolds RM (2013). Glucocorticoid excess and the developmental origins of disease: two decades of testing the hypothesis--2012 Curt Richter Award Winner. *Psychoneuroendocrinology* **38:** 1-11.

Richardson SI, Freedman BI, Ellison DH, Rodriguez CJ (2013). Salt sensitivity: a review with a focus on non-Hispanic blacks and Hispanics. *J Am Soc Hypertens* **7:** 170-179.

Risnes KR, Vatten LJ, Baker JL, Jameson K, Sovio U, Kajantie E, Osler M, Morley R, Jokela M, Painter RC, Sundh V, Jacobsen GW, Eriksson JG, Sorensen TI, Bracken MB (2011). Birthweight and mortality in adulthood: a systematic review and meta-analysis. *Int J Epidemiol* **40:** 647-661.

Robinson SM, Batelaan SF, Syddall HE, Sayer AA, Dennison EM, Martin HJ, Barker DJ, Cooper C (2006). Combined effects of dietary fat and birth weight on serum cholesterol concentrations: the Hertfordshire Cohort Study. *Am J Clin Nutr* **84:** 237-244.

Räikkönen K, Forsén T, Henriksson M, Kajantie E, Heinonen K, Pesonen AK, Leskinen JT, Laaksonen I, Osmond C, Barker DJ, Eriksson JG (2009). Growth trajectories and intellectual abilities in young adulthood: The Helsinki Birth Cohort study. *Am J Epidemiol* **170:** 447-455.

Sahin H, Erener T, Erginoz E, Vural M, Ilikkan B, Kavuncuoglu S, Yildiz H, Perk Y (2012). The relationship of active ghrelin levels and intrauterine growth in preterm infants. *Eur J Endocrinol* **166:** 399-405.

Salonen MK, Kajantie E, Osmond C, Forsén T, Ylihärsilä H, Paile-Hyvärinen M, Barker DJ, Eriksson JG (2009a). Role of childhood growth on the risk of metabolic syndrome in obese men and women. *Diabetes Metab* **35:** 94-100.

Salonen MK, Kajantie E, Osmond C, Forsén T, Ylihärsilä H, Paile-Hyvärinen M, Barker DJ, Eriksson JG (2009b). Childhood growth and future risk of the metabolic syndrome in normal-weight men and women. *Diabetes Metab* **35:** 143-150.

Salvi P, Revera M, Joly L, Reusz G, Iaia M, Benkhedda S, Chibane A, Parati G, Benetos A, Temmar M (2012). Role of birth weight and postnatal growth on pulse wave velocity in teenagers. *J Adolesc Health* **51:** 373-379.

Sandboge S, Perälä MM, Salonen MK, Blomstedt PA, Osmond C, Kajantie E, Barker DJ, Eriksson JG (2013). Early growth and non-alcoholic fatty liver disease in adulthood-the NAFLD liver fat score and equation applied on the Helsinki Birth Cohort Study. *Ann Med* **45:** 430-437.

Sarwar N, Sattar N, Gudnason V, Danesh J (2007). Circulating concentrations of insulin markers and coronary heart disease: a quantitative review of 19 Western prospective studies. *Eur Heart J* **28:** 2491-2497.

Schellenberg ES, Dryden DM, Vandermeer B, Ha C, Korownyk C (2013). Lifestyle interventions for patients with and at risk for type 2 diabetes: a systematic review and meta-analysis. *Ann Intern Med* **159:** 543-551.

Schellong K, Schulz S, Harder T, Plagemann A (2012). Birth weight and long-term overweight risk: systematic review and a meta-analysis including 643,902 persons from 66 studies and 26 countries globally. *PLoS ONE* **7:** e47776.

Schellong K, Neumann U, Rancourt RC, Plagemann A (2013). Increase of long-term 'diabesity' risk, hyperphagia, and altered hypothalamic neuropeptide expression in neonatally overnourished 'small-for-gestational-age' (SGA) rats. *PLoS ONE* **8:** e78799.

