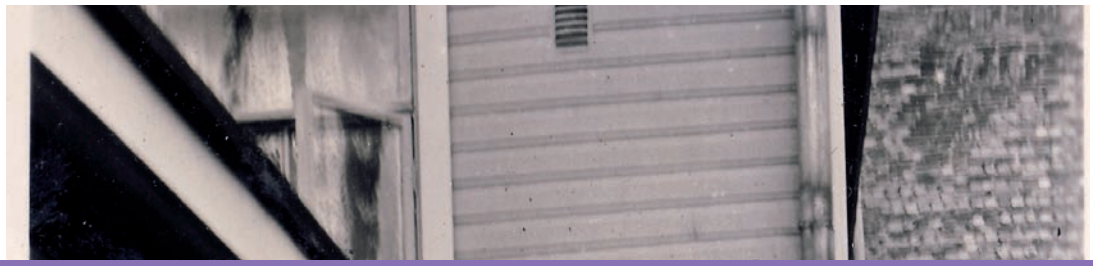
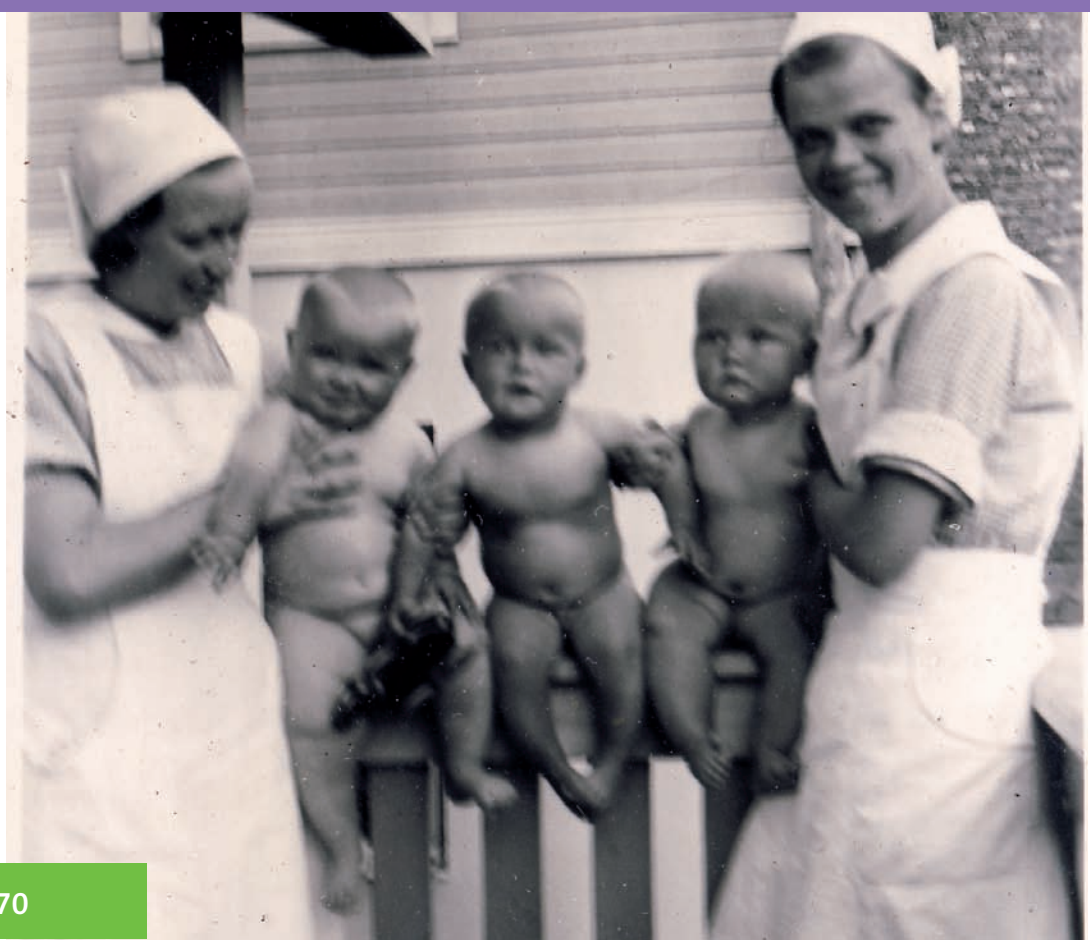


Salonen Minna

RESEARCH

Early Growth and Later Health

Focus on Metabolic Syndrome, Obesity and Physical Activity



RESEARCH 70

Minna Salonen

Early Growth and Later Health

Focus on Metabolic Syndrome, Obesity and Physical Activity

ACADEMIC DISSERTATION

To be presented with the permission of the Medical Faculty of the University of Helsinki, for public examination in the Auditorium XII, University Main Building, on December 16th, 2011 at 12 a.m.

Helsinki 2011

National Institute for Health and Welfare and
Department of Chronic Disease Prevention
and
Department of General Practice and Primary Health Care, University of Helsinki, Finland
and
Department of Public Health, Hjelt Institute, University of Helsinki, Finland

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To my Father

Abstract

Minna Salonen. Early Growth and Later Health. Focus on metabolic syndrome, obesity and physical activity. National Institute for Health and Welfare (THL). Research 70. 143 pages. Helsinki, Finland 2011.
ISBN 978-952-245-541-3 (printed); ISBN 978-952-245-542-0 (pdf)

Background. The Developmental Origins of Health and Disease Hypothesis proposes that adverse health outcomes in adult life are in part programmed during fetal life and infancy. It has been suggested that a "thrifty phenotype" occurs as a consequence of programming, i.e. restricted nutrition during pregnancy programmes the offspring to store fat more effectively, to develop faster and to reach puberty earlier. These adaptations could well be beneficial in terms of short term survival. However, in developed countries these adaptations can lead to a "mismatch", causing an increased risk of obesity and metabolic disturbances in later life.

Aims. This thesis aimed to study the role of early growth in people who are obese in adult life, but metabolically healthy and in those who are normal in weight but metabolically obese. Other study aims were to assess whether physical activity and cardiorespiratory fitness are programmed early in life. The role of socioeconomic status in the development of obesity from a life course setting was also one study objective.

Subjects and methods. These studies were part of the Helsinki Birth Cohort Study including 8760 men and women, born in Helsinki between 1934 and 1944, all of whom attended child welfare clinics; the majority also went to school in the city. They all had detailed information of their prenatal and childhood growth as well as living conditions in childhood. 2003 men and women participated in the detailed clinical examination during the years 2001-2004. The clinical examinations included blood sampling (i.e. glucose, lipids, insulin), oral glucose tolerance testing, blood pressure measurements, assessment of body composition, questionnaires on medication and exercise habits and UKK Institute 2-kilometre walk test. Metabolic syndrome was defined according to the 2005 criteria of the International Diabetes Federation.

Results. Prevalence of obesity was 22.3% in men and 27.2% in women. Lower educational attainment and lower adult social class were associated with obesity in both men and women. Childhood social class was inversely associated with body mass index (BMI) only in men while lower household income was associated with higher BMI in women.

Out of 499 obese (BMI $\geq$ 30 kg/m^2) men and women 20 % (n=99) were metabolically healthy. Those 400 with the metabolic syndrome had higher BMIs, and larger waist circumferences than those who did not. The two groups did not differ in birth size, but by two years of age, those with metabolic syndrome were lighter and thinner, and remained so up to 11 years. The period when changes in BMIs were predictive of the syndrome was from birth to seven years.

Out of the 588 normal weight individuals (BMI $\leq$ 25 kg/m^2) 98 (17%) were identified as metabolically obese. The metabolically obese had higher BMIs, body fat percentages and larger waist circumferences. Again, there were no differences in the body size at birth or at two years of age between the groups. By the age 7 years, those men who later developed metabolic syndrome were thinner. Gains in BMI during the first two years of life were protective of the syndrome.

Those with higher engagement in leisure time physical activity showed a more favourable adult anthropometric and body composition profile than those who were more sedentary. Leisure time physical activity was positively associated with adult social class. Higher weight and length at birth and weight at 2 years after adjustment for adult BMI, predicted higher intensity of total leisure time physical activity. Higher height at 2, 7 and 11 years predicted higher intensity of conditioning leisure time physical activity. Higher weight and height at 2, 7 and 11 years predicted higher energy expenditure of total leisure time physical activity. In addition, higher height at 2 and 11 years predicted higher energy expenditure of conditioning leisure time physical activity.

Body size at birth was not associated with adult cardiorespiratory fitness. An increase in height at 2 and 7 years was associated with higher maximal oxygen uptake (VO_{2max}). Adjustment for adult lean body mass strengthened these findings. Weight at 2 and 7 years and height at 11 years were positively associated with (VO_{2max}). However, higher BMI at the age of 11 was associated with lower adult VO_{2max}, and remained so after adjustment for adult lean body mass.

Conclusions. These findings suggest that both childhood and adult socioeconomic circumstances may play a role in development of obesity. Men seamed to be more vulnerable to the childhood social circumstances, and in women household income was the strongest predictor of obesity. Obese but metabolically healthy were those, who were heavier and had higher BMIs from 2 to 11 years of age, and grew faster in the period from birth to 7 seven years. In normal weight individuals, metabolically obese were those males who had smaller gains in BMI during the first two years of life and were thinner at age 7 years. Those who were heavier and taller in childhood engage more in leisure time physical activity and have higher aerobic fitness levels

in later life. These results support the role of early life factors in the development of metabolic syndrome and adult life style.

Keywords: cardioresrpiratory fitness, DOHaD, early growth, epidemiology, metabolic syndrome, obesity, physical activity, socioeconomic status.

Tiivistelmä

Minna Salonen. Varhainen kasvu ja aikuisiän terveys. Metabolinen oireyhtymä, lihavuus ja fyysinen aktiivisuus. Tutkimus 70. 143 sivua. Helsinki, Finland 2011.
ISBN 978-952-245-541-3 (painettu); ISBN 978-952-245-542-0 (pdf)

Tausta. Elämänkaarinäkökulman mukaan aikuisiän krooniset sairaudet voivat saada alkunsa sikiöaikana tai varhain lapsuudessa. Raskauden aikainen vajaaravitsemus voi johtaa siihen, että sikiö mukautuu epäsuotuisiin olosuhteisiin varastoimalla rasvaa tehokkaammin, kasvamalla nopeammin ja saavuttamalla puberteetin nuorempana. Kehittyneissä maissa, joissa nälkiintyminen on harvinaista, tämä ”ohjelmoituminen” voi altistaa yksilön terveyden kannalta epäsuotuisille muutoksille, kuten lihomiselle ja erilaisille myöhemmällä iällä ilmeneville aineenvaihdunnan häiriöille.

Tavoitteet. Tämän väitöskirjatyön tarkoituksena oli tutkia varhaiskasvun vaikutusta riskiin sairastua metaboliseen oireyhtymään lihavien sekä normaalipainoisten miesten ja naisten keskuudessa sekä tutkia varhaista kasvua suhteessa aikuisiän fyysiseen aktiivisuuteen ja fyysiseen kuntoon. Lisäksi sosio-ekonomisen aseman yhteyttä lihavuuteen tutkittiin elämänkaarinäkökulmasta käsin.

Aineisto ja menetelmät. Alkuperäiseen epidemiologiseen kohorttiin kuuluu 8760 vuosina 1934–44 Helsingissä syntynyttä miestä ja naista, joiden syntymä-, neuvola- ja koulutiedot sisältäen kasvumittoja sekä elinoloja koskevaa tietoa, ovat saatavilla. Heistä yhteensä 2003 henkilöä osallistui yksityiskohtaisiin kliinisiin tutkimuksiin vuosien 2001 – 2004 aikana keskimäärin 61 vuoden iässä. Kliinisiin tutkimuksiin sisältyi verinäytteiden otto, oraalinen sokerirasitustesti, verenpainemittaukset, kehon koostumuksen mittaukset sekä kyselyt lääkityksestä, liikunta-aktiivisuudesta sekä muista elintavoista. UKK-insituutin 2 kilometrin kävelytesti tehtiin osalle kliiniseen tutkimukseen osallistuneista. Metabolinen oireyhtymä määritettiin kansainvälisen diabetesliiton (IDF) 2005 – kriteereitä noudattaen.

Tulokset. Lihavuuden esiintyvyys miehillä oli 22,3 % ja vastaavasti naisilla 27,2 %. Alhaisemmat koulutustaso ja sosiaaliluokka olivat yhteydessä lihavuuteen sekä miehillä että naisilla. Lapsuusiän sosiaaliluokka ja painoindeksi olivat käänteisesti yhteydessä lihavuuteen miehillä. Vastaavasti talouskohtaiset tulot olivat käänteisesti yhteydessä painoindeksiin naisilla.

Lihaviksi luokiteltiin 499 henkilöä joiden painoindeksi oli $\geq$ 30 kg/m^2. Heistä 99 oli metabolisesti terveitä. Metabolista oireyhtymää sairastavilla oli korkeammat painoindeksit ja suuremmat vyötärönympärykset verrattuna metabolisesti terveisiin. Ryhmien välillä ei havaittu eroja syntymäpainon suhteen, mutta saavuttaessaan kahden

vuoden iän ne, jotka olivat metabolisesti sairaita aikuisena, olivat laihempia ja kevyempiä aina 11 ikävuoteen saakka. Se kasvukausi, jolla todettiin olevan oireyhtymää ehkäisevä vaikutus, sijoittui syntymän ja 7 ikävuoden välille.

Normaalipainoisia (painoindeksi $\leq$ 25 kg/m^2) oli kaikkiaan 588, joista metabolisesti sairaita 98. Myös normaalipainoisilla metabolista oireyhtymää sairastavilla oli korkeammat painoindeksit ja suuremmat vyötärönympärykset verrattuna metabolisesti terveisiin. Syntymäpainoissa ei havaittu eroja ryhmien välillä. Aikuisena oireyhtymään sairastuneet miehet olivat 7-vuotiaina hoikempia kuin miehet, jotka pysyivät metabolisesti terveinä. Kasvupyrähdys painoindeksillä mitattuna syntymän ja kahden ikävuoden välillä oli yhteydessä pienempään riskiin sairastua oireyhtymään aikuisiällä.

Vapaa-ajan liikuntaa enemmän harrastavat olivat hoikempia verrattuna vähemmän liikkuviin sekä kuuluivat ylempään aikuisiän sosiaaliluokkaan. Suuremmat syntymäkoko ja paino 2-vuotiaana ennustivat korkeampaa kokonaisliikunta-intensiteettiä. Pituus 2-, 7- ja 11-vuotiailla oli positiivisesti yhteydessä korkeampaan kuntoliikunta-intensiteettiin. Korkeampi paino ja pituus 2-, 7- ja 11-vuotiaana ennusti korkeampaa kokonaisliikunnan energiankulutusta. Lisäksi pituus 2- ja 11 -vuotiaana oli positiivisesti yhteydessä kuntoliikunnan energiankulutukseen.

Syntymäpainolla ei todettu olevan yhteyttä fyysiseen kuntoon. Pituuden kasvu 2 ja 7 vuoden iässä oli yhteydessä korkeampaan maksimaaliseen hapenottokykyyn. Aikuisiän rasvattoman massan huomioiminen mallissa voimisti yhteyttä. Paino 2- ja 7-vuotiaana ja pituus 11-vuotiaana olivat positiivisesti yhteydessä maksimaaliseen hapenottokykyyn. Kuitenkin 11 vuoden iässä suhteellisen painon lisääntyminen oli yhteydessä alhaisempaan maksimaaliseen hapenottokykyyn ja yhteys pysyi muuttumattomana aikuisiän rasvattoman massan huomioimisen jälkeen.

Päätelmät. Sekä lapsuuden että aikuisiän sosioekonomisilla olosuhteilla voi olla merkitystä lihavuuden kehittymiselle. Tämän tutkimuksen perusteella miehet saattavat olla herkempiä kuin naiset lapsuusajan sosiaalisille olosuhteille. Naisilla suuremmat talouskohtaiset tulot suojasivat lihavuudelta. Ihmiset, jotka olivat lihavia, mutta metabolisesti terveitä, olivat lapsuudessaan vankempia. Niin ikään normaalipainoiset, jotka täyttivät metabolisen oireyhtymän kriteerit, olivat lapsena suhteellisesti pienikokoisempia verrattuna terveisiin. Edelleen henkilöt, jotka lapsena olivat suurempikokoisia, harrastivat enemmän vapaa-ajan liikuntaa ja olivat fyysisesti parempikuntoisia. Lisäksi sosiaaliluokalla saattaa olla vaikutusta liikunta-aktiivisuuteen. Nämä tulokset vahvistavat aiempia tutkimustuloksia siitä, että varhainen kasvu tulisi huomioida tärkeänä tekijänä myöhemmän iän terveysriskejä arvioitaessa ennaltaehkäisevässä kansanterveystyössä.

Avainsanat: elämänkaarinäkökulma, epidemiologia, fyysinen aktiviteetti, fyysinen kunto, lihavuus, metabolinen oireyhtymä, sosio-ekonominen asema, varhainen kasvu.

