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CHILDHOOD OVERWEIGHT –

Predictors, Consequences and Prevention

by

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ABSTRACT

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Childhood Overweight - Predictors, Consequences and Prevention
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Childhood overweight has become more prevalent during the past three decades. The aim of the present study was to examine possible predictors of childhood overweight and to evaluate the effect of individualised, biannual dietary and lifestyle counselling, with onset in infancy and primary aim at decreasing serum LDL-cholesterol, on the development of overweight and related comorbidities.

The study was part of the Special Turku coronary Risk factor Intervention Project (STRIP), in which 7-month-old children were randomised into an intervention group (N=540) or to a control group (N=522). The children in the control group were followed up along with the intervention group but they did not receive the individualised counselling.

At the age of 15 years, 11.9 % of girls and 13.7 % of boys were overweight. The most important predictors of overweight at age 15 years were paternal weight status at the child's age 7 months, rapid weight gain during the first two years of life, and early adiposity rebound. Leptin, a protein secreted by adipocytes, did not predict the development of overweight. Homozygosity for the overweight-associated FTO gene variant was associated with increased BMI and risk of overweight in children older than 7 years of age. The intervention given in the STRIP trial was not intense enough to overcome the effect of the FTO genotype. Although the intervention given in the STRIP trial had no significant effect on the proportion of overweight girls and boys, it did reduce the number and clustering of overweight-related cardiometabolic risk factors.

This study showed that parental weight status, rapid weight gain early in life, and having two risk alleles in the FTO gene are strongly associated with overweight in adolescence. Biannual dietary and lifestyle counselling is not intense enough to prevent overweight but it has beneficial effects on the overweight-related cardiometabolic risk.

Key words: overweight, obesity, children, adolescents, prevention, dietary intervention, cardiometabolic risk, clustering, FTO genotype, serum lipids, blood pressure

TIIVISTELMÄ

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Lapsuusiän ylipaino – ennustavat tekijät, seuraukset ja ennaltaehkäisy
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Lapsuus- ja nuoruusiän ylipaino on lisääntynyt merkittävästi kolmen viime vuosikymmenen aikana. Tämän väitöskirjatyön tavoitteena oli tutkia lapsuusiän ylipainon kehittymistä ennustavia tekijöitä. Lisäksi tavoitteena oli selvittää, voidaanko yksilöllisen, toistetun ravitsemus- ja elämäntapaneuvonnan avulla vähentää ylipainon ja siihen liittyvien sydän- ja verisuonisairauksien riskitekijöiden esiintyvyyttä, vaikka neuvonnan ensisijaisena tavoitteena onkin vähentää veren LDL-kolesterolin määrää eikä niinkään painoa.

Tutkimus toteutettiin osana laajaa, pitkittäistä SepelvaltimoTaudin Riskitekijöiden InterventioProjektia (STRIP). Projektin alussa 7 kuukauden ikäiset lapset perheineen satunnaistettiin neuvonta- (N=540) ja seurantaryhmiin (N=522). Lasten kasvua ja sydän- ja verisuonisairauksien riskitekijöitä seurattiin vuosittain.

Viidentoista vuoden iässä 11.9 % tytöistä ja 13.7 % pojista oli ylipainoisia. 15-vuotiaan nuoren ylipainoa ennusti parhaiten isän korkea painoindeksi lapsen ollessa seitsemän kuukauden ikäinen, nopea painonnousu kahden ensimmäisen elinvuoden aikana ja aikainen painoindeksin kääntyminen nousuun. Rasvakudoksen tuottama leptiini ei ennustanut ylipainon kehittymistä. Ylipainoon liittyvän FTO-geenin vaikutus painoindeksiin ja ylipainon riskiin alkoi näkyä seitsemän vuoden iästä lähtien ja FTO-genotyypin vaikutus oli niin merkittävä, että annettu neuvonta ei sitä kumonnut. Vaikka ravitsemus- ja elämäntapaneuvonta ei merkitsevästi vähentänytkään ylipainon esiintyvyyttä, se vähensi ylipainoon liittyvien sydän- ja verisuonisairauksien riskitekijöiden kasautumista.

Tutkimus osoittaa, että vanhempien ylipaino, nopea painonnousu ensimmäisten elinvuosien aikana ja ylipainolle altistava perimä ovat tärkeimpiä murrosikäisen ylipainoisuutta ennustavia tekijöitä. Puolivuosittain annettu ravitsemus- ja elämäntapaneuvonta ei ole riittävän tehokasta estämään ylipainon kehittymistä, mutta sillä on suotuisia vaikutuksia ylipainoon liittyviin sydän- ja verisuonisairauksien riskitekijöihin.