Schou JH, Pilgaard K, Vilsboll T, Jensen CB, Deacon CF, Holst JJ, Volund A, Madsbad S, Vaag AA (2005). Normal secretion and action of the gut incretin hormones glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide in young men with low birth weight. *J Clin Endocrinol Metab* **90:** 4912-4919.

Shenkin SD, Starr JM, Deary IJ (2004). Birth weight and cognitive ability in childhood: a systematic review. *Psychol Bull* **130:** 989-1013.

Shigemura N, Ohta R, Kusakabe Y, Miura H, Hino A, Koyano K, Nakashima K, Ninomiya Y (2004). Leptin modulates behavioral responses to sweet substances by influencing peripheral taste structures. *Endocrinology* **145:** 839-847.

Shultis WA, Leary SD, Ness AR, Bain CJ, Emmett PM (2005). Does birth weight predict childhood diet in the Avon longitudinal study of parents and children? *J Epidemiol Community Health* **59:** 955-960.

Siahanidou T, Mandyla H, Vounatsou M, Anagnostakis D, Papassotiriou I, Chrousos GP (2005). Circulating peptide YY concentrations are higher in preterm than full-term infants and correlate negatively with body weight and positively with serum ghrelin concentrations. *Clin Chem* **51:** 2131-2137.

Siahanidou T, Mandyla H, Militsi H, Papassotiriou I, Chrousos G (2007). Peptide YY (3-36) represents a high percentage of total PYY immunoreactivity in preterm and full-term infants and correlates independently with

markers of adiposity and serum ghrelin concentrations. *Pediatr Res* **62:** 200-203.

Simonetti GD, Raio L, Surbek D, Nelle M, Frey FJ, Mohaupt MG (2008). Salt sensitivity of children with low birth weight. *Hypertension* **52:** 625-630.

Skibicka KP, Dickson SL (2011). Ghrelin and food reward: the story of potential underlying substrates. *Peptides* **32:** 2265-2273.

Skidmore PM, Hardy RJ, Kuh DJ, Langenberg C, Wadsworth ME (2007). Life course body size and lipid levels at 53 years in a British birth cohort. *J Epidemiol Community Health* **61:** 215-220.

Skilton MR, Mikkila V, Wurtz P, Ala-Korpela M, Sim KA, Soininen P, Kangas AJ, Viikari JS, Juonala M, Laitinen T, Lehtimaki T, Taittonen L, Kahonen M, Celermajer DS, Raitakari OT (2013). Fetal growth, omega-3 (n-3) fatty acids, and progression of subclinical atherosclerosis: preventing fetal origins of disease? The Cardiovascular Risk in Young Finns Study. *Am J Clin Nutr* **97:** 58-65.

Sloth B, Davidsen L, Holst JJ, Flint A, Astrup A (2007). Effect of subcutaneous injections of PYY1-36 and PYY3-36 on appetite, ad libitum energy intake, and plasma free fatty acid concentration in obese males. *Am J Physiol Endocrinol Metab* **293:** E604-609.

Smith BK, Berthoud HR, York DA, Bray GA (1997). Differential effects of baseline macronutrient preferences on macronutrient selection after galanin, NPY, and an overnight fast. *Peptides* **18:** 207-211.

Sonnenschein-van der Voort AM, Jaddoe VW, Raat H, Moll HA, Hofman A, de Jongste JC, Duijts L (2012). Fetal and infant growth and asthma symptoms in preschool children: the Generation R Study. *Am J Respir Crit Care Med* **185:** 731-737.

Spiller RC, Trotman IF, Higgins BE, Ghatei MA, Grimble GK, Lee YC, Bloom SR, Misiewicz JJ, Silk DB (1984). The ileal brake--inhibition of jejunal motility after ileal fat perfusion in man. *Gut* **25:** 365-374.

Stafford M, Lucas A (1998). Possible association between low birth weight and later heart disease needs to be investigated further. *BMJ* **316:** 1247-1248.

Stanner SA, Yudkin JS (2001). Fetal programming and the Leningrad Siege study. *Twin Res* **4:** 287-292.