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II Salonen MK, Kajantie E, Osmond C, Forsén T, Ylihärsilä H, Paile-Hyvärinen Maria, Barker DJP, Eriksson JG. Childhood growth and future risk of the metabolic syndrome in normal-weight men and women. Diabetes & Metabolism 2009: 35: 143-150.

III Salonen MK, Kajantie E, Osmond C, Forsén T, Ylihärsilä H, Paile-Hyvärinen M, Barker DJP, Eriksson JG. Role of socioeconomic indicators on development of obesity from a life course perspective. Journal of Environmental and Public Health 2009: doi:10.1155/2009/625168.

IV Salonen MK, Kajantie E, Osmond C, Forsén T, Ylihärsilä H, Paile-Hyvärinen M, Barker DJP, Eriksson JG. Prenatal and childhood growth and leisure time physical activity in adult life. European Journal of Public Health 2010: Epub 2010 Dec 1.

V Salonen MK, Kajantie E, Osmond C, Forsén T, Ylihärsilä H, Paile-Hyvärinen M, Barker DJP, Eriksson JG. Developmental origins of physical fitness: The Helsinki Birth Cohort Study. PlosOne 2011: 6: e22302.

Abbreviations

AACE	American Association of Clinical Endocrinologists
AHA	American Heart Association
BIA	Bioelectrical impedance analysis
BMI	Body mass index
CHD	Coronary heart disease
CRF	Cardiorespiratory fitness
CT	Computed tomography
CVD	Cardiovascular disease
DEXA	Dual-energy x-ray absorptiometry
DNA	Deoxyribonucleic acid
DOHaD	Developmental Origins of Health and Disease
EE	Energy expenditure
EGIR	European Group for the Study of Insulin Resistance
FPG	Fasting plasma glucose
HBCS	Helsinki Birth Cohort Study
HDL	High density lipoprotein
IAS	International Atherosclerosis Society
IASO	International Association for the Study of Obesity
IDF	International Diabetes Federation
IUGR	Intrauterine growth restriction
JIS	Joint Interim Societies
KIHD	Kuopio Ischaemic Heart Disease Study
LTPA	Leisure time physical activity
MET	Metabolic equivalent
MNO	Metabolically normal obese
MONW	Metabolically obese normal weight
MS	Metabolic syndrome
NCEP	National Cholesterol Education Program
NHANES	National Health and Nutrition Examination Survey
NHLBI	National Lung, Heart and Blood Institute
OGTT	Oral glucose tolerance test
OR	Odds ratio
SEP	Socioeconomic position
SES	Socioeconomic status
VO_{2max}	Maximal oxygen uptake
WC	Waist circumference
WHF	World Heart Federation
WHO	World Health Organization
WHR	Waist-to-hip ratio

1 Introduction

The obesity epidemic was recognized around 1980 and has been rising inexorably ever since. Obesity is one of the most important risk factors contributing to the overall disease burden worldwide (Ezzati et al. 2002). The major causes of premature morbidity and mortality and public health concerns associated with obesity are cardiovascular disease, type 2 diabetes, and certain cancers (WHO 2000). Overweight and obesity constitute to about 80% of cases of type 2 diabetes, 35% of ischaemic heart disease and 55% of hypertension among adults in the European region and cause more than 1 million deaths and 12 million life-years of ill health each year (WHO 2007). Non-communicable diseases such as cardiovascular disease, diabetes and metabolic syndrome account for 60% of all deaths globally (WHO 2008). While it is recognized that the increase in non-communicable diseases is mainly due to an adoption of a western life style, there is increasing evidence suggesting that early life and developmental factors play an important role.

A large number of recent epidemiological studies have shown an association between birth weight and several chronic diseases including cardiovascular disease and type 2 diabetes (Barker 1995; Eriksson et al. 2000; Forsen et al. 2004; Kajantie et al. 2008). Roots of the Developmental Origins of Health and Disease theory are based on epidemiological findings by David Barker in the 1980's together with experimental studies in animals (Barker 1998a). The original theory proposes that health outcomes in adult life may be the result of "programming" during fetal life and infancy. The underlying mechanisms of programming are not fully understood, but important, putative mechanisms include permanent changes in body composition as well as lifelong alterations in the function of key endocrine systems.

Major influences of postnatal growth patterns on later health are also well established, although results of studies are contradictory. While results from several studies show an association between slow gains in body size and cardiovascular disease and its risk factors (Barker et al. 2005; Eriksson et al. 2006; Kajantie et al. 2008), others have shown just the opposite effect of growth during infancy (Ekelund et al. 2007; Tzoulaki et al. 2010) on these diseases.

Research of the Developmental Origins of Health and Disease theory field has in recent years expanded from the original cardiovascular related studies to examine a variety of chronic diseases. In this thesis the focus remains in this traditional field of risk factors for cardiovascular diseases. The aim of this study was to explore the role of fetal and childhood growth in sub-groups of metabolic syndrome, in men and

women who are normal weight but metabolically obese, and in those who are obese but metabolically healthy. The aim was also to investigate the role of fetal and childhood growth on adult leisure time physical activity as well as on cardiovascular fitness, both highly important factors influencing human health. Obesity was examined in relation to several indicators of socioeconomic status from a life course perspective.

While the results assessing the relationships between early growth and adult cardiovascular disease and type 2 diabetes are shown to be quite consistent, there is a contradiction in the results of those studies assessing the relationships between early growth and several other diseases or conditions. Consistency of the results concerning the associations between early growth and cardiovascular disease and type 2 diabetes may partly be due to similarity of the methods that have been used in the diagnosis and in the risk assessments. However, measurements of e.g. obesity, metabolic syndrome, socioeconomic status and physical activity suffer from the variability of measure techniques as well as limit values in assessing these diseases or conditions, and therefore comparability of the study results is often challenging or even impossible.

2 Review of the literature

2.1 Developmental origins of health and disease (DOHaD) theory

2.1.1 Birth size and adult health

Fetal origins hypothesis

Nearly forty years ago Forsdahl reported that arteriosclerotic heart disease was associated with past infant mortality in 20 Norwegian counties, and he was the first to suggest that poor living conditions in childhood followed by prosperity was a risk factor for heart disease (Forsdahl 1977). A similar pattern has been observed all over the world (Hinkle 1973; Buck, Simpson 1982; Marmot, Shipley & Rose 1984; Notkola 1985). However, Barker and his colleagues were the first ones who expanded this to a theory of early life origins of health and disease. This is also known as "The Barker hypothesis". Barker and colleagues showed that men who had the lowest birth weights had the highest death rates from ischemic heart disease in a cohort of people born in Hertfordshire during 1911-1930 (Barker et al. 1989).

Several studies in different populations have shown that birth weight is inversely associated with morbidity and mortality from cardiovascular disease (CVD) (Barker et al. 1993; Osmond et al. 1993; Forsen et al. 1997; Forsen et al. 1999; Eriksson et al. 1999; Lawlor et al. 2005; Kajantie et al. 2005; Huxley et al. 2007), type 2 diabetes (Eriksson et al. 2003; Oken, Gillman 2003; Vickers, Krechowec & Breier 2007) and the metabolic syndrome (Hales et al. 1991; Eriksson et al. 2006). These results have been confirmed in over 40 populations worldwide. While earlier reports on early growth associations have focused mainly on hypertension, CVD and type 2 diabetes, the more recent studies in the field have expanded to a wider range of disorders including osteoporosis (Cooper et al. 2006), depression (Cheung et al. 2002; Paile-Hyvärinen et al. 2007; Räikkönen et al. 2007; Tuovinen et al. 2010), schizophrenia (Wahlbeck et al. 2001; Gunnell et al. 2005), autoimmune diseases (Kajantie et al. 2006), respiratory function (Canoy et al. 2007), cardiorespiratory fitness (Lawlor et al. 2008; Ortega et al. 2009; Ridgway et al. 2009), physical activity (Laaksonen et al. 2003; Eriksson et al. 2004) and cancers (Hilakivi-Clarke et al. 2001; McCormack et al. 2005). Furthermore, a high birth weight again has been found to be associated with later risk of obesity (Curhan et al. 1996a; Curhan et al. 1996b; Rasmussen, Johansson 1998) and type 2 diabetes (Harder et al. 2007) and

both low and high birth weights are associated with a higher risk of all-cause mortality in adulthood (Baker, Olsen & Sorensen 2008).

Measurements of birth size

Birth weight is the most commonly used indicator of fetal growth in epidemiological studies. Birth weight is frequently known and maternally reported weight is recalled even many years post delivery (Catov et al. 2006; Adegboye, Heitmann 2008). Importantly, birth weight is not necessarily a causal exposure in its own. However, it is a marker of growth and development in utero, which may be affected by several factors such as maternal size, age, parity, nutrition, stress and smoking, placental structure and function and genes.

The phrase intrauterine growth restriction (IUGR) is used when a fetus has failed to reach its optimum growth. In addition to birth weight, with the use of suitable reference curves it is possible to classify an individual based on their birth weight for their gestational age. Other commonly used measures of fetal growth include head circumference, birth length and ponderal index [birth weight (kg)/birth length $(cm)^3$].

2.1.2 Impact of childhood growth on adult health and disease

Growth during the first year of human life can be considered as a continuum of the fetal period. Hormonal regulation mechanisms of the child during the first year of life are similar to those of the fetal period; development is rapid, and even small alterations can lead to irreversible consequences. Growth in childhood is affected by genes as well as environmental influences. A fetus, which has failed to reach its optimum growth, may, however, achieve a similar body size compared with other children of the same age. The greatest variation in rates of weight gain is seen in infancy, during the 1-2 years of life when infants may show significant accelerated growth ("catch-up") or just the opposite ("catch-down") growth. These variable growth rates typically compensate for intrauterine restraint or enhancement of fetal growth.

Certain patterns of postnatal growth in early childhood have been shown to be associated with a wide range of chronic diseases in later life although the findings are still inconsistent. While results of several studies suggest that slow gain in body size during the first two years of life is associated with increased risk of CVD (Eriksson et al. 2001; Forsen et al. 2004; Barker et al. 2005), type 2 diabetes (Eriksson et al. 2006) and dyslipidemia (Skidmore et al. 2007; Kajantie et al. 2008) and poor intellectual ability (Räikkönen et al. 2009), others have shown just the opposite effect of growth during infancy (Ong et al.; 2000 Ekelund et al.; 2006

Tzoulaki et al. 2010). Findings from the Helsinki Birth Cohort Studies (HBCS) have indicated that a small body size at 1 year of age is associated with an increased risk of coronary heart disease (CHD), independently of birth size (Eriksson et al. 2001). Additionally, findings from the same cohort have shown that men, who later developed CHD had a small body size at birth and remained thin through infancy up to 2 years of age. Thereafter, they showed accelerated gain in weight and BMI compared with the rest of the study cohort (Eriksson et al. 2001).

2.1.3 Underlying mechanisms

Thinness at birth is a marker of inadequate fetal growth due to the lack of nutrients or to the dysfunction of the placenta. Nutrient insufficiency can lead to altered blood flow in the body, and the fetus redirects the nutrients to the most important organs such as the brain at the expense of tissues such as the muscle and the endocrine pancreas. The phenomenon has been called programming. Programming describes the process when events during critical periods of development may even permanently change structure and function of the organism (Barker 1995; Barker 1998a; Barker 1998b; Barker 2004; Barker 2007). Mechanisms underlying programming include diminished cell volume, abnormal gene structure, changes in gene expression, hormonal function and growth factors. However, the biological mechanisms behind early life programming and the developmental origins of health and disease are not fully understood. Other proposed mechanisms include altered hormone sensitivity and epigenetic modifications.

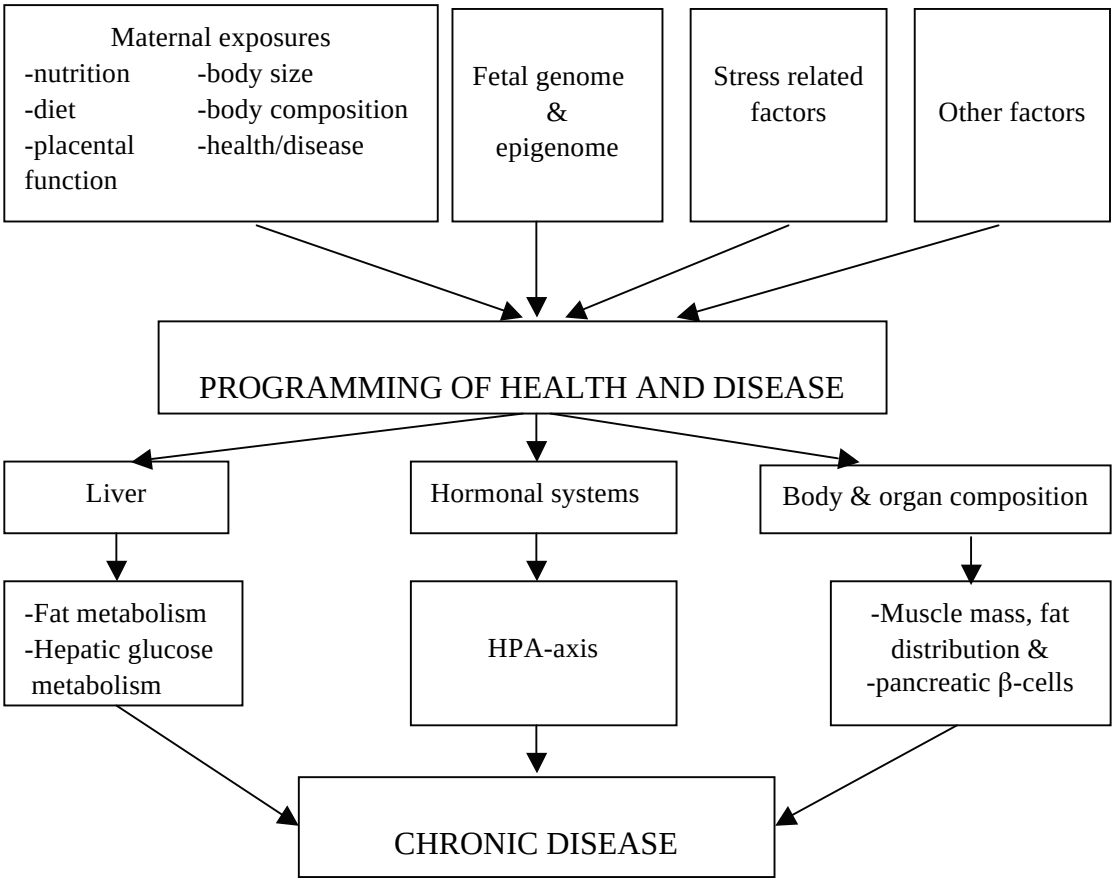
To account for the association between low birth weight and increased risk for type 2 diabetes in later life Hales and Barker proposed the “thrifty phenotype” hypothesis (Hales, Barker 1992). As a consequence of programming, e.g. due to undernutrition in fetal life or in childhood, the baby becomes thrifty. This may lead to permanent changes in the body’s structure, physiology and metabolism, e.g. to elevated fat storages, to faster development and to earlier maturation. In developed countries starvation is rare and these adaptations can lead to a “mismatch”, causing increased risk of obesity and metabolic disturbances in later life.

The patterns of growth predisposing to later diseases are complex. Growth retardation, either during fetal period or in infancy, followed by catch-up growth has been suggested to favour accumulation of disproportioned fat, especially abdominal fat, at the expense of muscle mass, and this tendency may persist into adulthood (Kahn et al. 2000; Ong et al. 2000; Sachdev et al. 2005). These alterations in body composition may play a role in the development of insulin resistance, the major metabolic disturbance behind the metabolic syndrome and related features.

Epigenetics

Recent advances in genetics have lead to the field of epigenetics. The potential mechanisms behind the programming are referred to as epigenetic alterations, i.e. changes in the regulation of gene transcription and expression, rather than changes in the DNA sequence itself. Regulators of gene expression are e.g. changes in DNA methylation, histone modification, acetylation and phosphorylation (Feinberg 2008; Gluckman et al. 2008). Epigenetic changes have been shown to be sensitive to intrauterine conditions and these changes may persist for subsequent generations (Painter et al. 2008). Suggested pathways of fetal programming are demonstrated in figure 1.

Figure 1. Pathways of fetal programming of adult disease. Modified from Eriksson JG, Diabetes 2010.



2.2 Obesity

2.2.1 Assessment of obesity

Obesity is defined as an excess of body fat that presents a health risk (WHO 2000). Excessive fat accumulation in adipose tissue is a consequence of imbalance between energy intake and energy expenditure. Obesity is a complex, multifactorial disease that develops from the interaction between genotype and the environment. How and why obesity occurs is still poorly understood; however it involves the integration of social, behavioural, cultural, physiological, metabolic and genetic factors.