Avainsanat: ylipaino, lapset, nuoret, ennaltaehkäisy, ravitsemusneuvonta, sydän- ja verisuonisairauksien riskitekijät, kasautuminen, FTO, perimä, seerumin rasva-arvot, verenpaine

CONTENTS

ABBREVIATIONS

ALAT	Alanine aminotransferase
ANOVA	Analysis of variance
BMI	Body mass index
CAPC	The Research Centre of Applied and Preventive Cardiovascular Medicine
CATCH	The Child and Adolescent Trial for Cardiovascular Health
CI	Confidence interval
CVD	Cardiovascular disease
EGIR	European Group for the Study of Insulin Resistance
E%	Percentage of daily energy intake
FTO	Fat mass and obesity related gene
HDL	High-density lipoprotein
IDF	International Diabetes Federation
IGT	Impaired glucose tolerance
IL-6	Interleukin 6
IMCL	Intra-myocellular lipid
IOTF	International Obesity Task Force
KOPS	Kiel Obesity Prevention Study
LDL	Low-density lipoprotein
NAFLD	Non-alcoholic fatty liver disease
NCEP	National Cholesterol Education Program
PAI	Leisure-time physical activity index
PAI-1	Plasminogen activator inhibitor-1
RIA	Radioimmunoassay
RM ANOVA	Repeated measures analysis of variance
SD	Standard deviation
SEM	Standard error of mean
SES	Socioeconomic status
SNP	Single nucleotide polymorphism
STRIP	Special Turku coronary Risk factor Intervention Project
TNF-α	Tumor necrosis factor α
VLDL	Very low-density lipoprotein
WHO	World Health Organization

LIST OF ORIGINAL PUBLICATIONS

The present thesis is based on the following original publications, which are referred to in the text by the Roman numerals (I-IV). Some previously unpublished data are also presented.

I Hakanen M, Rönnemaa T, Talvia S, Rask-Nissilä L, Koulu M, Viikari J, Bergendahl M, Simell O. Serum leptin concentration poorly reflects growth and energy and nutrient intake in young children. Pediatrics 113:1273-1278, 2004.

II Hakanen M, Lagström H, Kaitosaari T, Niinikoski H, Näntö-Salonen K, Jokinen E, Sillanmäki L, Viikari J, Rönnemaa T, Simell O. Development of overweight in an atherosclerosis prevention trial starting in early childhood. The STRIP study. Int J Obes 30:618-626, 2006.

III Hakanen M, Raitakari OT, Lehtimäki T, Peltonen N, Pahkala K, Sillanmäki L, Lagström H, Viikari J, Simell O, Rönnemaa T. FTO genotype is associated with body mass index after the age of seven years but not with energy intake or leisure-time physical activity. J Clin Endocrinol Metab 94:1281-1287, 2009.

IV Hakanen M, Lagström H, Pahkala K, Sillanmäki L, Saarinen M, Niinikoski H, Raitakari OT, Viikari J, Simell O, Rönnemaa T. Dietary and lifestyle counselling reduces the clustering of overweight-related cardiometabolic risk factors in adolescents. Submitted.

1. INTRODUCTION

Overweight and obesity have not always been considered a threat to an individual's well-being. In the course of history, a fat child was thought to be a healthy child with better chances to survive the periods of undernourishment and infections. The attribute considered a survival advantage in those days became a health risk in modern society where there is a constant abundance of food and where physical activity is decreasing.

The prevalence of overweight has increased rapidly during the past decades both in adults and in children. Currently, two out of three adults and one out of three children are overweight in the United States (Ogden et al. 2006, Ogden et al. 2008). In a recent Finnish study, the prevalence of overweight was lower than that in the United States, but still 13.8 % of girls and 17.1 % of boys aged 16 years being overweight (Pirkola et al. 2008) and the trend of childhood overweight is increasing in Finland (Vuorela et al. 2009). As the prevalence of overweight increases, the prevalence of overweight-related comorbidities increases. For example, type 2 diabetes, virtually unrecognised in children and adolescents previously, has become a common diagnosis in this age group (Fagot-Campagna et al. 2000, Kempf et al. 2008).

Dietary and physical activity habits are adopted mainly during childhood and these behaviours tend to persist into adulthood (Birch and Fisher 1998). Therefore, interventions aiming at healthy behaviours from early in life may establish behaviours that persist into adulthood (Kumanyika et al. 2008). So far, most of the overweight prevention programs have concentrated on school-aged children, and the results of these studies have not been convincing (Birch and Ventura 2009).

The Special Turku coronary Risk factor Intervention Project (STRIP) is a randomised, prospective trial with onset in infancy. The aim of the intervention is to reduce exposure of the children in intervention group to known environmental risk factors for atherosclerosis. At the beginning of the trial, families with 7-month-old infants were randomised either to receive dietary and lifestyle counselling biannually or to no such intervention (a control group). The primary goal was to reduce the concentration of serum low-density lipoprotein (LDL) cholesterol by reducing the intake of saturated fatty acids.