Stein AD, Rundle A, Wada N, Goldbohm RA, Lumey LH (2009). Associations of gestational exposure to famine with energy balance and macronutrient density of the diet at age 58 years differ according to the reference population used. *J Nutr* **139:** 1555-1561.

Stein LJ, Cowart BJ, Beauchamp GK (2006). Salty taste acceptance by infants and young children is related to birth weight: longitudinal analysis of infants within the normal birth weight range. *Eur J Clin Nutr* **60:** 272-279.

Strazzullo P, D'Elia L, Kandala NB, Cappuccio FP (2009). Salt intake, stroke, and cardiovascular disease: meta-analysis of prospective studies. *Bmj* **339:** b4567.

Stuart A, Amer-Wahlin I, Persson J, Kallen K (2013). Long-term cardiovascular risk in relation to birth weight and exposure to maternal diabetes mellitus. *Int J Cardiol* **168:** 2653-2657.

Suzuki K, Simpson KA, Minnion JS, Shillito JC, Bloom SR (2010). The role of gut hormones and the hypothalamus in appetite regulation. *Endocr J* **57:** 359-372.

Söderholm PP, Alfthan G, Tikkanen MJ, Adlercreutz H (2012). Rye bread intake improves oxidation resistance of LDL in healthy humans. *Atherosclerosis* **221:** 583-586.

Tanaka M, Kido Y (2008). Serotonergic regulation of galanin-induced selective macronutrient intake in self-selecting rats. *J Med Invest* **55:** 196-203.

Taylor DJ, Thompson CH, Kemp GJ, Barnes PR, Sanderson AL, Radda GK, Phillips DI (1995). A relationship between impaired fetal growth and reduced muscle glycolysis revealed by 31P magnetic resonance spectroscopy. *Diabetologia* **38:** 1205-1212.

Thompson FE, Byers T (1994). Dietary assessment resource manual. *J Nutr* **124:** 2245S-2317S.

Tzoulaki I, Sovio U, Pillas D, Hartikainen AL, Pouta A, Laitinen J, Tammelin TH, Jarvelin

MR, Elliott P (2010). Relation of immediate postnatal growth with obesity and related metabolic risk factors in adulthood: the northern Finland birth cohort 1966 study. *Am J Epidemiol* **171:** 989-998.

Umabiki M, Tsuzaki K, Kotani K, Nagai N, Sano Y, Matsuoka Y, Kitaoka K, Okami Y, Sakane N, Higashi A (2010). The improvement of sweet taste sensitivity with decrease in serum leptin levels during weight loss in obese females. *Tohoku J Exp Med* **220:** 267-271.

Wadsworth ME, Cripps HA, Midwinter RE, Colley JR (1985). Blood pressure in a national birth cohort at the age of 36 related to social and familial factors, smoking, and body mass. *Br Med J (Clin Res Ed)* **291:** 1534-1538.

van Abeelen AF, Elias SG, Bossuyt PM, Grobbee DE, van der Schouw YT, Roseboom TJ, Uiterwaal CS (2011). Cardiovascular consequences of famine in the young. *Eur Heart J* **33:** 538-545.

Weinberger MH (1996). Salt sensitivity of blood pressure in humans. *Hypertension* **27:** 481-490.

Whincup PH, Kaye SJ, Owen CG, Huxley R, Cook DG, Anazawa S, Barrett-Connor E, Bhargava SK, Birgisdottir BE, Carlsson S, de Rooij SR, Dyck RF, Eriksson JG, Falkner B, Fall C, Forsen T, Grill V, Gudnason V, Hulman S, Hypponen E, Jeffreys M, Lawlor DA, Leon DA, Minami J, Mishra G, Osmond C, Power C, Rich-Edwards JW, Roseboom TJ, Sachdev HS, Syddall H, Thorsdottir I, Vanhala M, Wadsworth M, Yarbrough DE (2008). Birth weight and risk of type 2 diabetes: a systematic review. *JAMA* **300:** 2886-2897.