Overweight and obesity can be measured in several ways. Most current epidemiological studies of body size use body mass index (BMI) to define degrees of obesity. BMI is calculated as the subject's weight in kilograms divided by the square of height in metres (kg/m^2). BMI is regarded as a useful, albeit crude population-level measure of obesity (WHO 2000). BMI does not provide information on body fat distribution and does not discriminate between muscle and adipose tissue.

Individuals, who are peripherally obese, have their fat distributed subcutaneously around the gluteofemoral region and in the lower part of the abdomen, are at low or no risk of the common medical complications of overweight. On the other hand, individuals with upper-body/central obesity have accumulated fat in the subcutaneous abdominal and visceral depots and are prone to metabolic and cardiovascular complications, e.g. type 2 diabetes (de Koning et al. 2010).

In epidemiological studies intra-abdominal body fat is most commonly estimated using measurements of waist and hip circumference. Waist-to-hip ratio (WHR) is calculated as the ratio of the waist circumference to the hip circumference. Waist circumference (WC) is simpler to measure and interpret, and also correlates better than WHR with visceral fat measured by computed tomography (CT) or magnetic resonance imaging (MRI), the "gold standards" for such determination (Pouliot et al. 1994; Molarius, Seidell 1998; Rankinen et al. 1999). Additional measurements of obesity are dual-energy X-ray absorptiometry (DEXA), isotope dilution, air-displacement plethysmography (Bod Pod) and underwater weighing. These methods are more precise than BMI, WHR or WC, albeit expensive and more difficult to use in practice. Another tool which is practical in body composition measures in epidemiological studies is bioelectrical impedance analysis (BIA). It is based on differences in electrical conductivity between fat and fat-free mass (Bedogni et al. 2002).

2.2.2 Classification of obesity

Obesity is clinically commonly defined using BMI (table 1), although there is no clear agreement as to which anthropometric measure is the single best indicator for abdominal obesity. Because WC is relatively easy to measure, its use is favoured over WHR. Despite the fact that BMI and WC are highly correlated, it is preferred to obtain BMI, and if possible, to consider the joint use of the two indicators (WHO 2008). However, there is no agreement on which cut-off points are best for disease risk assessment. More over, numerous studies world wide have suggested ethnic specific cut-off points (table 2).

Table 1. Classification of body size according to BMI.

Body size	BMI (kg/m^2)
Underweight	< 18.5
Normal	18.5-24.9
Overweight	25.0-29.9
Obesity (Class I)	30.0-34.9
Obesity (Class II)	35.0-39.9
Extreme obesity (Class III)	$\geq$ 40.0

Adapted from "Preventing and Managing the Global Epidemic of Obesity. Report of the World Health Organization Consultation of Obesity." WHO, Geneva, June 1997.

Table 2. International Diabetes Federation criteria for ethnic or country specific values for waist circumference.

Country or ethnic group	Sex	Waist circumference (cm)
Europid	Men Women	> 94 > 80
South Asian	Men Women	> 90 > 80
Chinese	Men Women	> 90 > 80
Japanese	Men Women	> 90 > 80

Adapted from Alberti, Zimmet & Shaw (2006).

2.2.3 Prevalence of obesity

According to National Health and Nutrition Examination Survey (NHANES) data from a 2007-2008 period, 68% of adults in the United States aged 20-74 years are overweight or obese, with rates of 72% for men and 64% for women. For men, the age-adjusted prevalence of obesity was 32% while the corresponding figure for women was 36% (Selassie, Sinha 2011). Recent reports from the United States indicate that the linear increase may have entered a period of relative stability. However, the prevalence of obesity (BMI $\geq$ 30 kg/m^2) still remains high, exceeding 30% in most age groups in both genders (Flegal et al. 2010).

Although worldwide increase in the prevalence of obesity during the past decades has been widely documented, including the European region (WHO 2000), there is a great variability in the reported prevalence of obesity between the countries as well as within the countries.

Prevalence of obesity in Finland

According to the results of the nationwide Finnish risk factor survey (FINRISK), upward trends have been observed in BMI measured every five years in 1972, 1977, 1982 in men (table 3). Between the surveys in 1987 and 1992, the increase in the BMI prevalence levelled, until increasing again in 2002. However, there was no increase in BMI between the surveys conducted in 2002 and 2007 (Vartiainen et al. 2010). In women, the downward trend in BMI was observed between the surveys in 1972 and 1982 and thereafter the trend has began to rise slightly and has continued to do so until 2007 (Vartiainen et al. 2010). Based on results from another extensive Finnish survey (Health 2000) carried out in Finland in 2000 and 2001, the prevalence of obesity among men was 20.7% and 24.1% in women (Lahti-Koski et al. 2010).

Table 3. Prevalence of different BMI categories in Finland in 1972, 1982,1992, 2002 and 2007.

	BMI					
	Men			Women		
Survey years	<24.9 kg/m^2 (%)	25.0-29.9 kg/m^2 (%)	>30.0 kg/m^2 (%)	<24.9 kg/m^2 (%)	25.0-29.9 kg/m^2 (%)	>30.0 kg/m^2 (%)
1972	43	46	11	40	39	22
1982	37	47	16	50	34	16
1992	37	44	19	52	31	18
2002	31	46	23	48	33	19
2007	31	47	21	47	32	21

Figures are based on the study of Vartiainen et al. 2010.

Prevalence and trends in overweight and obesity in Finnish children

At the beginning of the 1970's 3.5% of school-aged prepubertal boys and 3.0% of girls, and 10% of preschool children were reported to be obese according to a study by the Helsinki school health service (Helve a, Kantero RL, Koli T 1971; Kantero 1975). In the 1980's obesity was prevalent in 6.9% in boys and and 17.3% in girls aged 6 years. Correspondingly, 4.8% of boys and 3.3% of girls from 9 to 18 years of age were obese (Nuutinen et al. 1991). The prevalence of overweight has doubled and obesity tripled among adolescents between 1980 and 1992/1993 (Laitinen, Soivio 2005). In the 2000's, according to results of the Special Turku Coronary Risk Factor Intervention Project for Children, the overall prevalence of overweight was reported to be 17.8% and 23.6% in boys and girls at 10 years of age, respectively (Hakanen et al. 2006). Based on results from another study, the corresponding prevalence figures were 26.5% and 17.9% in 12-year-old boys and girls and 25.1% and 12.5% at the age of 18 years (Kautiainen et al. 2009). Overall prevalence of overweight has doubled or even tripled between the 1970's and the 2000's. In these days, on average every tenth of young child and fourth of adolescents is at least overweight (Mäki et al. 2010).

Consequences of obesity

Overweight and obesity cause or exacerbate a large number of health problems either independently or in association with other diseases. The major obesity-related contributors to ill health are shown in table 4. Although effective methods are in urgent demand for weight reduction in overweight and obese adults, serious attention should be directed to the prevention of overweight and obesity in children and young people.

Table 4. Most common physical health risks associated with increasing BMI and obesity.

Cardiovascular diseases	
Coronary artery disease	
Stroke	
Hypertension	
Cardiac insufficiency	
Metabolic diseases	
Insulin resistance	
Type 2 diabetes	
Dyslipidemia	
Gout	
Lung diseases	
Wheezing	
Bronchial hyper-responsiveness	
Pulmonary heart disease	
Sleep apnoea	
Gastro-intestinal diseases	
Cholelithiasis	
Fatty liver	
Esophagitis	
Joint diseases	
Gout	
Arthrosis	
Cancers	
Men:	*Women:*
Intestinal	Breast
Prostate	Ovarian
Kidney	Cervical
Others	
Hirsutism	
Menstrual disturbances	
Hypogonadism	

2.2.4 Adipose tissue as a metabolic organ

Obesity can also be characterised according to increased size (hypertrophy) and increased number (hyperplasia) of adipocyte (Faust et al. 1978). Based on recently presented data, obese subjects are described as having a higher total adipocyte number than lean indivuals (Spalding et al. 2008). The number of adipocytes is set during childhood and adolescence and continues to stay approximately the same in adulthood. About 10% of the total fat cell pool is renewed by ongoing adipogenesis and adipocyte death annually through entire adulthood at all BMI levels (Spalding et al. 2008).

Only few decades ago, adipose tissue was considered mainly as an inert reservoir storing triglycerides. Currently, it is regarded as a complex, highly active metabolic and endocrine organ (Juge-Aubry, Henrichot & Meier 2005; MacDougald, Burant 2007). Adipose tissue produces a large variety of proteins and adipokines, regulating systemic processes, such as food intake and nutrient metabolism, insulin sensitivity, stress responses, reproduction, bone growth and inflammation. Highly important aspect of adipose tissue endocrinology is the recognition that besides adipocytes, adipose tissue contains pre-adipocytes, macrophages, endothelial cells, fibroblasts, and leukocytes (Weisberg et al. 2003; Fain et al. 2004; Juge-Aubry, Henrichot & Meier 2005). This varied composition renders adipose tissue an important mediator of inflammation and whole body metabolism.

2.2.5 Early growth and obesity in adult life

Results from several studies have shown that the individuals born with higher birth weight are at increased risk of becoming overweight or obese later in life (Curhan et al. 1996a; Curhan et al. 1996b; Whitaker, Dietz 1998; Oken, Gillman 2003; Rogers, EURO-BLCS Study Group 2003). Some other studies have found a J- or U-shaped relationship with birth weight and later obesity (Fall et al. 1995; Curhan et al. 1996a; Rogers, EURO-BLCS Study Group 2003;).

A study of young adults exposed in utero to the Dutch famine showed that the effect of prenatal exposure to famine depended on its timing. The rate of obesity was higher in men exposed to famine in the first half of gestation and lower in men exposed in the last trimester or in the immediate postnatal period than non-exposed men (Jelliffe 1966; Ravelli, Stein & Susser 1976). Another study found that the BMIs of 50 years old women exposed to famine in early gestation was significantly higher than in those non-exposed (Ravelli et al. 1999). Eriksson and co-authors have shown that birth weight and ponderal index were associated with incidence of obesity in later life in men. This study also found that those who were heavier, taller

and had higher BMI by the age 7 and remained so up to 15 years, were also more obese as adults (Eriksson et al. 2001).

2.2.6 Obesity and socioeconomic status

Concepts of socioeconomic status (SES) and socioeconomic position (SEP) are commonly used to define social and economic factors and the position individuals or groups hold within the societal culture (Krieger, Williams & Moss 1997; Lynch, Kaplan 2000). Most commonly used fundamental indicators of SES are occupation, education and income. For a more complete picture of the socioeconomic phenomenon in relation to the outcome of interest, the use of multiple indicators is recommended, including early life indicators.

In developed countries, obesity has been strongly and negatively linked to SES. In the late 1980's a strong negative association between SES and obesity was found in women across the developed world. Of 54 studies including women 85% showed a negative association, 13% no association, and the rest showed a positive association (Sobal, Stunkard 1989). Among men and children the association was found to be less consistent. In developing countries the association has appeared to be just the opposite, a positive one in both sexes and children. Approximately 10 years later another comprehensive study found, both in males and females, a strong consistent negative association between childhood SES and obesity in adulthood in developing countries (Parsons et al. 1999).

Obesity is known to track from childhood into adult life (Power, Lake & Cole 1997; Eriksson et al. 2001), and those who already are overweight or obese as children, also tend to be obese as adults. While genetic and lifestyle factors are well known high risk factors in the development of obesity, social circumstances are strongly linked to adult overweight and obesity (Sobal, Stunkard 1989; Parsons et al. 1999; Eriksson et al. 2003). It has been suggested that parental overweight, low SES and high birth weight are the major determinants of overweight and obesity in childhood (Danielzik et al. 2004; Dubois, Girard 2006) and in later life (Whitaker, Dietz 1998). Childhood overweight has been linked with severe obesity in both men and women, although more strongly in men, which demonstrates the importance of childhood overweight as a risk factor for severe obesity over the life-course (Whitaker et al. 1997; Ferraro, Thorpe & Wilkinson 2003).

2.3 Metabolic syndrome

Metabolic syndrome (MS) is characterized by the co-occurrence of abdominal obesity, dyslipidemia, hyperglycaemia, and hypertension. The pathogenesis of the syndrome has multiple origins, but obesity, a sedentary lifestyle, and still largely unknown genetic factors clearly interact to in causing the syndrome. People with the MS are at increased risk of coronary heart disease, other atherosclerotic diseases (e.g. stroke and peripheral vascular disease) and type 2 diabetes.

2.3.1 Definition of metabolic syndrome

There have been several different definitions for MS, the most commonly used are presented in table 5; 1) The criteria of the WHO (Alberti, Zimmet 1998), 2) the criteria of the European Group for the Study of Insulin Resistance (EGIR) (Balkau, Charles 1999), 3) the criteria of the National Cholesterol Education Program-Third Adult Treatment Panel (NCEP ATP III) (Grundy, 2001), updated by AHA/NBLHI (Grundy et al. 2005), 4) the criteria of the American Association of Clinical Endocrinologists (AACE) (Bloomgarden 2003) and 5) criteria by the International Diabetes Federation (IDF) (Alberti, Zimmet & Shaw 2006). The latest initiative to develop one global unified definition for the clinical criteria, is a joint statement by IDF, National Lung, Heart and Blood Institute (NHLBI), American Heart Association (AHA), World Heart Federation (WHF), International Atherosclerosis Society (IAS), and International Association for the Study of Obesity (IASO) in 2009 (Alberti et al. 2009). The organization agreed on the definition in which three simultaneously occurring abnormal findings out of five would qualify a person for the MS.

Table 5. Definitions for metabolic syndrome according to the WHO, EGIR, NCEP ATP III, IDF and JIS.

Components	**WHO (1999)**	**EGIR (1999)**	**NCEP ATP III (2001)**	**IDF (2005)**	**JIS (2009)**
1) Fasting plasma glucose (mmol/L)	Glucose intolerance, IGT/diabetes/insulin resistance	≥ 6.1 mmol/L	≥ 5.6 mmol/L	≥ 5.6 mmol/L or type 2 diabetes	≥ 5.6 mmol/L or type 2 diabetes
2) Blood pressure (mmHg)	≥ 140/90 mmHg	≥ 140/90 mmHg	≥ 130/85 mmHg	≥ 130/85 mmHg or treatment	≥ 130/85 mmHg or treatment
3) Triglycerides (mmol/L)	≥ 1.7 mmol/L	> 2.0 mmol/L	> 1.7 mmol/L	> 1.7 mmol/L or treatment	> 1.7 mmol/L or treatment
4) HDLcholesterol (mmol/L)	< 0.9 mmol/L ♂ < 1.0 mmol/L ♀	> 1.0 mmol/L	< 1.03 mmol/L ♂ < 1.29 mmol/L ♀	< 1.03 mmol/L ♂ < 1.29 mmol/L ♀ or treatment	< 1.03 mmol/L ♂ < 1.29 mmol/L ♀ or treatment
6) WC/WHR (cm/ ratio of waist to hip)	WHR: > 90 ♂ WHR: > 85 ♀	WC: ≥ 94 cm ♂ WC: ≥ 80 cm ♀	WC: ≥ 102 cm ♂ WC: ≥ 88 cm ♀	WC: ≥ 94 cm ♂ WC: ≥ 80 cm ♀	WC: ≥ 94 cm ♂ WC: ≥ 80 cm ♀
5) Microalbuminuria	Urinary albumin excretion rate ≥ 20 µg/min of albumin-creatinine ratio ≥ 30 mg/g				
Definition of MS and number of components required for diagnosis	Fasting glucose + ≥2 of the components above	Insulin resistance + ≥2 of the components above		Increased waist circumference + ≥2 of the components above	≥3 of the components above

♂=male;♀=female

2.3.2 Metabolically healthy obese individuals

In 1947, Vague concluded that android obesity, with upper body predominance and pronounced muscle development, is associated with metabolic and cardiovascular disturbances. In contrast, gynecoid obesity, with predominance of lower body fat, and less muscular development, mainly presents mechanical and aesthetic problems (Vague 1947; Vague 1996). Later on, in 1965, Albrink et al. reported that upper body obesity was associated with blood lipid disorders (Albrink, Meigs 1965). In 1968, Salans et al. reported that adipocyte size varied inversely with their insulin sensitivity, and that obesity with normal sized adipocytes was associated with onset in childhood (Salans, Knittle & Hirsch 1968).

A concept of metabolically normal but obese individuals (MNO) refers to a subgroup of obese individuals with relatively high degree of insulin sensitivity and a favourable metabolic profile (Ferrannini et al. 1991; Bonora et al. 1998). However, similarly to the existence of many multiple definitions of the MS, a uniform definition for these obesity phenotypes is still lacking. Depending on the definitions applied and on the study population it is assessed that between 10 to 40 % of overweight individuals have been described as metabolically normal (Ferrannini et al.1997; Bonora et al. 1998; Brochu et al. 2001; Karelis, Brochu & Rabasa-Lhoret 2004; Karelis et al. 2005). Furthermore, a recent study reported that in comparison between two different methods, the prevalence of MNO was nearly as high as 50% in those measured by DEXA technique compared to the 34% in those measured by BMI (Shea, Randell & Sun 2011).