The main aim of the present study was to examine the effect of dietary and lifestyle intervention given in the STRIP trial on the development of overweight and related comorbidities among children aged 7 months to 15 years. Predictors of excess weight gain were also evaluated.

2. REVIEW OF THE LITERATURE

2.1. Epidemiology of childhood overweight and obesity

2.1.1. Definitions of overweight and obesity

Excessive accumulation of adipose tissue leads to overweight and obesity. The amount of adipose tissue may be measured with different methods. Laboratory methods include dual energy X-ray absorptiometry, underwater weighing, air displacement plethysmography and isotope dilution, which provide highly accurate means for assessing adiposity. However, these methods are not very practical in large epidemiologic studies and they are difficult to perform in paediatric populations. Bioelectric impedance and skin folds thickness provide estimates of adiposity, but require population-specific equations for derivation of the body fat percentage (Paineau et al. 2008). Body mass index (BMI) and waist circumference are the most widely used methods to define overweight and obesity in children because they are inexpensive, easy to perform, and well reproducible.

In adults, there are internationally agreed BMI cut-off points for underweight (<18.5), normal weight (18.5-24.9), overweight (25.0-29.9), and obesity (≥30). BMI is also considered to be a reliable estimate of adiposity in children, because it correlates with the more direct measures of adiposity (Pietrobelli et al. 1998). Also, a higher BMI in childhood associates with an increased number of cardiovascular disease (CVD) risk factors and with increased morbidity and mortality of CVD in adulthood (Freedman et al. 2007, Baker et al. 2007). Because age, gender, and pubertal status affect the BMI, different national growth charts have been developed (Kuczmarski et al. 2002, Wright et al. 2002). To facilitate international comparison, the International Obesity Task Force (IOTF) developed age- and gender-specific BMI cut-off points for overweight and obesity for children aged 2 to 18 years (Cole et al. 2000). These cut-off points were developed on the basis of growth-curve data from large epidemiological studies in six countries and pass through the BMI of 25 and 30 at age 18 which is consistent with adult definition.

Many of the health risks of overweight are associated with central obesity (Freedman et al. 1999a, Goran and Gower 1999). The length of waist circumference provides an estimate of abdominal adiposity, but there are no international age- and gender-specific cut-off points for central obesity in children. In its recent criteria for metabolic syndrome in children aged 6 years and above, the International Diabetes Federation (IDF) suggested a waist circumference cut-off point of ≥90th percentile for age, gender, and ethnic origin (Zimmet et al. 2007).

2.1.2. Prevalence and trends

In England, the prevalence of overweight or obesity in 2006-2007 was 22.9 % for children aged 4 to 5 years and 31.6 % for children aged 10 to 11 years when the 85th percentile of the UK 1990 reference charts was used for cut-off (National Child Measurement Programme, Information Centre 2008). According to the IOTF criteria, the prevalence of overweight was highest in the United States (36.0 % among girls and 35.1 % among boys) (Lobstein and Jackson-Leach 2007) and somewhat lower in the Western European countries, e.g., 18.8 % among German children aged 3 to 17 years (Kleiser et al. 2009). In a recent Finnish study, the prevalence of overweight or obesity (according to the IOTF criteria) was 13.8 % among girls and 17.1 % among boys aged 16 years (Pirkola et al. 2008).

In the United States, the prevalence of obesity (BMI for age ≥95th percentile on the 2000 Centers for Disease Control and Prevention growth charts for the United States, Kuczmarski et al. 2002) among children aged 6 to 11 years increased from 4.0 % in the early 1970's to 15.3 % by the end of the 1990's (Ogden et al. 2002). During the same period, the prevalence of obesity among 12- to 19-year-old adolescents increased from 6.1 % to 15.5 % (Ogden et al. 2002). The rise in the prevalence of obesity was more marked in the population of non-Hispanic blacks and Mexican Americans than non-Hispanic whites (Ogden et al. 2002). The prevalence of overweight in Finland increased from 1977 to 1999 from 4.0 % to 9.8 % among girls and from 7.2 % to 16.7 % among boys (Kautiainen et al. 2002). In the United States, the prevalence of obesity continued to increase until 2004 (Ogden et al. 2006), but the most recent data suggest that the increase is levelling off (Ogden et al. 2008); currently 31.0 % of girls and 32.7 % of boys are overweight (BMI for age ≥85th percentile) (Ogden et al. 2008). Consistent with these data, the prevalence of overweight seems to be stabilizing in France (Péneau et al. 2009). However, the prevalence of overweight seems still to be increasing in Finland (Vuorela et al. 2009).