Vickers MH, Breier BH, McCarthy D, Gluckman PD (2003). Sedentary behavior during postnatal life is determined by the prenatal environment and exacerbated by postnatal hypercaloric nutrition. *Am J Physiol Regul Integr Comp Physiol* **285:** R271-273.

Willett W, Stampfer MJ (1986). Total energy intake: implications for epidemiologic analyses. *Am J Epidemiol* **124:** 17–27.

Willett WC, Howe GR, Kushi LH (1997). Adjustment for total energy intake in epidemiologic studies. *Am J Clin Nutr* **65:** 1220S-1228S; discussion 1229S-1231S.

Vincent RP, Ashrafian H, le Roux CW (2008). Mechanisms of disease: the role of gastrointestinal hormones in appetite and obesity. *Nat Clin Pract Gastroenterol Hepatol* **5:** 268-277.

Winick M, Noble A (1966). Cellular response in rats during malnutrition at various ages. *J Nutr* **89:** 300-306.

Woods LL, Ingelfinger JR, Nyengaard JR, Rasch R (2001). Maternal protein restriction suppresses the newborn renin-angiotensin system and programs adult hypertension in rats. *Pediatr Res* **49:** 460-467.

Woods LL, Weeks DA, Rasch R (2004). Programming of adult blood pressure by maternal protein restriction: role of nephrogenesis. *Kidney Int* **65:** 1339-1348.

Woods SC, D'Alessio DA (2008). Central control of body weight and appetite. *J Clin Endocrinol Metab* **93:** S37-50.

World Health Organization (1985). Energy and protein requirements, Report of a joint FAO/WHO/UNU consultation. *WHO Technical Report No. 724*.

World Health Organization (1998). Carbohydrates in human nutrition. Report of a joint FAO/WHO Expert Consultation. Rome, 14–18 April, 1997. *FAO Food and Nutrition Papers*.

World Health Organization (2004). Human energy requirements. Report of a Joint FAO/WHO/UNU Expert Consultation. Rome, 17-24 October 2001. *FAO Food and Nutrition Technical Report Series*.

World Health Organization (2011). Global status report on noncommunicable diseases 2010. World Health Organization.

World Health Organization Expert Commitee on Physical Status (1995). The newborn infant. In Physical Status: The use and interpretation of anthropometry. World Health Organization: Geneva. pp 121-160.

Xiao X, Zhang ZX, Li WH, Feng K, Sun Q, Cohen HJ, Xu T, Wang H, Liu AM, Gong XM, Shen Y, Yi Z (2010). Low birth weight is associated

with components of the metabolic syndrome. *Metabolism* **59:** 1282-1286.

Xu X, Dailey AB, Peoples-Sheps M, Talbott EO, Li N, Roth J (2009). Birth weight as a risk factor for breast cancer: a meta-analysis of 18 epidemiological studies. *J Womens Health (Larchmt)* **18:** 1169-1178.

Yousheng J, Nguyen T, Desai M, Ross MG (2008). Programmed alterations in hypothalamic neuronal orexigenic responses to ghrelin following gestational nutrient restriction. *Reprod Sci* **15:** 702-709.

Yu Q, Gao F, Ma XL (2011a). Insulin says NO to cardiovascular disease. *Cardiovasc Res* **89:** 516-524.

Yu ZB, Han SP, Zhu GZ, Zhu C, Wang XJ, Cao XG, Guo XR (2011b). Birth weight and subsequent risk of obesity: a systematic review and meta-analysis. *Obes Rev* **12:** 525-542.

Zandi-Nejad K, Luyckx VA, Brenner BM (2006). Adult hypertension and kidney disease: the role of fetal programming. *Hypertension* **47:** 502-508.

Zhao Y, Wang SF, Mu M, Sheng J (2012). Birth weight and overweight/obesity in adults: a meta-analysis. *Eur J Pediatr* **171:** 1737-1746.

Zidar N, Cor A, Premru Srsen T, Stajer D (1998). Is there an association between glomerular density and birth weight in healthy humans. *Nephron* **80:** 97-98.