2.3.3 Metabolically obese normal weight individuals

The existence of a subgroup of individuals who are normal in weight (BMI < 25 kg/m^2), but have a clustering of metabolic risk factors which usually are closely related to obesity, was first introduced by Ruderman and his co-workers (Ruderman, Schneider & Berchtold 1981; Ruderman, Berchtold & Schneider 1982). They suggested that the metabolically obese normal weight (MONW) individuals, despite having a normal body mass index, present hyperinsulinemia and/or insulin resistance with the co-existence of hyperlipidemia and hypertension - the major risk factors for cardiovascular diseases.

Prevalence of MONW individuals varies between study cohorts from 5 to 45% (Dvorak et al. 1999; Molero-Conejo et al. 2003; Park et al. 2003; Conus et al. 2004; St-Onge, Janssen & Heymsfield 2004; Meigs et al. 2006). The percentage varies with the method and criteria used, and with age, sex and ethnicity of the subject.

The fact that an individual has BMI $\leq$ 25 kg/m^2 does not necessarily imply that he/she would not suffer from excessive adipose tissue, which plays a major role in the development of insulin resistance (Kelley et al. 2000; Freedland 2004). Increased adiposity in the abdominal and visceral areas in particular, are typical feature of MONW subjects.

2.3.4 Early growth, type 2 diabetes and metabolic syndrome

Studies within the DOHaD field have convincingly shown that small body size at birth or non-optimal early growth is associated with separate components on the MS (Hales et al. 1991; Barker et al. 1993; Barker et al. 1993; Yarbrough et al.1998; Eriksson et al. 2000; Kajantie et al. 2008). Less consistent findings have been reported when an accepted definition for the syndrome have been used. This is obviously due to variety of definitions.

It has been shown in elderly men that there is an inverse association between prenatal and infant growth and subsequent impaired glucose tolerance (Hales et al. 1991), and the prevalence of metabolic syndrome in both men and women (Barker et al. 1993). Since the early 1990's, several studies have shown negative association between birth weight and glucose tolerance (Ravelli et al. 1998; Rich-Edwards et al. 1999). Furthermore, higher prevalence of impaired glucose tolerance has been reported to be greater in those who were exposed to the famine in Holland in 1944-1945 during mid or late gestation. Impairment of glucose regulation was also more common in offspring of thin mothers and in those who became obese (Ravelli et al. 1998).

Associations described in statistics as the U-shape have been reported as well (McCance et al. 1994). The Pima Indian residents of the Gila River Indian community in Arizona have the highest ever reported prevalence of type 2 diabetes, which often has its onset at an early age. Studies examining this Indian community have reported the strong association between high birth weight and type 2 diabetes, mainly due to maternal glucose intolerance together with genetic make-up. McCance et al., however, found a U-shaped relation of the prevalence of diabetes to birth weight in the Pima Indians which was related to maternal gestational diabetes. Low birth weight was associated with type 2 diabetes (McCance et al. 1994). These results are in line with the results from previous studies suggesting the associations between low birth weight and later disease risk.

2.4 Physical activity

2.4.1 Physical activity, exercise and physical fitness

Physical activity is generally defined as any body movement produced by skeletal muscles resulting in energy expenditure above resting level (Caspersen, Powell & Christenson 1985). The terms exercise and physical fitness are closely related to, but are different from physical activity, even though they share several common elements. Exercise is a subcategory of physical activity; it is planned, structured, repetitive, and purposive in a sense that improvement or maintenance of one or more components of physical fitness is an objective (Caspersen, Powell & Christenson 1985).

Physical fitness is a set of attributes that people have or achieve that relates to ability to perform physical activity (Caspersen, Powell & Christenson 1985). Measurable components of physical fitness often fall into two categories; one being a health-related, and the other being an athletic ability related skill (Pate 1983). The most commonly used measures in health-related fitness assessment are the measurements of certain components of fitness, such as cardiorespiratory, body composition, muscular strength, muscular endurance and flexibility.

Physical activity or inactivity related to intensity or energy expenditure can be categorised in several ways. Moderate-intensity physical activity, when carried out regularly, is the most effective for most people. Moderate-intensity physical activity is the type of activity that raises the heartbeat, produces some sweating and slight shortness of breath. It is often considered equivalent to a brisk walking, meaning that the metabolism is raised to at least three times its resting level (three metabolic equivalents, METs) (Cavill, Kahlmeier & Racioppi 2007). Vigorous-intensity physical activity is the type of activity that works up a sweat and gets out of breath, for example running and fast cycling. Vigorous physical activity raises the metabolism to at least six times its resting level, six METs.

2.4.2 Effects of exercise on mortality

Exercise therapy can have positive effects on overall health. The most consistent finding of this study was that aerobic/functional capacity and/or muscle strength can be improved by exercise training in patients with different chronic diseases (Kujala 2009). According to a systematic review, exercise therapy in cases of documented coronary heart disease reduced all-cause mortality by 27% and total cardiac mortality by 31% (Jolliffe et al. 2001). Another study showed that exercise training increased heart rate variability in patients with coronary artery disease (Taylor et al. 2004).

Equally, physiological benefits of exercise therapy in heart failure patients are well documented. The findings have shown increases in maximal oxygen uptake (VO_{2max}), exercise duration, maximum work capacity and distance walking (Lloyd-Williams, Mair & Leitner 2002; Rees et al. 2004). Benefits of aerobic training on blood pressure, HDL cholesterol and triglycerides have been well documented as well (Cornelissen, Fagard 2005; Kelley, Kelley & Franklin 2006).

Effects of exercise on cardiovascular risk factors

It is proven, that exercise reduces visceral fat among adults (Ohkawara et al. 2007) and body fat percentage in children despite having similar total body weight (Atlantis, Barnes & Singh 2006; Thomas, Elliott & Naughton 2006) indicating increased muscle mass as a consequence of exercise training.

Post-intervention glycated haemoglobin values have been found to be significantly lower in the groups exercising than in control groups suggesting a reduced risk for type 2 diabetes complications (Thomas, Elliott & Naughton 2006). Additionally, regular exercise has been shown to increase maximal oxygen uptake (Boule et al. 2003) while resistance training improves glycaemic control (Snowling, Hopkins 2006; Sigal et al. 2007) in type 2 diabetic patients.

2.4.3 Early growth and physical activity in later life

Results based on animal studies have suggested that restricted fetal growth may well play a role in exercise habits and sedentary behaviour in later life. Severe malnourishment of a pregnant rat led to smaller body size at birth and inactivity among the offspring and sedentary behaviour was exacerbated by post-natal hypercaloric nutrition (Vickers et al. 2003). However, studies in humans in this field of research are scarce. While lower activity levels have been reported in children (Rogers et al. 2005) as well as in adults (Hovi et al. 2007) among those who were born with very low birth weight, other studies assessing the association of birth size with physical activity in both childhood (Boreham et al. 2001; Hallal et al. 2006; Mattocks et al. 2008) and in later adult life (Laaksonen et al. 2003; Eriksson et al. 2004; Andersen et al. 2009) have been inconsistent. Based on recent findings from a larger study, the authors found that both low and high birth weights were associated with lower leisure time physical activity (Andersen et al. 2009).

2.4.4 Early growth and cardiorespiratory fitness in later life

Cardiorespiratory fitness is undoubtedly a good indicator of overall health. As physical activity increases physical fitness and the other way around, association of cardiorespiratory fitness with several health outcomes remain when physical activity levels are taken into account.

It has been proposed that physical activity may be on the causal pathway between early life and later metabolic health (Andersen et al. 2009). Reduced fetal growth may lead into reduced muscle mass, lower levels of physical performance and aerobic fitness, and potentially lower levels of physical activity, which may all play a role in higher metabolic risk associated with low birth weight. In a Finnish study, reduced size at birth was found to be associated with metabolic syndrome but not among those who showed a favourable fitness profile and physical activity (Laaksonen et al. 2003). Earlier findings in HBCS have suggested that people who have experienced a fetal growth restriction would benefit most from exercise as adults by getting the highest protective effect against type 2 diabetes (Eriksson et al. 2004). Studies investigating the association between birth weight and physical performance, most commonly measured by grip-strength, have shown positive associations between birth weight and grip-strength in adulthood (Sayer et al. 2004; Kuh et al. 2006; Inskip et al. 2007; Ylihärsilä et al. 2007; Ortega et al. 2009;).

How and to what extent cardiorespiratory fitness in later adult life, in itself, is programmed early in life has been little studied. Publications in the field have mainly focused on children, adolescents or young adults (Lawlor et al. 2008; Ortega et al. 2009; Ridgway et al. 2009). Therefore the long term influences of early growth on cardiorespiratory fitness remain to be studied.

3 Aims of the study

The overall aim of this thesis was to explore the associations of early growth with obesity-related complications and sedentary behaviour in terms of metabolic syndrome and physical activity in later adult life. Another aim was to study the associations of socioeconomic status and obesity using a longitudinal study design.

The specific aims were:

1. To identify the characteristics of early growth that protect obese individuals from metabolic syndrome.

2. To identify the characteristics of early growth that predispose the normal weight individuals to metabolic syndrome.

3. To explore the role of socioeconomic factors from a life-course perspective on the development of obesity in later life.

4. To explore whether physical activity in later life is programmed.

5. To explore whether early growth predicts cardiovascular fitness in later life.

4 Subjects and methods

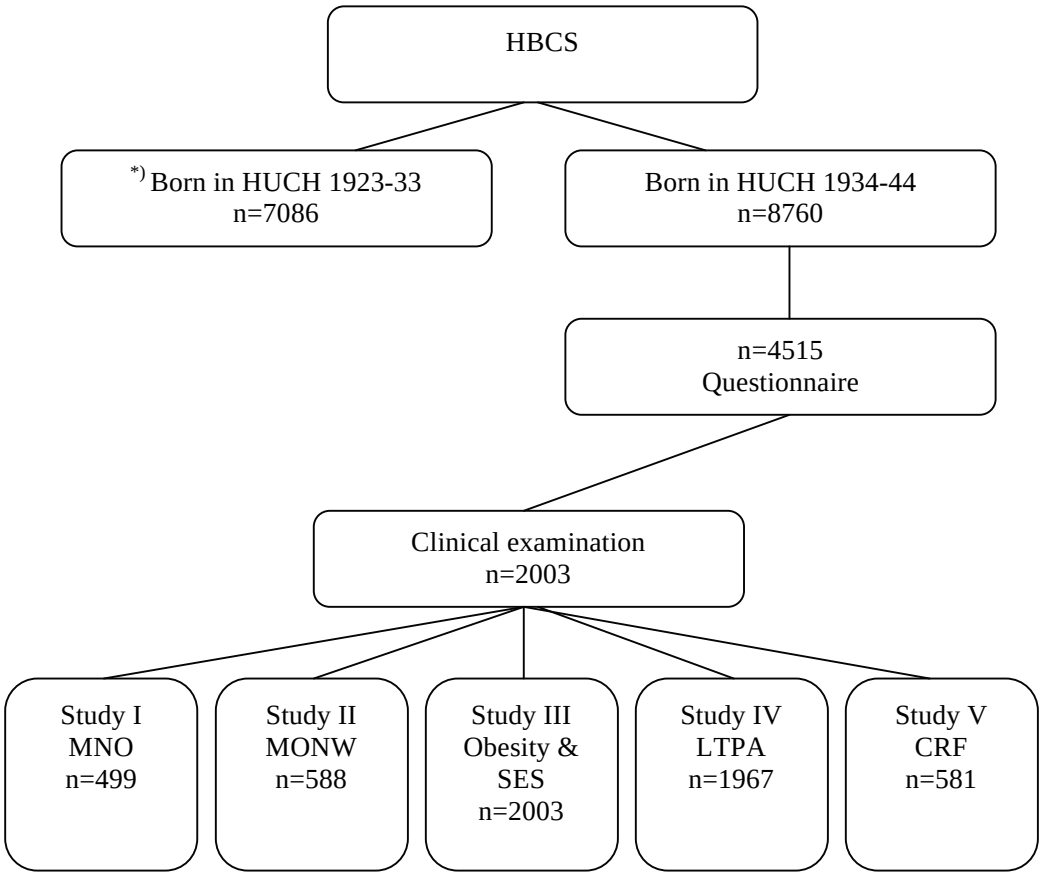
4.1 Helsinki Birth Cohort Study

The Helsinki Birth Cohort Study (HBCS) consists of two historical birth cohorts. The older cohort comprises of 7086 men and women born in Helsinki during 1924-1933. Participants of the present study belong to a younger cohort comprising 8760 individuals, 4630 men and 4130 women, born 1934-44. The participants of these studies were born in Helsinki University Central Hospital (HUCH), attended child welfare clinics, the majority also went to school in Helsinki, and were alive and residing Finland in 1971.

The birth records contain data on the newborn babies as well as their mothers. Data on the newborn babies include birth weight, length, head circumference and placental weight. Data on the mothers include age, height, parity, date of the last menstrual period, and weight measured on admission in labour. Child welfare records include serial measurements of height and weight in infancy and at intervals thereafter. School health records include serial height and weight measurements recorded from 7 to 12 years of age. All three childhood records contain information on paternal occupation as well as living conditions at the time.

A unique identification number was allocated to each resident in Finland in 1971. The people belonging to the cohort were traced by using this identification number. All 7079 people who belonged to the original cohort, and who were still alive and resident in Finland in the year 2000 were sent a questionnaire. In brief, this questionnaire was based on questionnaires used in the FINRISK and Health 2000 studies and aimed to gather information on their general background including social circumstances, health and diseases, medication, height and weight, life style, and background information on the parents. A total of 4515 responded. In order to achieve a sample size over 2000 people for a clinical study, random number tables were used to select 2902 subjects. Of them 2003 men (n=928) and women (n=1075) participated in the clinical study.

Figure 2. Flow chart on sub-groups of the HBCS participants included to the present study.



*) This cohort was not included in the present study

4.2 Clinical examination

Studies I-V

The participants attended the clinic in the morning after an overnight fast. Written informed consent was obtained from each participant before any study procedure was initiated. A standard 75 g oral glucose tolerance test (OGTT) was performed. Plasma glucose concentrations were measured by a hexokinase method from samples drawn at 0, 30 and 120 min. The results were interpreted according to the WHO 1999 criteria (WHO 1999). Insulin concentrations were determined by a two-site immunoradiometric assay. The homeostatic model assessment index of basal insulin resistance was calculated as the product of fasting glucose and insulin (mU/I) divided by 22.5. Blood pressure was measured with a standard sphygmomanometer and recorded as the mean of two successive readings. Serum total cholesterol, HDL cholesterol and triglyceride concentrations were measured with the use of standard enzymatic methods.

Several anthropometric measurements were performed. Height was measured to the nearest millimetre, and body weight to the nearest 0.1 kg in light clothing without shoes. Body mass index (BMI) was calculated as kg/m^2. Waist circumference (WC) was measured at midway between the lowest ribs and the iliac crest. Estimates of total lean and fat mass were measured by a bioelectrical impedance analysis (BIA) using the InBody 3.0 eight-polar tactile electrode system (Biospace Co., Ltd, Seoul, Korea). This method has been found to be practical in large epidemiological studies (Bedogni et al. 2002; Malavolti et al. 2003) as well as accurate in several ethnic groups with age-ranges of great variability (Gibson et al. 2008).

Detailed information on smoking habits, leisure time physical activity (LTPA), educational attainment, marital status and family history of type 2 diabetes among others were obtained from a self-administered questionnaire which was completed at the clinic. Occupation-based social class was obtained from census data. Data on taxable household income in Finnish marks per year were derived from Statistics Finland. The basic data are drawn from the Tax Administration's database which is based on data including all people who have received income and are subject to taxation or own property which is subject to taxation.

At the clinical examination the subjects completed the validated Kuopio Ischemic Heart Disease Study exercise questionnaire (KIHD 12-month LTPA history) (Lakka, Salonen 1992; Lakka et al. 1994). The questionnaire was used to assess duration, frequency and intensity of the most common forms of LTPA including indoor and outdoor activities performed during the previous 12 months.

Studies I ja II

For studies 1 and 2 metabolic syndrome (MS) was defined according to the International Diabetes Federation (IDF) 2005 criteria: central obesity (waist circumference $\geq$94 cm in men and $\geq$80 cm in women) and at least two of the following factors: 1) serum triglycerides $\geq$1.70 mmol/l or specific treatment for this lipid abnormality; 2) serum HDL cholesterol < 1.03 mmol/l in males and < 1.29 mmol/l in females or specific treatment for this lipid abnormality; 3) systolic blood pressure $\geq$130 or diastolic $\geq$85 mmHg, or treatment of previously diagnosed hypertension; 4) fasting plasma glucose (FPG) $\geq$ 5.6 mmol/l or previously diagnosed type 2 diabetes (Alberti, Zimmet & Shaw 2006). In the first study the focus was on the 499 individuals who were obese (body mass index $\geq$ 30 kg/m^2), while the second study comprised of 588 normal weight individuals (body mass index $\leq$ 25 kg/m^2).