2.2. Development of overweight

Childhood overweight is a result of genetic and environmental factors and their interactions. The increase in the prevalence of overweight during the past decades may be seen as a sum of genetic susceptibility and obesogenic environment. Twin studies have demonstrated that genetic factors play an important role in the variation of BMI, and it has been estimated that heritability in adults ranges from 50 % to 90 % (Maes et al. 1997). The heritability of the BMI is also high in preadolescent children and was reported to be 77 % among twins born in the United Kingdom since the beginning of the recent obesity epidemic (Wardle et al. 2008a). In another twin study, the genetic component explained 63.6 % of the total variance of the BMI, the common environment 25.7 % and unshared environment 10.7 % (Segal et al. 2009).

2.2.1. Genetic background

Single gene disorders account for a very small fraction of obesity in children but associate usually with severe, young-onset obesity. Mutations in genes of the leptin-melanocortin pathway are the most common causes of monogenic obesity (Farooqi 2005). Congenital leptin deficiency, caused by mutations in the leptin gene, results in a severe early-onset obesity, which can be successfully treated with recombinant leptin (Farooqi et al. 2002). Mutations in the melanocortin 4 receptor gene may be responsible for a larger number of obesity cases than mutations in the leptin gene (Alharbi et al. 2007). These genetic defects disrupt satiety mechanisms, and it has, therefore, been suggested that obesity may be considered a neurobehavioral disorder (O'Rahilly and Farooqi 2008). Obesity is also an important clinical feature in many monogenetic (e.g., Bardet-Biedl, Fragile X, Cohen, Alström) or chromosomal (e.g., Prader-Willi) pleiotropic syndromes. In these syndromes, obesity is associated with mental retardation, dysmorphic features and organ-specific developmental abnormalities (Farooqi 2005).

Identification of gene variants predisposing to common, polygenic forms of obesity became possible with genome-wide association studies (Li and Loos 2008). Such a genome-wide search for genes predisposing to type 2 diabetes identified a common variant in the fat mass and obesity associated (FTO) gene, rs9939609, that predisposes to diabetes through an effect on BMI (Frayling et al. 2007). The association between the FTO gene variant, BMI, and risk of obesity has been confirmed in Caucasian adults and children (Peeters et al. 2007, Price et al. 2008, Hunt et al. 2008, González-Sánchez et al. 2009, Hinney et al. 2007, Jacobsson et al. 2008). The FTO genotype is not associated with birth weight suggesting that it is not associated with fetal growth, but the genotype effect on BMI is evident by the age of 7 years (Frayling et al. 2007).

FTO is located in chromosome 16; it is a 400 kilobase gene with nine exons. In the first intron of the FTO gene there is a single nucleotide polymorphism (SNP) rs9939609 which represents a cluster of 10 SNPs. Other variants in the FTO gene (rs1121980, rs1421085, rs17817449, rs9930506) also associate with increase in BMI (Dina et al. 2007, Peeters et al 2007, Scuteri et al. 2007, Do et al. 2008, Loos et al. 2008). The function of the FTO gene is thus far unknown. Computational analysis indicates that the protein coded by the FTO gene is a member of the nonheme dioxygenase superfamily (Sanchez-Pulido and Andrade-Navarro 2007, Gerken et al. 2007). The FTO gene is expressed in many tissues, including several feeding-related sites of the central nervous system and adipose tissue (Fredriksson et al. 2008, Klöting et al. 2008). Recent studies suggest that the FTO gene polymorphisms are associated with satiety, energy intake, fat intake, and measured food intake as of prepubertal age (Wardle et al. 2008b, Cecil et al. 2008, Timpson et al. 2008, Wardle et al. 2009).

FTO SNPs also associate with various obesity-related traits, e.g., insulin sensitivity, fasting insulin, glucose, triglycerides, and high-density lipoprotein (HDL) cholesterol, in adults (Andreasen et al. 2008, Freathy et al. 2008), in addition to the mentioned associations with BMI and the risk of overweight and obesity. These associations may,

however, be mediated by adiposity, since the associations loose statistical significance after adjustment for BMI.

2.2.2. Environmental risk factors

Although genetic factors explain more than half of the variance in BMI, environmental factors clearly contribute (Segal et al. 2009). The current obesity epidemic is principally attributable to changes in the environment, because genes remain fairly well conserved over a short period of time. In the study of Danielzik and colleagues (2004), the analysed environmental determinants of overweight [socioeconomic status (SES), parental weight status, birth weight, breastfeeding, smoking of the parents, diet, and physical activity/inactivity] explained 28-59 % of the variability of the BMI. The environmental risk factors for overweight are, further, modifiable and they may provide a guide as to which risk factors should be considered when developing prevention programs.

The children in families with low SES are at risk of becoming overweight compared to children from medium and high SES families (Danielzik et al. 2004, Kleiser et al. 2009). The impact of SES is so strong that the prevalence of obesity is higher among children with low SES but who have favourable behaviours (e.g., being predominantly breastfed or being less sedentary) compared with children who have medium or high SES but unfavourable behaviours (Kleiser et al. 2009). Low SES also associates with many other risk factors of overweight and obesity. Thus, children from low SES families are less often predominantly breastfed, they spend more time at TV- and computer screens and are less physically active (Kleiser et al. 2009).