Studies I-V

Socioeconomic and sociodemographic predictors were parental and own social class based on occupation, educational attainment, household income, and marital status. The data on the fathers' occupation were gathered from the birth, child welfare clinic and school health records. The fathers were grouped into three groups (labourers, lower middle, and upper middle class) based upon a social classification system used by Statistic Finland (Central Statistical Office of Finland 1989). Childhood social class was based on fathers' highest occupation.

In study 3 subjects with BMI $\geq$ 30 kg/m^2 were considered obese. Data on subjects' own occupation recorded in the 1990 census were derived from the Central Statistical Office of Finland, and in a similar way they were regrouped into three categories (Central Statistical Office of Finland 1993). Data on schooling (number of years studied) and information on marital status were obtained from the questionnaire at the clinical examination. Data on taxable household income in the year 1990 were obtained from the Central Statistical Office of Finland. The basic data was drawn from the Tax Administration's database and was based on data including all individuals who received income and were subject to taxation or own property subject to taxation.

Study IV

The KIHD 12-month LTPA questionnaire was used in study 4. For each intensity grade, activity-specific metabolic equivalent (MET) values were used. MET was defined as the ratio of the metabolic rate during activity to the rate at rest [MET corresponds to an energy expenditure (EE) of 1 kcal×kg^{-1}×h^{-1}]. Total exercise comprises a variety of leisure time activities, from house keeping and gardening (non-conditioning) to e.g. jogging and resistance training (conditioning).

Conditioning exercise is defined as more dedicated and vigorous physical activity. The rates of EE during physical activity depend on intensity, duration and frequency of activity and on the body size of the person, and thus LTPA was calculated accordingly. A total of 1967 subjects (907 men and 1060 women) with adequate information on their LTPA were included in this study.

Study V and the UKK 2-km walk test

A subset of the original clinical cohort took part in the UKK Insititute 2-km walk test. The test is an indirect measurement of cardiorespiratory fitness (CRF), which can be used within a majority of the adult population without requirements of maximal physical efforts. The test has been validated against maximal effort test by treadmill or bicycle ergometry in multiple populations including the obese and the elderly (Laukkanen et al. 1992; Rance et al. 2005). During the test, subjects are directed to walk through a 2-km course on flat ground as fast as possible. The test results are expressed either as fitness index or as VO_{2max}, by using a formula in which the subjects' age, sex, BMI, time spent walking and heart rate are taken into account.

Several health status requirements for the UKK test were set. A subject was excluded if he/she had any of the following conditions affecting the walk test: myocardial infarction within the past year, unstable blood pressure, CHD with symptoms, active arthritis or other joint disorder with pain, arrhythmia, asthma or other breathing difficulties, and if the subject had other medical restrictions concerning physical activity. Subjects on drug therapy affecting pulse rate were also excluded from the analyses. From the clinical cohort 606 people participated. However, individuals (n=25) whose test result indicated a VO_{2max} under 10 ml/kg/min were excluded from further analysis, because those with the VO_{2max} value of this low can not reach the level required in the UKK test, and thus 581 subjects (269 men and 312 women) remained in the study.

4.3 Statistical methods

The children had a median of seven (quartiles: 4, 12) measurements of height and weight from birth to 2 years of age, and eight (quartiles: 6, 9) measurements from 2 to 11 years of age. Each growth measurement was converted for each individual into a Z-score (standard deviation score). Because the children were not measured exactly on their birthdays, a Z-score was obtained for birthdays by interpolating the available measurements. This procedure enabled the estimation of height, weight and BMI for each child on birthdays from age 1 to 11 years. Most of the visits to child welfare clinics occurred before the age of two, and fewer measurements were performed during the time period from two years and enrolment at school. Therefore the chosen measurements assessing childhood body size at different time points were at birth, 2, 7 and 11 years of age. Fore the same reason assessment of childhood growth during the periods from birth to 2 years, from 2 to 7 years and from 7 to 11 years were used. To determine how much body size at any age differed from that predicted by the body size attained at an earlier age, we used the residuals from linear regression analyses, which we refer to as "conditional growth". By this construction, the residuals are not correlated with the earlier measurements (De Stavola et al. 2006).

In studies 1 and 2 the odds ratios for the metabolic syndrome (MS) were calculated in relation to estimates of adult body size/anthropometrics including height, weight, BMI, lean body mass and percentage of body fat. In a similar way, we calculated the odds ratios for the MS and the individual components of the MS in relation to estimates of childhood body size (height, weight and BMI at birth and at 2, 7 and 11 years of age) and gestational age at birth. We examined the effect of gains in height and BMI after birth according to three periods of growth (from birth to 2 years, from 2 to 7 years and from 7 to 11 years of age) on the MS. Measures of adult anthropometrics, life style and social factors, treated as covariates, were included in the analyses. We tested the difference in effect-size estimates between men and women by creating interaction terms as the product of a predictor variable and dummy variable. When interactions were observed, the analyses for men and women were presented separately; otherwise the analyses were pooled.

In study 3 tests for trends in body mass index were based on linear regression models, always including age. We calculated the odds ratios for obesity (BMI $\geq$ 30 kg/m^2) in relation to estimates of socioeconomic status. Also individual effects of socioeconomic status were studied. Modest correlations between the indicators gave opportunity to use approaches in which by adding the indicator one by one until all the indicators were included which constituted a full adjusted model. Analyses were conducted separately for men and women.

In study 4 a multiple linear regression analysis was conducted to explore the relations of body size at birth, at 2, 7 and 11 years, adult body composition, socioeconomic and life style factors with frequency, duration, intensity and energy expenditure levels of total and conditioning LTPA. Variables with skewed distribution were log-transformed. Interactions between sex and growth variables were tested. Independent effects of childhood and adult social class were studied in relation to LTPA as well.

For study 5 a multiple linear regression was used to assess the associations of birth size, childhood height, weight and BMI with CRF. The basic models were always adjusted for age and in the pooled analysis also for sex. Additional analysis included the adjustments for gestational age, maternal BMI, childhood and adult socioeconomic class, exercise habits, smoking status and current lean body mass. The regression models were further investigated using a quadratic term for each of the childhood body size variables (height and weight at birth, at 2, 7 and 11 years); however, there was no evidence for nonlinear associations. Interaction terms were created to explore potential interactions between gender and growth measures in association to CRF. No interactions were found.

4.4 Ethics

The study protocols were approved by the Ethics Committee of the National Public Health Institute, City of Helsinki, Ministry of Social Affairs and Health, and the Ethics Committee of Epidemiology and Public Health of the Hospital District of Helsinki and Uusimaa. Written informed consent was obtained from each subject. The study was conducted in accordance with the guidelines of the Declaration of Helsinki.

5 Results

5.1 Early growth and metabolically normal obese individuals

Of the 2003 subjects 499 were obese (BMI $\geq$ 30 kg/m^2), and 99 of them (20%) were metabolically healthy. As shown in table 6 the metabolically normal obese (MNO) adults were lighter, had lower BMIs and smaller waist circumferences. In men, the association between metabolic syndrome (MS) and lean body mass was attenuated after adjustment for BMI. Adjustments for smoking or exercise habits did not affect these associations.

Table 6. Clinical characteristics of the 499 obese study participants with and without the metabolic syndrome.

	Metabolic syndrome				
	Present (n=400) (185 m, 215 f)		**Absent** (n=99) (21m, 78 f)		
	Mean	SD	Mean	SD	p-value
MEN					
Age (years)	61.4	2.7	61.7	2.1	0.7
Height (cm)	177.0	6.3	174.5	4.2	0.09
Weight (kg)	105.2	14.2	97.2	7.3	0.006
BMI (kg/m^2)	33.6	4.1	31.9	1.5	0.04
Waist circumference (cm)	116.3	8.9	110.3	5.6	0.003
Lean body mass (kg)	72.4	8.0	67.8	5.4	0.02
Body fat (%)	30.8	5.2	29.9	3.1	0.5
WOMEN					
Age (years)	61.6	3.1	61.7	3.2	0.8
Height (cm)	162.6	5.7	162.2	6.5	0.7
Weight (kg)	91.0	11.9	88.2	10.6	0.07
BMI (kg/m^2)	34.4	4.2	33.5	3.3	0.08
Waist circumference (cm)	107.2	10.0	103.0	9.4	0.002
Lean body mass (kg)	52.6	5.5	51.6	5.7	0.2
Body fat (%)	41.6	4.6	41.1	3.8	0.4

P-values represent statistical significance of odds ratios for the metabolic syndrome in relation to age adjusted adult body composition

Childhood growth and metabolically healthy obesity

Body size at birth was similar in the metabolically healthy and unhealthy groups. However, by the age of two years, those who later developed the MS were lighter and thinner, and remained so until 11 years of age (figure 3). There was no association with height. There were no differences in the heights and weights of their mothers, and there were no differences in childhood socioeconomic status (SES). Family history of type 2 diabetes was similar in the both groups. The pattern of growth in weight and BMI were similar in boys and girls.

Table 7 shows the odds ratios for the MS according to body size at birth, and conditional growth measurements at 2, 7 and 11 years. Increases in BMI during periods of infancy (from birth to 2 years of age) and from 2 to 7 years were both associated with reduced risks of MS. Adjustments for adult lean body mass or body fat percentage did not affect these associations. However, after adult lean body mass adjustment, a more rapid gain in height from birth to 2 and from 2 to 7 seven years were associated with a lower risk of the MS.

Figure 3 shows the odds ratios for the MS associated with 1 standard deviation (SD) greater height, weight and BMI on each birthday from birth 11 years. At each age from two to 11 years, a higher weight and BMI was associated with a reduced risk of later MS.

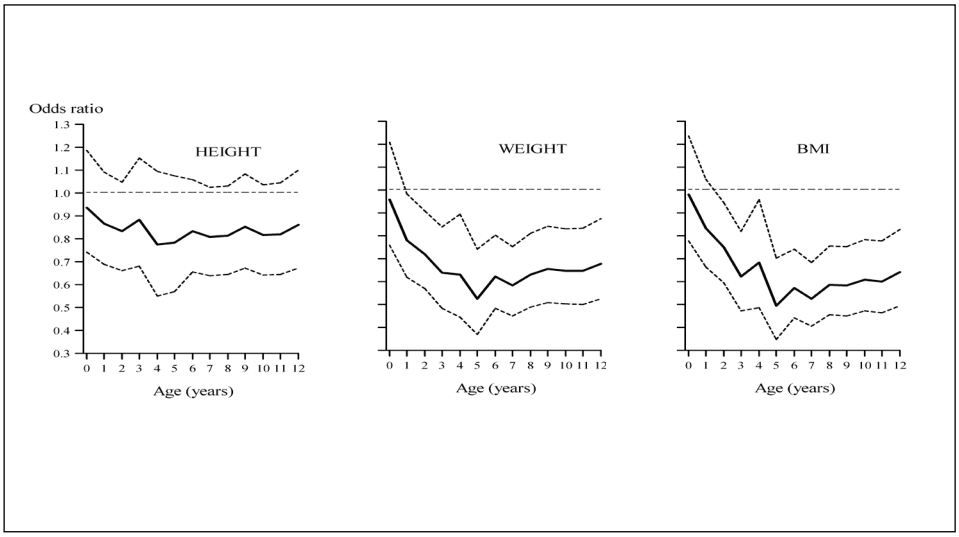


Figure 3. Odds ratios (solid lines) and 95% confidence intervals (broken lines) for the metabolic syndrome according to height, weight and body mass index (BMI) at each year from birth to age 11 years. On each graph, the horizontal broken line indicates an odds ratio of 1.0. Odds ratios for which the confidence interval does not include 1.0 are statistically significant at the 5% level.

Table 7. Odds ratios for the metabolic syndrome associated with 1 SD increase in childhood conditional growth during the first 11 years of life among 499 obese men and women.

	OR	CI (95%)		OR	CI (95%)
BMI (SD)			Height (SD)		
Birth	0.89	0.69-1.14	Birth	0.75	0.56-0.99
0-2 y	0.72	0.57-0.92	0-2 y	0.62	0.46-0.83
2-7 y	0.61	0.47-0.79	2-7 y	0.65	0.49-0.86
7-11 y	0.98	0.76-1.26	7-11 y	1.05	0.82-1.35

BMI=body mass index; OR=odds ratio; CI=confidence interval; SD=standard deviation
Height 7-11y is the standardised residual of height at age 11 years regressed on heights at ages 0, 2, and 7 years. The conditional measures are adjusted on all earlier values.
The table describes the results of two regression analyses – one for height, one for BMI. All predictors are statistically uncorrelated by construction.
Measurements are adjusted for adult age, sex and lean body mass.

5.2 Early growth and metabolically obese normal weight individuals

The prevalence of MS among the normal weight (BMI $\leq$ 25 kg/m^2) adult individuals (43 men and 55 women) was 16.7%. In a similar way as in the obese group, those with the MS were heavier and had higher body fat percentages than those without the MS. The men with MS in the normal weight group were taller. These differences remained after adjustments for childhood and adult SES, exercise, smoking and educational attainment (table 8).

Table 8 . Clinical characteristics of normal weight individuals with and without the metabolic syndrome.

	Metabolic syndrome					
	Present (n=98) (43 m, 55 f)		Absent (n=490) (199 m, 291f)			*)Adjusted
	Mean	SD	Mean	SD	p-value	p-value
MEN						
Age (years)	62.1	3.3	61.4	2.7	0.11	
Height (cm)	179.6	5.8	176.3	6.2	0.001	
Weight (kg)	78.1	5.5	71.3	6.2	<0.001	
BMI (kg/m^2)	24.2	0.7	22.9	1.5	<0.001	
Lean body mass (kg)	61.7	5.6	58.7	5.8	0.001	0.10
Body fat (%)	21.0	3.5	17.7	3.6	<0.001	0.003
Waist circumference (cm)	97.3	2.8	87.8	5.4	<0.001	<0.001
Triglyceride (mmol/L)	1.50	0.45	1.17	0.47	<0.001	0.002
Fasting glucose (mmol/L)	6.37	2.38	5.68	0.85	0.01	0.04
HDL-cholesterol (mmol/L)	1.43	0.37	1.66	0.44	0.004	0.06
SBP (mmHg)	150.7	22.2	140.2	20.2	0.01	0.14
DBP (mmHg)	93.2	11.8	86.7	10.4	0.001	0.01
WOMEN						
Age (years)	61.4	3.0	61.3	2.8	0.77	
Height (cm)	164.3	6.3	163.8	5.3	0.51	
Weight (kg)	63.8	5.0	60.6	6.5	0.001	
BMI (kg/m^2)	23.6	1.0	22.6	1.8	<0.001	
Lean body mass (kg)	44.6	4.7	44.2	4.4	0.50	0.23
Body fat (%)	30.1	3.6	26.6	4.8	<0.001	0.002
Waist circumference (cm)	84.7	3.5	77.7	6.0	<0.001	<0.001
Triglyceride (mmol/L)	2.16	0.90	1.10	0.51	<0.001	<0.001
Fasting glucose (mmol/L)	5.89	0.89	5.17	0.54	<0.001	<0.001
HDL-cholesterol (mmol/L)	1.65	0.46	1.95	0.41	<0.001	<0.001
SBP (mmHg)	146.0	16.9	136.5	18.9	0.001	0.001
DBP (mmHg)	89.0	9.8	83.1	9.5	<0.001	<0.001

SD: standard deviation; BMI: body mass index; m: male; f: female; SBP: systolic blood pressure; DBP: diastolic blood pressure.
* Adjusted also for current BMI

Childhood growth in normal weight but metabolically obese individuals

The normal weight men with the MS were taller throughout childhood. They also tended to have a lower BMI although the statistical significance was reached only at 7 years of age (figure 4). These results remained unchanged after adjusting for childhood and adult socioeconomic status, smoking, exercise and education. Adjustments for family history of type 2 diabetes or maternal BMI did not affect the results. Increase in BMI during infancy was associated with reduced risk of the MS, but only in men.

Figure 4 shows the odds ratios and 95% confidence intervals for the MS associated with 1 standard deviation increase in height, weight and body mass index among 588 normal weight individuals at each age from birth to eleven years.

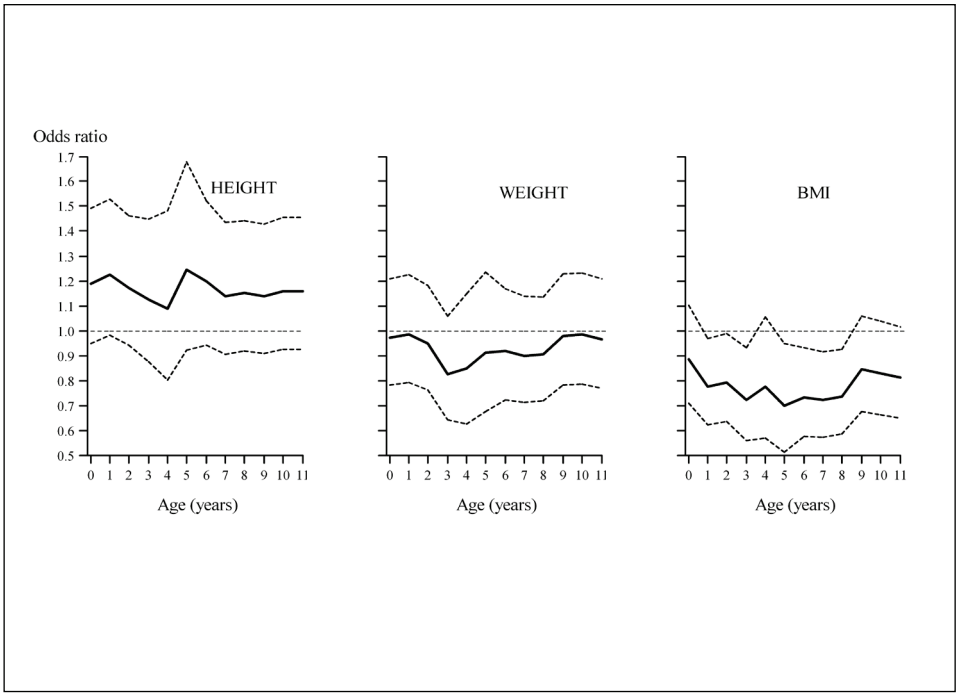


Fig 4. Odds ratios (Ors: solid lines) and 95% confidence intervals (CI: broken lines) for the metabolic syndrome according to height, weight and body mass index (BMI) at each year from birth to age 11 years. On each graph, the horizontal broken line indicates an OR of 1.0.
OR for which the CI does not include 1.0 are statistically significant at the 5% level.

Effects of childhood growth measurements and changes in growth during the three periods in childhood on the separate components of the MS were also examined.

The statistically strongest effects of childhood growth measurements were found to be on WC, fasting glucose and blood pressure (both systolic and diastolic) (table 9). There were no associations between childhood body size or change in growth and HDL cholesterol levels, and thus these results are excluded from the table 9.

Table 9. Odds ratios for components of metabolic syndrome according to height and body mass index at birth, at 2, 7 and 11 years of age and 1 standard deviation increase of childhood conditional growth during the first 11 years of life for 588 normal weight men and women.

	Waist circumference		Plasma triglycerides		Fasting glucose		Blood pressure	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Height (SD)								
Birth	**1.13**	**1.01-1.26**	1.04	0.91-1.18	0.96	0.88-1.05	**0.89**	**0.80-0.98**
2y	**1.29**	**1.04-1.59**	**0.77**	**0.59-1.00**	0.92	0.76-1.11	**0.75**	**0.61-0.91**
7y	**1.63**	**1.30-2.04**	**0.73**	**0.55-0.95**	**0.80**	**0.66-0.97**	**0.80**	**0.65-0.97**
11y	**1.61**	**1.29-2.01**	0.81	0.63-1.05	**0.81**	**0.67-0.97**	0.92	0.76-1.12
0-2y	1.22	0.98-1.51	**0.68**	**0.52-0.88**	0.92	0.76-1.11	0.88	0.72-1.07
2-7y	**1.60**	**1.27-2.03**	0.88	0.68-1.16	**0.82**	**0.68-0.99**	0.97	0.80-1.19
7-11y	1.10	0.84-1.31	1.08	0.83-1.40	0.90	0.75-1.10	1.19	0.98-1.46
BMI (SD)								
Birth	0.91	0.74-1.11	0.90	0.70-1.15	1.00	0.83-1.18	**0.78**	**0.65-0.95**
2y	**0.78**	**0.63-0.96**	0.81	0.62-1.05	0.87	0.72-1.04	0.85	0.70-1.03
7y	**0.64**	**0.51-0.80**	0.79	0.61-1.03	**0.78**	**0.64-0.94**	**0.75**	**0.62-0.92**
11y	**0.71**	**0.57-0.88**	0.78	0.60-1.02	**0.82**	**0.68-0.99**	**0.75**	**0.61-0.92**
0-2y	**0.76**	**0.61-0.95**	0.87	0.67-1.13	0.84	0.70-1.02	0.90	0.74-1.09
2-7y	**0.70**	**0.56-0.88**	0.88	0.67-1.15	**0.82**	**0.70-1.00**	0.84	0.69-1.03
7-11y	1.07	0.86-1.32	0.90	0.69-1.18	1.03	0.85-1.24	0.88	0.72-1.07

CI:confidence interval; BMI: body mass index; SD: standard deviation; bolded figures indicate statistically significant associations

5.3 Association between socioeconomic factors and obesity

73.8 % of the men and 67.6 % of the women in the study were overweight or obese. Being overweight was more prevalent in men than in women while obesity was more common in women. Mean BMI was 27.5 kg/m^2 in men and 27.7 kg/m^2 in women (table 10).

Table 10. Prevalence of overweight and obesity according to BMI at the clinical examination among men and women aged 57 – 70 years.

		Men n=927	Women n=1074
	BMI (kg/m^2)	%	(%)
Underweight	<18.5	-	0.6
Normal	18.5–24.9	26.1	31.7
Overweight	25.0–29.9	51.5	40.4
Obesity, class I	30.0–34.9	17.3	18.4
Obesity, class II	35.0–39.9	3.8	6.5
Obesity, class III	$\geq$ 40	1.2	2.3

Table 11. Mean body mass index (BMI) and 95% confidence intervals (95% CI) according to socioeconomic status in childhood and adulthood among men and women aged 61.5 (SD ± 2.9) years. *P*-value for linear trend (adjusted for age).

	Men n=920			**Women** n=1067		
	BMI	95% CI	n	BMI	95% CI	n
Childhood social class						
Lower	28.0	(27.6-28.3)	525	27.9	(27.5-28.3)	667
Middle	27.3	(26.8-27.8)	254	27.7	(27.1-28.3)	276
Higher	26.5	(25.9-27.1)	141	26.9	(26.2-27.7)	124
p for trend		*<0.001*			*0.10*	
Education						
Basic	28.1	(27.6-28.6)	256	28.3	(27.7-28.8)	299
Secondary	27.3	(26.8-27.8)	262	28.1	(27.6-28.6)	347
Higher	27.3	(26.9-27.8)	388	26.9	(26.4-27.4)	402
p for trend		*0.03*			*<0.001*	
Occupation						
Lower	28.4	(27.6-29.1)	191	28.9	(27.9-29.9)	108
Middle	27.5	(27.1-27.9)	333	27.8	(27.4-28.2)	643
Higher	27.0	(26.6-27.4)	350	26.8	(26.2-27.4)	257
p for trend		*<0.001*			*<0.001*	
Household income						
Lowest quartile	27.7	(27.0-28.3)	166	28.1	(27.5-28.7)	332
2nd quartile	27.7	(27.2-28.3)	229	28.4	(27.8-29.0)	262
3rd quartile	27.4	(27.0-27.8)	272	27.5	(26.8-28.2)	233
Highest quartile	27.4	(26.9-28.0)	255	26.7	(26.1-27.2)	243
p for trend		*0.38*			*<0.001*	

p-value for age adjusted linear trend

When the independent effects of the indicators were further studied, in men the childhood social class remained, although weakly, associated with obesity after adjustment for adult socioeconomic indicators (social class and educational attainment) whereas these two no longer were associated with obesity. In addition to childhood and adult social class and education, household income was also included; however childhood social class remained associated with obesity.

There was no linear trend suggesting an association between BMI and childhood social class in women. However, the results from the logistic regression analysis indicated that those who belonged to the middle or lower childhood social class had slightly higher risk of being obese compared to those from the higher class with an odds ratios 1.7 (95% CI: 1.0-2.8) and odds ratios 1.6 (95% CI: 1.0-2.6), respectively. All the adult indicators for socioeconomic status were inversely associated with obesity. After inclusion of educational attainment, childhood social class was no longer associated with obesity. After further adjustment for adult social class, these associations were mostly attenuated. At the end, household income was the only indicator which remained associated with obesity in women. Those who belonged to the lowest or the second lowest income group had higher risk of being obese compared to those of the highest household income group with OR 1.5 (95% CI: 1.0-2.2) and OR 1.7 (95% CI: 1.1-2.6) respectively.

5.4 Role of early growth on leisure time physical activity and fitness in later life

Of the 2003 men and women 1967 (98%) adequately reported their total leisure time physical activity (LTPA) including both conditioning and non-conditioning LTPA during the past 12 months. Women exercised more frequently and spent more time on LTPA then men (P<0.001 for both), whereas men exercised with higher intensity and had higher energy expenditure (EE) of their LTPA (P=0.001 and P=0.02). Individuals with higher engagement in LTPA showed a more favourable adult anthropometric and body composition profile than those who were less active.

Association between birth and childhood body size and intensity of LTPA

Birth size was positively associated with intensity of total LTPA (table 12). The results remained the same after adjustments for adult social class and BMI. However, after adjustment for adult lean body mass, these associations attenuated and were no longer statistically significant. Height during infancy and childhood was not associated with intensity of total LTPA. However, height at 2, 7 and 11 years of age was positively associated with intensity of conditioning LTPA. Further adjustments for adult lean body mass did not affect these results. Adjustments for smoking did not change the results and adjustments for social class and educational attainment influenced the results only little. Figure 5 shows the age and sex adjusted correlations between childhood body size from birth to 11 years and the intensity of conditioning LTPA.

Figure 5. Intensity of conditioning leisure time physical activity

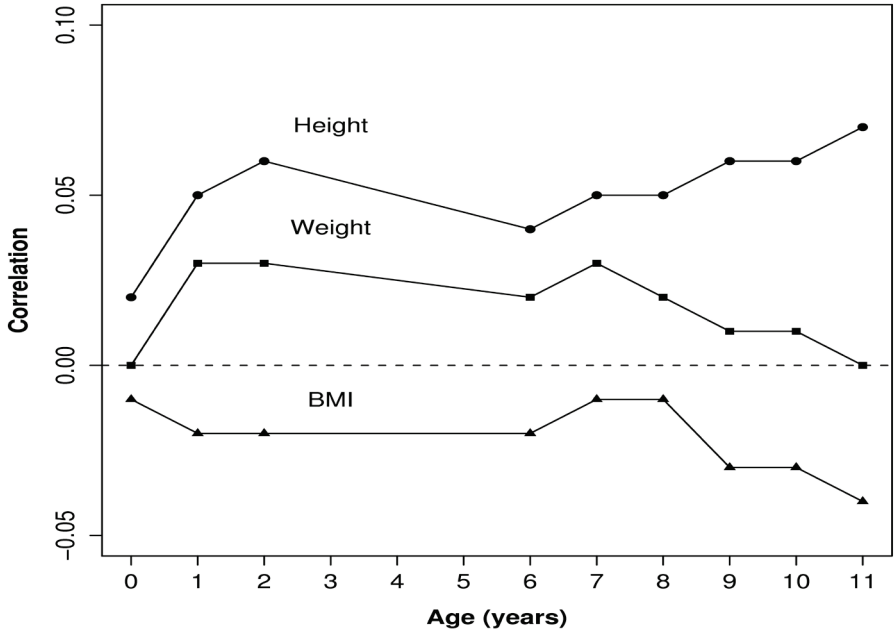


Figure 5 represents adult age- and sex-adjusted correlations between intensity of conditioning LTPA and height, weight and BMI annually from birth to 11 years. The horizontal dashed line indicates a correlation of 0.

Association between childhood body size and EE of LTPA

Weight and height at 2, 7 and 11 years of age were positively associated with EE of total LTPA. Height at 2 and 11 years were associated with EE of conditioning LTPA (table 13 and figure 6). Adult BMI adjustments slightly attenuated the associations between weight and EE of total LTPA, but did not affect the associations between height and EE of LTPA. Adjustments for adult lean body mass and height made all the associations non significant. Further adjustments for childhood and adult social class, educational attainment and smoking habits had no significant impact on the associations between body size and EE of LTPA.

Figure 6. Energy expenditure of conditioning physical activity

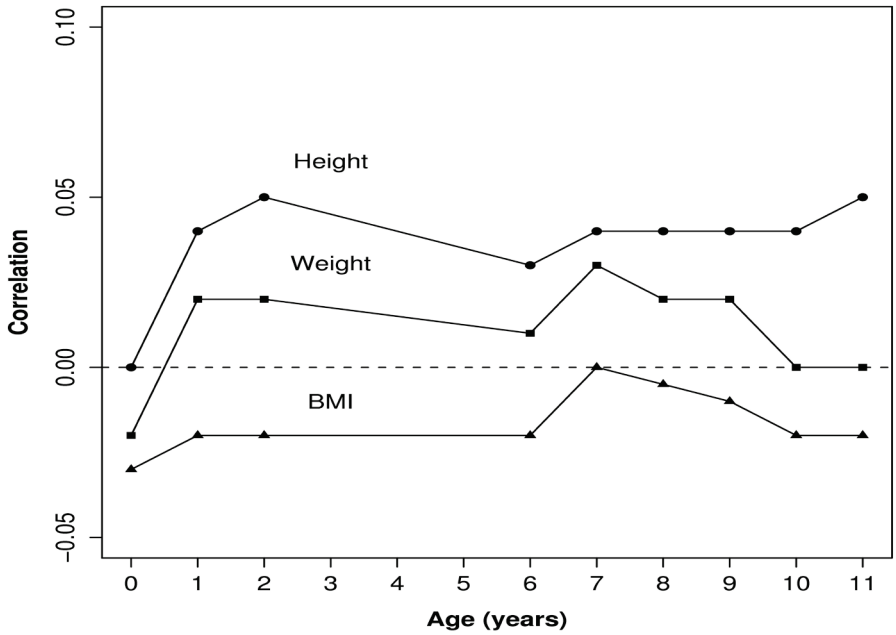


Figure 6 represents adult age- and sex-adjusted correlations between energy expenditure (EE) of conditioning LTPA and height, weight and BMI annually from birth to 11 years. The horizontal dashed line indicates a correlation of 0.

Table 12. Intensity of total and conditioning LTPA according to tertiles of body size at birth, and at 2, 7, and 11 years of age

	Total LTPA				**Conditioning LTPA**			
	Mean intensity (SD) according to tertiles of weight (kg)		Mean intensity (SD) according to tertiles of height (cm)		Mean intensity (SD) according to tertiles of weight (kg)		Mean intensity (SD)according to tertiles of height (cm)	
Time point	Mean MET		Mean MET		Mean MET		Mean MET	
Birth								
Lowest	4.51	(1.01)	4.47	(1.00)	4.97	(1.81)	4.93	(1.87)
Middle	4.64	(1.13)	4.64	(1.13)	5.12	(2.01)	5.10	(1.94)
Highest	4.66	(1.14)	4.70	(1.15)	5.06	(2.10)	5.12	(2.13)
Model[a]	***0.11 (0.01, 0.20)*** [b] [*]		***0.30 (0.05, 0.54)*** [b] [*]		*0.09 (-0.09, -0.27)* [b]		*0.36 (-0.09, 0.81)* [b]	
2 years								
Lowest	4.49	(1.00)	4.53	(1.06)	4.93	(1.87)	4.90	(2.03)
Middle	4.63	(1.13)	4.60	(1.15)	5.02	(2.05)	5.03	(2.02)
Highest	4.69	(1.16)	4.67	(1.08)	5.19	(2.00)	5.21	(1.87)
Model[a]	*0.04 (-0.001, -0.08)* [b]		*0.10 (-0.06, 0.26)* [b]		*0.08 (-0.001, -0.15)* [b]		***0.38 (0.09, 0.67)*** [b] [**]	
7 years								
Lowest	4.56	1.07	4.57	1.10	4.95	1.98	4.91	2.03
Middle	4.66	1.18	4.58	1.09	5.11	2.03	5.03	1.97
Highest	4.58	1.05	4.66	1.12	5.07	1.93	5.20	1.94
Model[a]	*0.00 (-0.02, 0.02)* [b]		*0.01 (-0.10, 0.11)* [b]		*0.09 (-0.01, 0.19)* [b]		***0.20 (0.01, 0.39)*** [b] [*]	
11 years								
Lowest	4.60	1.11	4.58	1.12	5.03	1.97	4.89	2.04
Middle	4.64	1.15	4.59	1.11	5.02	2.05	5.03	1.98
Highest	4.59	1.03	4.66	1.06	5.10	1.90	5.22	1.88
Model[a]	*-0.002 (-0.01, 0.01)* [b]		*0.03 (-0.04, 0.11)* [b]		*0.003 (-0.01, 0.02)* [b]		***0.21 (0.06, 0.35)*** [b] [*]	

MET: metabolic equivalent; CI: confidence interval. [a]Model is adjusted for adult age and sex. [*]P<0.05; [**]P≤0.01. [b]Regression coefficients (with 95% CI) express changes in intensity of adult LTPA associated with a 1 kg increase in weights and 10 cm increase in heights at birth, and at 2, 7 and 11 years.