Parental overweight seems to be the strongest predictor of childhood overweight (Danielzik et al. 2004, Reilly et al. 2005, Kleiser et al. 2009). Kleiser and colleagues (2009) found that children with both parents overweight or obese had a 4.9-fold odds ratio for overweight and a 10.2-fold odds ratio for obesity compared with children whose both parents were of normal weight. Aggregation of overweight in families includes both genetic and behavioural aspects. In addition to genetic factors, shared environmental factors, e.g., similar eating patterns, dietary composition, and physical activity, explain the familial patterns of body composition (Davison and Birch 2001, Ritchie et al. 2005).

Birth weight associates more closely with obesity than with overweight in childhood (Danielzik et al. 2004). This association is U-shaped, as children with low as well as high birth weight are at risk of becoming obese and of having obesity-associated comorbidities (Danielzik et al. 2004). Birth weight is an indicator of prenatal growth, which in turn is affected by numerous variables. The developmental overnutrition hypothesis proposes that the fetus, while in the uterus of an overweight or obese mother, is exposed to high glucose and free fatty acid levels and that this exposure may lead to permanent changes in appetite control, insulin metabolism, and ratio of fat to lean mass, and to increased birth weight (Oken and Gillman 2003). Exposure to maternal diabetes during pregnancy is also associated with increased birth

weight and a risk of overweight and obesity in childhood and adolescence (Huang et al. 2007). Prenatal exposure to maternal smoking associates with reduced birth weight and with overweight in childhood (von Kries et al. 1999, Huang et al. 2007, Oken et al. 2008). Children born small for gestational age are at risk of reduced insulin sensitivity in childhood and CVD in adulthood, especially if they experience a rapid catch-up growth during the first years of life (Arends et al. 2005, Barker et al. 2005).

Various aspects of diet are associated with overweight and obesity. The effect of breastfeeding on the mean BMI later in life appears to be quite small, but exclusive breastfeeding is associated with a lower systolic blood pressure later in childhood and in adolescence (Owen et al. 2005, Butte 2009, Lawlor et al. 2005). Longitudinal studies have shown a positive association between caloric intake as well as percent fat intake and BMI (Berkey et al. 2000, Klesges et al. 1995). The results from the Bogalusa Heart Study indicate that specific eating patterns (consumption of low-quality food, sweets and meats) are associated with a risk of overweight (Nicklas et al. 2003). Overweight and obese children also consume more soft drinks than normal-weight children (Ludwig et al. 2001, Danielzik et al. 2004, Kleiser et al. 2009). Behavioural aspects of eating also associate with overweight and obesity. Lower satiety responsiveness, higher food cue responsiveness, emotional overeating, and enjoyment of food are associated with excess adiposity (Carnell and Wardle 2008, Webber et al. 2009). Frequent eating away from home associates with excess adiposity (Ritchie et al. 2005). On the other hand, certain foods with high nutritive value relative to their energy content, e.g., fruits, vegetables, and low-fat dairy products, may have a protective effect against overweight (Ritchie et al. 2005).

Physical activity is inversely associated with body weight in most studies (Must and Tybor 2005). In a large, representative sample of American young people, increased weekly moderate to vigorous physical activity was associated with lower risk of becoming overweight (Gordon-Larsen et al. 2002). Screen-time gives an estimate of inactivity or sedentary behaviour, and overweight children are known to spend more time daily at TV- and computer screens than normal-weight children (Danielzik et al. 2004). Positive association between television viewing time and excess adiposity has also been observed in prospective studies (Must and Tybor 2005), especially among children. There have been no major changes in moderate to vigorous leisure-time physical activity or physical inactivity among young people during the recent years of the obesity epidemic, but the amount of commuting physical activity, e.g., walking to school, has decreased markedly (Katzmarzyk et al. 2008). Thus, a large proportion of children do not simply have the opportunity to reach the recommended 60 minutes per day of physical activity (Strong et al. 2005).

It appears to be extremely detrimental, if risk factors accumulate in the same individual, since 33.4 % of girls and 29.2 % of boys with three risk factors (low SES, parental overweight, high birth weight) were overweight or obese in a German study (Danielzik et al. 2004). In another study, the probability of overweight at age 3 years was 29 % for children who were exposed to four risk factors (maternal smoking and excessive weight gain during pregnancy, breastfeeding for less than 12 months, and

less than 12 hour of sleep per day during infancy), whereas the probability of overweight was only 6 % for children without these risk factors (Gillman et al. 2008).