Table 13. EE of total and conditioning LTPA according to tertiles of body size at birth, and at 2, 7, and 11 years of age

	Total LTPA				**Conditioning LTPA**			
	Mean EE (SD) according to tertiles of weight (kg)		Mean EE (SD) according to tertiles of height (cm)		Mean EE (SD) according to tertiles of weight (kg)		Mean EE (SD)according to tertiles of height (cm)	
Time point	Mean EE		Mean EE		Mean MET		Mean MET	
Birth								
Lowest	2486	(0.05)	2536	(0.05)	532	(0.36)	517	(0.40)
Middle	2593	(0.05)	2453	(0.05)	563	(0.42)	530	(0.42)
Highest	2530	(0.05)	2706	(0.05)	427	(0.60)	461	(0.55)
Model[a]	*1.020% (0.932, 1.116%)* [b]		*1.010% (0.990, 1.030%)* [b]		*0.878% (0.657, 1.174%)* [b]		*0.999% (0.932, 1.073%)* [b]	
2 years								
Lowest	2414	(0.05)	2382	(0.05)	483	(0.42)	427	(0.51)
Middle	2574	(0.05)	2595	(0.05)	497	(0.51)	469	(0.52)
Highest	2624	(0.05)	2637	(0.05)	530	(0.43)	634	(0.34)
Model[a]	***1.041% (1.004, 1.083%)*** [b*]		***1.020% (1.002, 1.030%)*** [b*]		*1.062% (0.932, 1.972%)* [b]		***1.062% (1.010, 1.105%)*** [b*]	
7 years								
Lowest	2360	(0.05)	2445	(0.05)	2445	(0.47)	477	(0.49)
Middle	2597	(0.05)	2536	(0.05)	502	(0.46)	476	(0.47)
Highest	2590	(0.05)	2559	(0.05)	512	(0.44)	544	(0.42)
Model[a]	*1.020% (1.004, 1.040%)* [b]		***1.010% (1.001-1.020%)*** [b*]		*1.030% (0.980, 1.083%)* [b]		*1.020% (0.990, 1.051%)* [b]	
11 years								
Lowest	2411	(0.05)	2548	(0.05)	483	(0.42)	472	(0.53)
Middle	2411	(0.05)	2493	(0.05)	497	(0.51)	465	((0.48)
Highest	2612	(0.05)	2517	(0.05)	530	(0.43)	562	(0.36)
Model[a]	***1.010% (1.003, 1.020%)*** [b**]		***1.010% (1.001-1.010%)*** [b*]		*1.001% (0.970, 1.030%)* [b]		***1.030% (1.002-1.051%)*** [b*]	

MET: metabolic equivalent; CI: confidence interval. [a]Model is adjusted for adult age and sex. [*]P<0.05; [**]P≤0.01. [b]Regression coefficients (with 95% CI) express changes in a EE of adult LTPA associated with a 1 kg increase in weights and 10 cm increase in heights at birth, and at 2, 7 and 11 years.

Early life origins of physical fitness

Out of 2003 clinical participants the 606 who participated in the UKK Institute 2 km walk test showed no difference in social background, engagement in exercise, birth size or growth during childhood, except for length at birth in women, which was slightly higher for those who took part in the walk test (p=0.04). They also had smaller BMIs, WCs and lower body fat percentages than their nonparticipant peers. The findings related to anthropometric characteristics did not differ between men and women. Men who did not participate in the walk test were more often smokers than those who did.

The analyses which were performed in order to compare the associations of the childrens' body size at different time points on potential components of cardiorespiratory fitness (CRF) did not show differences between the walk test participants and nonparticipants. Furthermore, effect of childhood body size on adult BMI, body fat percentage, lean body mass and grip strength were similar in the two groups. Figure 7 shows the correlations between height, weight and BMI from birth to 12 years of age and adult CRF.

Figure 7. Correlation between childhood body size and VO_{2max} in adult life

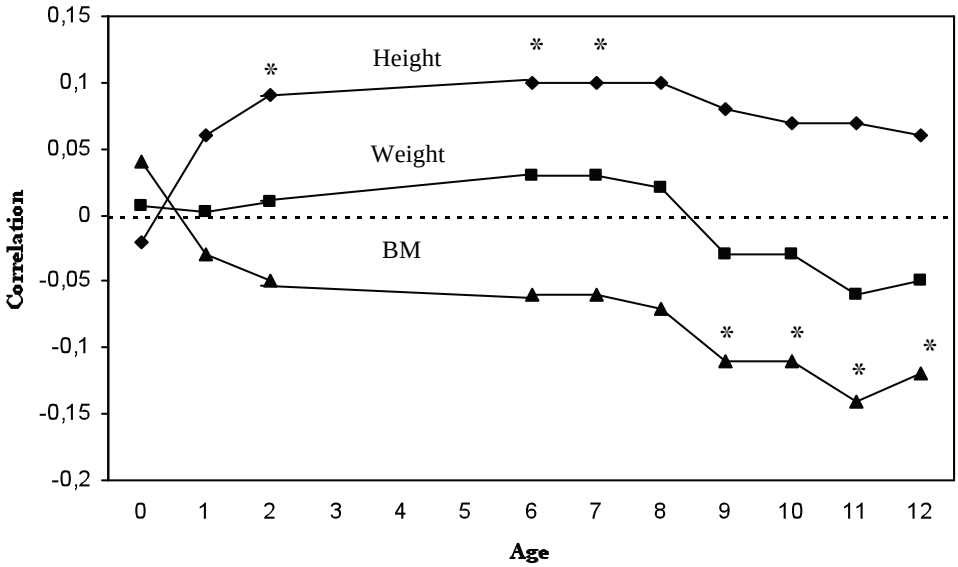


Figure 7. Age- and sex adjusted correlations between VO_{2max} and height weight and BMI annually from birth to 12 years. The horizontal dashed line indicates a correlation of 0.

In addition to birth length, height and BMI, also ponderal index, gestational age and maternal BMI, the potential factors related to early growth, were studied in relation to adult CRF. None of these characteristics was associated with adult CRF. Height at 2 and 7 years were positively associated with CRF in the basic age- and gender-adjusted models (table 14). Adjustment for adult lean body mass strengthened these findings and height at 11 years became associated with CRF. Additional adjustments for childhood and adult social class, exercise and smoking habits did not change these findings.

Weight at 2 and 7 years became associated with CRF when adult lean body mass, and the other confounders, such as social background, exercise and smoking were controlled for. Higher BMI at 11 years of age, independently of the confounders, predicted lower adult CRF (table 14).

Gains in body size from birth to 11 years, during three different periods, were also studied. In the age- and sex-adjusted models gain in height from birth to 2 years of age predicted higher adult CRF while gains in weight and BMI during the childhood period from 7 to 11 years were associated with lower adult CRF. A 1 SD increase in height from birth to 2 years was associated with 0.72 ml/kg/min (95% CI: 0.13 to 1.32) higher VO_{2max}. A 1 SD increase in weight and BMI from 7 to 11 years was associated with -1.10 ml/kg/min (95% CI: -1.69 to -0.51) and -0.99 ml/kg/min (95% CI: -1.58 to -0.40) lower VO_{2max}, respectively. However, when adult lean body mass was controlled for gains in height in the period from birth to 2 years remained and the period from 2 to 7 years became associated with higher adult CRF; a 1 SD increase in height predicted 0.97 ml/kg/min (95% CI: 0.35 to 1.59) higher VO_{2max}. Again, gain in weight from birth to 2 years became positively associated with adult CRF, a 1 SD increase in weight was associated with 0.69 ml/kg/min (95% CI: 0.05 to 1.33) higher VO_{2max}, while gain in weight and BMI during the period from 7 to 11 years still predicted lower adult CRF level.

Table 14. Adult cardiorespiratory fitness in relation to height and body mass indices at birth and at 2, 7, 11 years of age.

*VO_{2max} ml/kg/min (Range)	N	Childhood height (cm)				Childhood body mass index (kg/m^2)			
		Mean (SD) at birth	Mean (SD) at 2y	Mean (SD) at 7y	Mean (SD) at 11y	Mean (SD) at birth	Mean (SD) at 2y	Mean (SD) at 7y	Mean (SD) at 11y
10.4 – 24.3	193	50.5 (2.1)	85.9 (3.0)	119.9 (4.9)	141.0 (6.5)	13.5 (1.3)	16.6 (1.2)	15.5 (1.2)	17.2 (1.8)
24.3 – 30.2	194	50.2 (1.9)	86.0 (2.9)	120.4 (4.6)	141.9 (6.2)	13.3 (1.1)	16.5 (1.1)	15.5 (1.3)	16.9 (1.7)
30.2 – 57.8	194	50.7 (1.8)	86.6 (3.1)	121.2 (4.6)	142.2 (5.6)	13.5 (1.1)	16.6 (1.2)	15.4 (1.2)	16.6. (1.6)
RC and		-0.06	0.21	0.16	0.08	0.21	-0.30	-0.37	-0.57
95% CI		(-0.36, 0.24)	(0.02, 0.40)	(0.03, 0.28)	(-0.02, 1.17)	(-0.27, 0.69)	(-0.78, 0.18)	(-0.84, 0.11)	(-0.91, -0.24)
p for trend		*0.7*	*0.03*	*0.01*	*0.1*	*0.4*	*0.2*	*0.1*	*0.001*
[1]RC and		0.08	0.50	0.40	0.25	0.33	-0.06	-0.13	-0.43
95% CI		-0.22, 0.39	(0.29, 0.71)	(0.26, 0.55)	(0.14, 0.36)	(-0.15, 0.81)	(-0.54, 0.43)	(-0.63, 0.36)	(-0.78, -0.08)
[1]*p* for trend		*0.6*	*<0.001*	*<0.001*	*<0.001*	*0.2*	*0.8*	*0.6*	*0.001*

*VO_{2max} in tertiles; RC = regression coefficients with 95% CI (= confidence interval) express changes in VO_{2max} (ml/kg/min) per 1 cm increase in heights and per1kg/m^2 increase in BMIs at birth, 2, 7 and 11 years; all the analysis were adjusted for age and sex; [1]adjusted additionally for adult lean body mass.

6 Discussion

Overweight and obesity has alarmingly reached an epidemic dimension world wide. Several chronic diseases are strongly linked to overweight and obesity. Many of these obesity related diseases are of major public health concerns affecting a wide range of people in all age groups, including children. At the same time sedentary behaviour, e.g. in terms of physical inactivity, has taken over a considerable part of leisure time in the modern society.

6.1 Early growth in MNO individuals

Obesity, when expressed as BMI, is most often defined as BMI equal to or exceeding 30 kg/m^2. However, BMI does not discriminate between muscle and fat mass. Increasing evidence has strongly pointed out that accumulation of visceral fat is the form of obesity which is most detrimental in pathophysiological traits. Obesity is a multifactorial and complex state which is not completely understood as a whole.

In our study 20 % of the obese were identified as metabolically healthy according to the IDF criteria for the metabolic syndrome (MS). This observed prevalence is in accordance with most previous studies examining the metabolically obese normal weight subjects (Ferrannini et al. 1997; Bonora et al. 1998; Brochu et al. 2001; Karelis, Brochu & Rabasa-Lhoret 2004; Shea, Randell & Sun 2011) with rates varying from 10 to 50%. A high variability is mostly explained by several different definitions of MS. The use of variable cut points in definition of obesity also partly explain the differences in reported prevalences, e.g. in some studies also overweight people have been included, BMI cut point thus being set at 25 or 27 kg/m^2.

The focus of this study was to examine whether early growth plays a role in development of MS in the obese subgroup (BMI$\geq$30 kg/m^2). We found that people with the MS were at each age from two years onwards up to 11 years lighter and thinner compared to those who did not develop the MS. Reduced gains in weight from birth to seven years also predicted the risk of MS. Higher BMI at 7 years was most beneficial in relation to blood pressure, whereas higher BMIs at 2, 7 and 11 years had favourable effects on glucose regulation. Childhood body size or change in body size was not associated with plasma lipid profiles. Regardless of presence or absence of MS, all individuals belonging to this study fulfilled the International Diabetes Federation (IDF) criteria for MS concerning waist circumference.

It is well documented that thinness during infancy together with a small body size at birth are risk factors for several cardiometabolic disorders, such as impaired glucose tolerance and diabetes (Hales et al. 1991; Hales, Barker 1992). Our data have previously shown that different critical periods of early growth are associated with various adult health outcomes including coronary heart disease or type 2 diabetes (Barker et al. 2005; Eriksson et al. 2006). In accordance with earlier studies, analysis of the present study shows that in those who are obese in adult life, slow weight gain during the first two years of life increases the risk of MS. The novel finding is that a slow gain in BMI in the period after age two up to age 7 years similarly increases the risk of adult MS. It was shown in a recent study that obese children and adolescents who had higher birth weights and weight gains in infancy were more insulin sensitive and had lower truncal fat percentages, while weight gains after four years had a negative influence on insulin sensitivity (Bouhours-Nouet et al. 2008), which represents both similarities and yet contradictions with respect to our findings.

The findings in the present study could be due to differences in body composition. Previously reported results from HBCS have indicated that rapid gain in BMI before the age of 2 years increased adult lean body mass without excess fat accumulation, while rapid gain in BMI in later childhood predicted relatively larger increases in fat mass, despite the concurrent rise in lean mass (Ylihärsilä et al. 2008). In the present study, a rapid gain in childhood body size was protective in relation to the risk of adult MS even after adjustments for adult body measurements. Furthermore, a rapid spurt in height between birth and seven years appeared to be protective in these obese individuals of similar lean body mass.

Not surprisingly, individuals with MS had larger waist circumferences. An increase in visceral fat has shown to be associated with a decrease in insulin sensitivity, a highly relevant component of MS (Brochu et al. 2001). Evidence from previous studies have shown that a small body size at an early age or during childhood may lead to an increased risk of visceral fat accumulation in later life. Data from a follow-up study in England have shown that among men, the waist-to-hip ratio fell with higher birth weight as well as higher weight at age one (Law et al. 1992). Also the female offspring of women exposed to the Dutch famine during early pregnancy were heavier as adults, and had higher BMIs and waist circumferences (Ravelli et al. 1999). Authors of another study found an inverse, although small, effect of birth weight on the waist-to-hip ratio after adjustment for adult body size in a cohort of women born immediately after World War II (Kuh et al. 2002a). They also found, similarly to our finding, that a higher relative weight at 7 years of age was associated with lower abdominal obesity in later adult life.

One of the mechanisms behind the association between early growth trajectories and adult metabolic disturbances could be the alteration in body composition. Early poor

gain in BMI might predispose to deficiency in lean mass (Ylihärsilä et al. 2008). Lean body mass consists mainly of muscle tissue, which is an important site for insulin mediated glucose metabolism. Thus this deficiency in lean mass may predispose to reduced insulin sensitivity (Ylihärsilä et al. 2008). Currently, adipose tissue is regarded as a complex, highly active metabolic organ that secretes several agents that regulate processes involved in carbohydrate and fat metabolism (Rosen, Spiegelman 2006). Increased fat mass in those with low compensatory lean mass, may lead to insulin resistance, type 2 diabetes and CVD.

Another explanation could be duration (Muscelli et al. 1998) or earlier age at onset of obesity. It has been suggested that an earlier onset of obesity (between 13 and 19 years of age) has a favourable impact on insulin sensitivity, plasma lipid profile and visceral adipose tissue in obese post-menopausal women (Brochu et al. 2001). Unfortunately we can not confirm these findings with our data, which is limited to growth measurements available before or during early puberty.

Certain life style factors, such as physical activity and healthy diet are well known to have beneficial influences on the MS risk profile (Rennie et al. 2003; Villareal et al. 2006), whereas detrimental effects of smoking on chronic diseases including cardiovascular ones are indisputable. However, in the present study, the level of physical activity and smoking habits were not associated with MS. Socioeconomic status did not explain our findings either.

6.2 Early growth in MONW individuals

Obesity typically plays a central role in the pathogenesis of metabolic syndrome. However, not all obese individuals develop metabolic consequences of obesity. Likewise, all normal weight individuals (BMI$\leq$25 kg/m^2) do not remain metabolically healthy (Ruderman et al. 1998). This sub-group of people, despite of normal weight, may represent a cluster of obesity-related risk factors, including visceral adiposity, dyslipidemia, hyperglycaemia and hypertension (Alberti, Zimmet 1998; National Cholesterol Education Program 2002; Alberti, Zimmet & Shaw 2006). According to the DOHaD hypothesis, we aimed to study possible early growth determinants in relation to obesity-related metabolic outcomes in a sub-group of individuals within the normal weight range. The MONW individuals in this study represent those who do fulfil the IDF criteria for metabolic syndrome despite of normal weight. To our knowledge, there are no other studies that have been exploring the relationships between early growth and MONW with a long follow-up and with detailed data of childhood growth.

The prevalence of the MONW subjects was 16.7%. According to the present literature, the prevalence of the MONW ranges between 5% and 45%, depending on

the criteria being used, and on age, BMI and ethnicity. Metabolically obese subjects belonging to our study were heavier, and had higher waist circumferences and body fat percentages than their healthy counterparts.

We observed that those who developed MS despite being normal weight, had slower gains in BMI between birth and 2 years of age and were thinner at 7 years, compared to those who did not have MS. Adjustments for childhood and adult social class, exercise, smoking and educational attainment did not alter these findings. The findings were, however, statistically significant in men only. In women the pattern of childhood growth was similar to those of the men. We did not observe associations between birth size and MS. Only one study besides ours has reported potential associations between birth weight and MS in normal weight subjects (Conus et al. 2004). However, they found that birth weight was identical in MONW and control subjects.

Higher BMI at ages 2, 7 and 11, and a more rapid growth between birth and 7 years were associated with lower abdominal obesity in adulthood. Higher BMI at 7 and 11 years had beneficial effect on fasting glucose and higher BMI at birth, at 7 and 11 years predicted lower blood pressure. Another study has reported a negative association between catch-up growth and insulin sensitivity while BMI at birth was positively associated with insulin sensitivity (Jaquet et al. 2005). However, periods of childhood growth, which may play an important role in the development of insulin sensitivity, were not reported in this study.

It is not clear why lower gain in BMI during infancy seems to increase the risk of metabolic syndrome in otherwise normal weight individuals. One explanation could involve differences in body composition. Lower rates of growth have shown to predispose to an increased risk of abdominal obesity in later life (Ravelli et al. 1999; Kuh et al. 2002a). Adjustments for adult body composition measures in our study had only modest affect on the associations we found between childhood BMI and MS. However, the body composition measurements available in this study are unable to reflect possible alterations in visceral fat which could act as a mediator to the present relationship. Furthermore, there is the possibility that there are different mediating mechanisms in people who are lean as adults compared to people belonging to the whole range of BMI scores.

6.3 Socioeconomic indicators and obesity in the HBCS

The prevalence of obesity in men was 22.3% and 27.0% in women which is slightly higher compared with other reported obesity prevalences in Finland (Vartiainen et al. 2010; Lahti-Koski et al. 2010). This is most likely explained by the participants' higher age, the mean age being 61.5 years (range 57-70). Several factors contribute

to the development of obesity, including biological, genetic, life style, environmental and socioeconomical factors as well as complicated interactions between them. Obesity is known to track from childhood into adult life (Power, Lake & Cole 1997; Eriksson et al. 2001), and children with higher BMI tend to be obese as adults. Socioeconomic circumstances are closely linked to adult overweight and obesity (Sobal, Stunkard 1989; Parsons et al. 1999; Eriksson et al. 2003). In this study we concentrated on socioeconomic factors. We aimed to examine how several indicators of SES, from a life course, are related to obesity (BMI>30 kg/m^2) in 2003 HBCS participants.

In this study the indicator of childhood SES was based on father's occupation. Adult SES was described with three key indicators of SES including occupation, educational attainment and household income. We found that all indicators of low SES were associated with obesity in both genders, with the exception of lower household income which was associated with obesity in women but not in men. The effect of childhood SES on obesity seemed to be more persistent in men, while adult socioeconomic circumstances and especially lower income played a bigger role in obesity in women.

Our findings are in line with previous studies reporting associations between adverse socioeconomic circumstances both in childhood and in adult life and poor health outcomes in Finland, Europe and North America (Galobardes, Lynch & Davey Smith 2004; Mackenbach et al. 2008). Many studies have found that even if adult SES is taken into account, a modest association between childhood socioeconomic position and adult health remains (Kuh et al. 2002b; Claussen, Davey Smith & Thelle 2003). This is similar to our findings in men, which showed that childhood SES remained, although in the final model modestly, associated with later life obesity after adjustment for adult socioeconomic indicators.

A traditional life course approach model takes into account the possibility of critical periods in early life but emphasises the accumulation of risk factors resulting from exposure to adverse environments during childhood, adolescence, and adulthood (Kuh, Ben-Shlomo 1997). We based this study on previous ones using a similar approach (Langenberg et al. 2003; Laaksonen, Sarlio-Lähteenkorva & Lahelma 2004). A strong link between SES and health has been found across various industrial societies for several major diseases and causes of death. The ways in how the SES effects is not fully understood. Associations between low SES and greater overweight and obesity in studies of adults have been attributed to main causal models; low SES may contribute to the development of obesity, or obesity may lead to downward social mobility and thus lower SES. SES is a multidimensional theoretical construction that covers a variety of social and economical circumstances. The longitudinal study design is a major strength of our study, enabling the use of several SES indicators from a life course perspective.

6.4 Early growth and LTPA in later life

People who are inactive are well known to be at higher risk for several chronic diseases such as obesity, type 2 diabetes, hypertension, coronary heart disease and osteoporosis. This risk can be decreased by physical activity (Pescatello et al. 2004; Kohrt et al. 2004; Orozco et al. 2008). While there is existing awareness of the adverse consequences of non optimal fetal growth and childhood growth on later physical health, also behavioural factors have been suggested to be programmed in later life (Räikkönen, Pesonen 2009). However, whether early growth itself plays a role in PA later in life has been little studied. Even though it seems clear that those born severely preterm are more sedentary compared to those born at term (Rogers et al. 2005; Saigal et al. 2007; Hovi et al. 2009), the results of the studies linking birth size with PA in childhood (Boreham et al. 2001; Hallal et al. 2006; Mattocks et al. 2008) as well as in adult life (Laaksonen et al. 2003; Eriksson et al. 2004; Andersen et al. 2009) have been inconsistent.

Obviously, there is a true call for more studies focusing upon foetal factors and childhood growth in relation to PA from a life course perspective. Exercise habits can be modified and more over they could mediate part of the effect of early growth on later health. Our aim was to study the role of birth size and childhood growth on LTPA in those who participated in the clinical examinations of the HBCS. Potential role of SES in both childhood and adult life was also studied in relation to LTPA.

We found that among the 1967 men and women, women were more active and spent more time on LTPA than men. On the other hand, men exercised with higher intensity and had higher EE of their LTPA. As expected, those who had a higher engagement in LTPA were characterized as having a more favourable adult anthropometric and body composition profile than those who were more sedentary. Smokers, both men and women, were less active with respect to all components of LTPA, except for the duration of total LTPA. In men, both childhood social class and educational attainment were positively associated with the frequency of the total LTPA. The men and women, in the highest social class as adults were physically more active than those from the lower social class.

Those, who as children had a higher weight and length at birth, as well as during infancy, were found to have higher intensity levels of total LTPA in adult life. Tallness at ages of 2, 7 and 11 years predicted higher intensity levels of conditioning LTPA, and higher EE of total LTPA, while those with higher EE levels of conditioning LTPA were taller at the age of 2 and 11 years. Gains in height from birth to two years, and from 7 to 11 years were related to both, higher intensity and

EE levels of conditioning LTPA, and gains in height and weight from birth to 2 years were related to EE of total LTPA.

The existing literature concerning the associations between early growth and physical activity in adult life is not only scarce but those studies have also come up with contradictory findings. While authors of one study did not find associations between birth size and cardio-respiratory fitness or duration of strenuous LTPA in adult life (Laaksonen et al. 2003), the authors of the other study reported positive association between birth weight and regular PA (Davies et al. 2006), and again, the authors of another did not find significant relationships between early growth and PA in later life (Martin et al. 2009). Previously reported results from the HBCS have suggested that those men with higher birth weight exercised less than these with lower birth weight (Eriksson et al. 2004). The more recent findings from the extensive NordNet study group suggest that the associations between birth weight and LTPA are weak within the normal birth weight range, but both low and high birth weight were associated with lower LTPA (Andersen et al. 2009).

Studies among children and adolescents have showed inconsistent findings as well. Results from the Northern Ireland Young Hearts Project have shown that higher birth weight was associated with higher aerobic fitness in 12 year old boys and girls (Boreham et al. 2001). Findings from another study of 10-12 year old adolescents suggested that genetic factors or habit formation during early childhood were of greater importance in relation to physical activity, than physiological factors as consequences of programming (Hallal et al. 2006). In the longitudinal study of parents and children (ALSPAC), birth size was not related to physical activity in the 11-12 year old, where as parental activity levels did predict the activity level of their child (Mattocks et al. 2008).

One mechanism which may explain our findings with the positive association between childhood body size and LTPA later in life, is the higher muscle growth in pre-puberty and the tracking of muscle size. This theory is supported with previous finding from the HBCS. Both birth size and size during infancy was found to be strongly and positively associated with adult lean body mass (Ylihärsilä et al. 2008). Lean body mass consist mainly of muscle, and birth weight was found to be associated with grip strength as well, which may well be an indicator of functional capacity in elderly individuals (Ylihärsilä et al. 2007). Another potential mechanism may involve quality of muscle mass, including the number and composition of muscle fibres. There is now evidence, different from what was formerly believed, that the number of muscle fibres is not fixed by the time of birth. The role of satellite cells in postnatal growth and regeneration is increasingly recognized (Bailey, Holowacz & Lassar 2001). Furthermore, it has been suggested that adverse foetal environment may induce primary changes in muscle fibre composition (Ozanne et al. 2005; Jensen et al. 2007; Jensen et al. 2008).

6.5 Early growth and cardiorespiratory fitness in later life

High levels of aerobic fitness are recognised to have wide ranging health benefits. The lack of physical activity and low cardiorespiratory fitness (CRF) are associated with the risk of all cause mortality, cardiometabolic diseases and several cancers (Lakka et al. 1994; Laaksonen et al. 2002; Kodama et al. 2009; Lee, Sui & Blair 2009; Sillanpaa et al. 2009; Farrell et al. 2010); brain structure and function could be associated with CRF as well (Colcombe et al. 2003). It has been suggested that improvements in CRF due to exercise training are implicated in the restoration of neural and cognitive functioning in older adults (Kramer et al. 1999; Colcombe et al. 2004; Colcombe et al. 2006).

CRF refers to the ability of the body to supply oxygen to skeletal muscles during sustained PA, which is commonly measured by a maximal or sub-maximal exercise test. Regular PA is a major determinant of CRF by increasing the amount of oxygen that is inhaled and distributed to body tissues. Even though CRF and PA are closely related, health benefits may more strongly associate with CRF to its behavioural nature (Pescatello et al. 2004; Kohrt et al. 2004; Orozco et al. 2008). It has also been proposed that CRF and PA may be differentially influenced by age, gender, social, environmental and behavioural factors as well as genotypes and subclinical disease (Eaton et al. 1995; Tager, Hollenberg & Satariano 1998; Bouchard, Rankinen 2001; Lee et al. 2010). There is some evidence from animal and human studies suggesting that early life development may act as a biological determinant of aerobic fitness (Vickers et al. 2003; Andersen et al. 2009; Kajantie et al. 2010). However, there are few studies examining explicitly the relationship between early growth and CRF. We hypothesized that reduced prenatal growth characterized by small birth size and slow postnatal growth predicts lower CRF in later adult life.

Of adult characteristics, higher age, weight, BMI, WC, body fat percentage, fat mass and lean body mass were all associated with lower levels of CRF in both genders, while height was positively linked with CRF in both men and women. Lower adult SES predicted lower CRF. Men, who had at least moderate exercise three or more times per week had higher CRF levels, whereas this finding was not observed in women. Lower CRF levels were observed in smokers, in both genders.

Birth size was not associated with later CRF. However, childhood growth did associate with adult CRF. Children who were taller at ages 2, 7 and 11 years, had higher CRF levels as adults, while higher BMI at age of 11 years predicted lower levels of CRF in adult life. Body weight at 2 and 7 years showed a positive association with CRF only after adjustment for adult lean body mass. Gain in height during the first two years of life predicted higher CRF, and gains in weight and BMI

between 7 and 11 years predicted lower adult CRF. After adult lean body mass adjustments, gains in height in infancy remained, whereas gain in height between 2 and 7 years became associated with higher CRF. Further more, after adult lean body mass adjustment, gain in weight during the first years became positively associated with adult CRF, and gain in weight and BMI from 7 to 11 years remained negatively associated with adult CRF. These associations remained after adjustments for several confounders, such as childhood and adult SES, exercise and smoking.

Mechanisms behind the relationship between early growth and CRF are not well known and obviously some of the mechanisms are the similar to those of the physical activity. Based on earlier findings from HBCS, higher birth weight was shown to predict higher lean body mass, while grip strength, an important indicator of frailty and functional capacity in elderly people, was linked with birth weight through its association with lean mass (Yliharsila et al. 2007). Another study including younger people from ages 13 to 18.5 have shown a positive association with birth weight and hand grip strength. These associations were mostly explained by fat free mass, and there were no associations between birth weight and CRF (Ortega et al. 2009). However, opposite findings have shown that those born with bigger size also had higher CRF levels at the age 9 years (Lawlor et al. 2008). Motor development may also be an important predictor; based on results from a Finnish cohort, it has been shown that higher birth weight, lower infant weight gain and earlier infant motor development predict higher levels of adult physical performance for muscle strength, muscle endurance and aerobic fitness at the age of 31 years (Ridgway et al. 2009).

6.6 Methodological aspects

6.6.1 Study design and population

The HBCS is an epidemiological longitudinal birth cohort study on subjects born 1934-44. One of the primary aims of HBCS is to study how fetal and childhood growth and living conditions affect adult health status from a life course perspective. Since adult health status was examined in clinical setting at one time point, the detected associations do not indicate causality.

Men and women in the HBCS study were born as singletons in the Helsinki University Central Hospital, attended voluntary child welfare clinics, went to school in Helsinki, did not emigrate, were still alive in the years 2001-2004 and were willing to participate. The people in the study may therefore not be representative of all people born in Helsinki. However, our findings are based upon internal comparisons within the sample and thus unlikely to be attributed to selection bias. Furthermore, our subjects were born during the Second World War or were children

at the time, and thus some of them may have suffered from food shortages. We can not exclude the possible impact of intergenerational effects, either. Factors causing low birth weight back then may be different from factors we have today. Also body composition of historical children, e.g. fatness for a given BMI, may differ from contemporary children.

In study V, of the 2003 clinical participants only 606 attended the UKK 2-km walk test, which means that the statistical power is lower than in the original study. Participation number of this low was due to several health status requirements. Subjects on drug therapy affecting pulse rate were excluded. Furthermore, 25 subjects whose test results indicated a VO_{2max} status under 10 ml/kg/min were excluded from further analysis because those with a value this low cannot reach the intensity required in the UKK-test. However, a comparison of the associations of childhood body size measurements on potential components of CRF did not show differences between the participants and non-participants. The effect of childhood body size on adult BMI, body fat percentage, lean body mass and grip strength were similar in both groups.

6.6.2 Measurements

We used paternal occupation to assess childhood socioeconomic status (SES). Quality of the information based on the records was somewhat diverse and occasionally it was difficult to attain adequate classification. Additionally, distribution of the childhood SES was skewed, the lowest class comprising of 60% of the fathers. However, this prevalence is close to the known prevalence of labourer families in Helsinki, being approximately 60%.

We used bioelectrical impedance analysis (BIA) for body composition measures. The eight polar BIA has been shown to give accurate estimates of body composition in variable populations without the requirements for population-specific algorithms (Bedogni et al. 2002; Malavolti et al. 2003; Sartorio et al. 2005; Gibson et al. 2008).

Physical activity is difficult to measure, and is highly subjective in nature especially when questionnaires are involved. Physical activity and exercise are culture and society-dependent matters, and thus we used the KIHD 12-month LTPA questionnaire, which is validated in Finland (Lakka, Salonen 1992). The questionnaire has a representative time frame, is diverse, has relatively small intra-person variability, and is therefore suitable for the assessment of LTPA.

Cardiorespiratory fitness (CRF) was measured by using the UKK Institute 2 kilometre walk test. The UKK 2 km test is an indirect measurement of CRF, and can be used within majority of the adult population without requirements of maximal

physical efforts. It has been validated against maximal effort tests by treadmill or bicycle ergometry in multiple populations including the obese and elderly (Laukkanen et al. 1992; Rance et al. 2005). The test results are expressed as fitness index, or VO_{2max}, by using a formula in which the subject's age, sex, BMI, time spent in walking and heart rate are taken into account.

7 Conclusions

1. We found, in both metabolically normal obese and metabolically obese normal weight individuals that higher body size and higher gains in body size had beneficial implications on metabolic profile of these individuals.

2. About one fifth of the study subjects were metabolically normal but obese, and similar amount were MONW. This result emphasises the crudeness of BMI as a measurement, especially if used alone, and when forecasting a future health profile. Furthermore, these conditions were not due to the common risk factors such as physical activity, smoking or family history.

3. Increased risk for development of obesity was apparent in those who had lower socioeconomic status. Adult socioeconomic circumstances, particularly lower income, played a bigger role in increasing the risk of obesity in women.

4. Additionally, as children the more physically fit and active individuals tend to be more sturdily built and taller compared to those who were less active.

DOHaD hypothesis might offer an explanation since early detection of the risk factors predisposing to these conditions is highly relevant from the public health point of view. As shown in this study, the nature of the developmental origins of health and disease is complex. Further research with longitudinal study designs are obviously needed for the complicated associations between early risk factors and so that later adverse outcomes can be discovered and more accurately explained.

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