2.2.3. Energy homeostasis

A positive energy balance may be caused by excessive energy intake or reduced energy expenditure. Overweight and obesity usually develop as a result of a relatively small caloric imbalance over time (Wang et al. 2006). Wang and colleagues (2006) estimated that a reduction in energy intake or increase in energy expenditure of 110-165 kilocalories per day could prevent the excessive weight gain in preadolescent children. In children, the basal metabolic rate, physical activity, and growth are the major components of energy expenditure; of these, physical activity is the most easily modifiable component. Fat free mass and gender are the most important determinants of the basal metabolic rate in children (Goran et al. 1994). Thus, physical activity may also increase the basal metabolic rate by increasing the fat free mass.

Energy homeostasis is regulated by both short-term and long-term signals. The short-term signals are mainly secreted by the gastrointestinal tract and they act in the brain to control hunger, food intake, and satiety (Woods 2004). Cholecystokinin and peptide YY have been studied most of the gastrointestinal peptides that inhibit food intake (Woods 2004 and Batterham et al. 2003). Of the gastrointestinal peptides, ghrelin is an exception, as it stimulates rather than inhibits food intake (Daniels et al. 2005). Leptin is the most important long-term signal; it is secreted by the adipocytes and acts in the brain (Daniels et al. 2005).

2.2.4. Role of adipokines in overweight and related comorbidities

The cloning of the *ob* gene and identification of the gene product, leptin, were a breakthrough in understanding the physiology of body weight control (Zhang et al. 1994, Halaas et al. 1995). Leptin is a protein sized 16 kilodaltons. It is secreted by adipocytes and circulates in the blood in concentrations that correlate strongly with the amount of adipose tissue (Maffei et al. 1995). Leptin receptors are expressed in many tissues, including the hypothalamus (Campfield et al. 1995, Cheung et al. 1997). In the hypothalamus, leptin acts as part of a negative feedback loop that maintains energy homeostasis. The anorectic effect of leptin is mediated through activation of the proopiomelanocortin neurons and inhibition of the Agouti-related peptide and neuropeptide Y neurons (Cowley et al. 2001, Stephens et al. 1995). Other hypothalamic and extra-hypothalamic pathways may also be involved (Williams et al. 2009).

In humans, leptin deficiency is an extremely rare cause of obesity and these patients benefit from recombinant leptin therapy (Farooqi et al. 2002). In patients with complete leptin deficiency, treatment with recombinant leptin also results in the normalization of several neuroendocrine axes (reproductive and thyroid axis) and immune function, suggesting that leptin plays a crucial role in regulating these functions (Blüher and Mantzoros 2009). Recombinant leptin may also have beneficial

effects for obese individuals who have inappropriately low serum leptin concentrations (Ravussin et al. 1997, Farooqi and O'Rahilly 2009). However, most obese patients have high plasma leptin concentration (Considine et al. 1996). Obese children and adolescents also have higher plasma leptin concentrations than their normal-weight peers (Hassink et al. 1996, Argente et al. 1997). These results suggest that the vast majority of human obesity is, in fact, caused by leptin insensitivity. These patients do not respond to leptin therapy (Farooqi and O'Rahilly 2009).

Since the discovery of leptin, many other adipokines have been identified (Ronti et al. 2006). Adiponectin is one of the most common cytokines produced by adipocytes. Adiponectin receptors are expressed predominantly in the liver and muscles, and adiponectin sensitises these tissues to insulin (Yamauchi et al. 2002). Individuals with high plasma adiponectin concentrations are less likely to develop type 2 diabetes than those with low concentrations (Spranger et al. 2003). Adiponectin has also antiatherogenic properties: high levels of adiponectin in the plasma are associated with a lower risk of myocardial infarction (Pischon et al. 2004). Overweight is associated with reduced levels of adiponectin that present already during childhood (Nemet et al. 2003) and levels are lower in obese, insulin-resistant adolescents than in obese, insulin-sensitive adolescents (Weiss et al. 2005a). Adipose tissue also secretes proinflammatory cytokines, e.g., tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6), and the plasma concentrations of these cytokines are increased in overweight and obese individuals (Ronti et al. 2006). TNF-α has autocrine and paracrine effects on the adipose tissue, e.g., it increases the release of free fatty acids from the adipocytes, inhibits adiponectin synthesis, and impairs insulin signalling, and contributes in this way to insulin resistance (Ruan et al. 2002). Of the other cytokines involved in obesity, IL-6 is associated with insulin resistance (Bastard et al. 2000). Apelin is a peptide secreted by the adipocytes (Boucher et al. 2005). Apelin may be involved in the regulation of inflammation, since its concentrations correlate with the concentrations of TNF-α in the plasma (Heinonen et al. 2009). Resistin is another cytokine produced by adipose tissue which is overexpressed in obese individuals and associates with insulin resistance (Ronti et al. 2006). Plasminogen activator inhibitor-1 (PAI-1), produced in liver and adipose tissue, inhibits the activity of tissue-type plasminogen activator which is an anticlotting factor. PAI-1 is strongly associated with the incidence of diabetes (Festa et al. 2002). Adipocytes produce angiotensinogen which may be a link between overweight and high blood pressure (Ronti et al. 2006).

2.2.5. Critical periods for the development of overweight

The size of adipocytes increases markedly during the first year of life, and this period constitutes a critical period for the development of overweight. Rapid weight gain in infancy is associated with overweight and obesity in childhood and adolescence with similar risk for average-birth weight and low-birth weight infants (Ong and Loos 2006). Two recent studies suggest that rapid weight gain during the first months of life is an important risk factor for higher percent body fat later in childhood (Taveras et al. 2009, Ong et al. 2009). Rapid weight gain in infancy associates also with metabolic risk factors in adolescence, and this association is independent of birth weight and

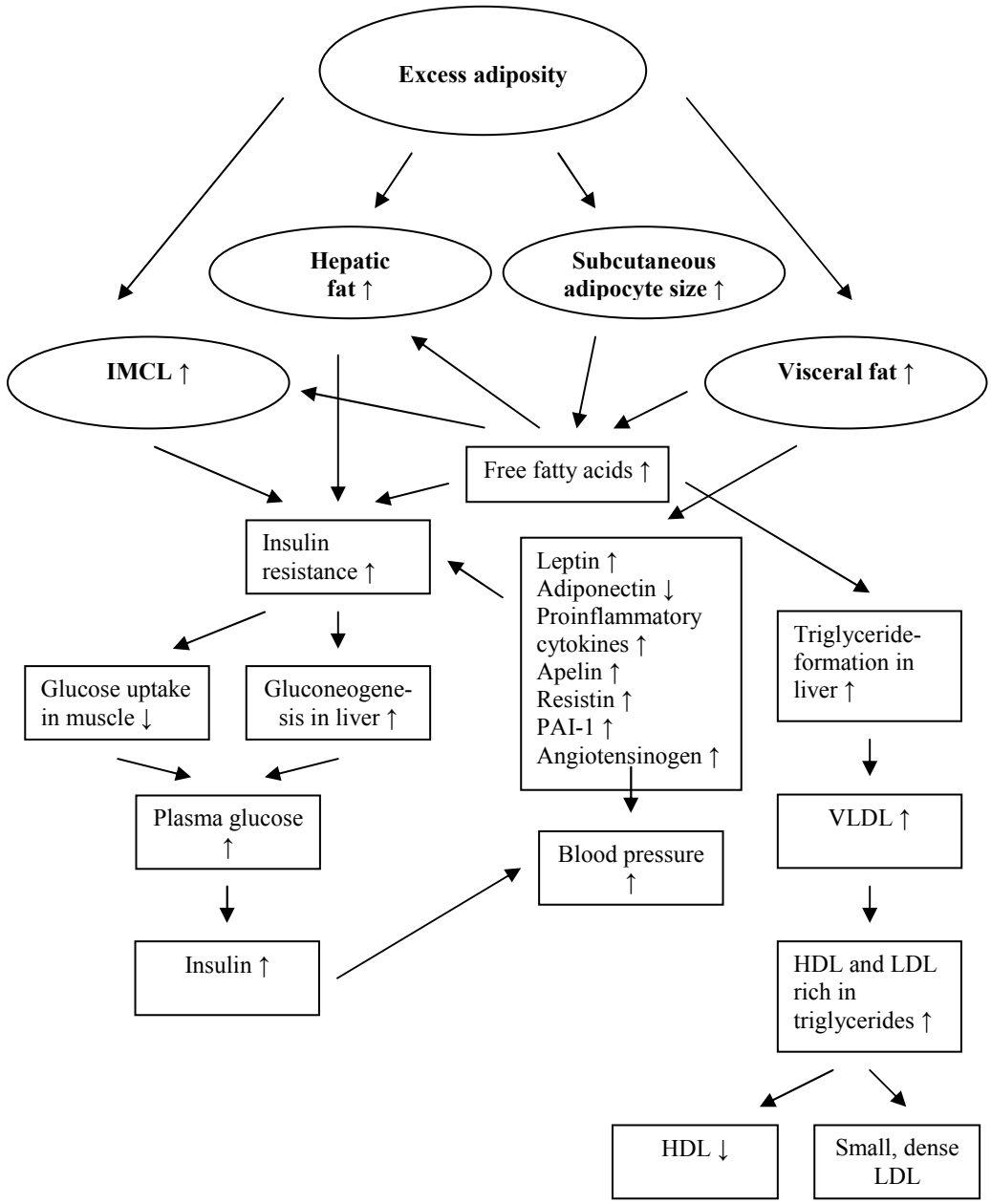
socioeconomic status (Ekelund et al. 2007). The rapid catch-up growth in infancy may, however, also have beneficial effects in certain infants and must not be seen exclusively as a risk factor of overweight and obesity later in life (Yeung 2006). The partitioning of weight gain in infancy into fat and lean mass plays a key role for subsequent obesity and is probably determined by genetic and nutritional factors.

The second critical period for the development of overweight is the adiposity rebound which typically begins in children aged between 5 and 7 years. During the adiposity rebound, both the size and number of adipocytes increase. The onset of the adiposity rebound may be determined from the BMI-curve of an individual: it begins at the age when the BMI starts to increase again after an initial decrease (Rolland-Cachera et al. 1984). If the age at the onset of adiposity rebound is low (<5.5 years), there is an increased risk of overweight and obesity in adolescence and an increased risk of metabolic complications, including type 2 diabetes, in adulthood (Rolland-Cachera et al. 2006, Lagström et al. 2008, Eriksson et al. 2003).

The third critical period for the development of overweight is adolescence. During puberty, body composition and fat distribution change so that the fat free mass increases in boys and the fat free as well as the fat mass increase in girls (Daniels et al. 2005). Physiological insulin resistance occurs in puberty and may play a role in the excessive weight gain and development of various comorbidities of overweight (Travers et al. 1995).

2.3. Consequences of childhood overweight

Adipose tissue functions as energy storage, in addition to being an active endocrine organ. Energy is stored in adipose tissue in the form of triglycerides (Fig. 1). The "overflow hypothesis" states that if the capacity of the peripheral subcutaneous adipocytes to store triglycerides is exceeded, triglycerides accumulate in visceral adipocytes, liver, skeletal muscle, and enlarged peripheral adipocytes (Miranda et al. 2005). Adipose tissue plays a key role in the pathogenesis of insulin resistance, the most common metabolic alteration in overweight and obese children and adolescents and the underlying mechanism for many other metabolic complications of obesity (Weiss and Kaufman 2008). Non-esterified fatty acids, cytokines, and proinflammatory factors produced by adipocytes affect insulin action at different levels, and thus contribute to insulin resistance (Chiarelli and Marcovecchio 2008). The amount of visceral fat correlates better than the amount of subcutaneous fat with insulin resistance (Caprio et al. 1995). Ectopic fat accumulation in the liver and muscles contributes also to the development of insulin resistance by impairing insulin signalling in these tissues (Weiss and Kaufman 2008).



IMCL Intramyocellular lipids
PAI-1 Plasminogen activator inhibitor-1
VLDL Very low-density lipoprotein
HDL High-density lipoprotein
LDL Low-density lipoprotein

Figure 1. Pathophysiology of overweight-related metabolic comorbidities.

2.3.1. Glucose homeostasis

The key determinants of glucose homeostasis are insulin sensitivity and pancreatic beta cell reserve capacity. Individuals with impaired insulin sensitivity are euglycemic as long as the beta cells are able to secrete excess insulin. When the beta cell reserve is no longer able to overcome the excess need, blood glucose begins to rise resulting first in impaired glucose tolerance (IGT) and, later, in type 2 diabetes. Skeletal muscle plays an important role in glucose homeostasis; under insulin-stimulated conditions, 70% of all glucose disposal occurs in skeletal muscle. In obese adolescents, intramyocellular lipid (IMCL) accumulation is associated with IGT (Weiss and Caprio 2005).

The prevalence of IGT is high among obese children and adolescents. In an American study, 25 % of obese children and 21 % of obese adolescents had IGT and a further 4 % of the obese adolescents had undiagnosed type 2 diabetes (Sinha et al. 2002). Similar prevalence rates have been reported in Germany (Wiegand et al. 2004). Impaired glucose tolerance seems to progress quite rapidly into type 2 diabetes in adolescents and this progression is associated with a significant increase in weight (Weiss et al. 2005b). Due to the rapid increase in the prevalence of overweight and obesity among children and adolescents over the past decades, type 2 diabetes has also become more common in this age group (Fagot-Campagna et al. 2000, Kempf et al. 2008). The Centers for Disease Control has estimated that one out of every three person born in 2000 will develop diabetes during his or her lifetime, if current obesity rates continue (Narayan et al. 2003).

2.3.2. Lipid metabolism

The excess free fatty acids released from the adipocytes of an overweight individual are either oxidised or, preferentially, reesterified into triglycerides in the liver (Miranda et al. 2005). Triglyceride-rich VLDL-particles enter the circulation, where triglycerides are exchanged for cholesteryl ester in HDL- and LDL-particles. HDL and LDL rich in triglycerides are subject to lipolysis by hepatic lipase and become smaller. Lipolysed HDL-particles are cleared from the circulation more rapidly than non-lipolyzed HDL-particles resulting in a reduced HDL cholesterol concentration.

Results from the Bogalusa Heart Study show that obese children (BMI $\geq 95^{th}$ percentile) have often high total cholesterol, LDL-cholesterol, triglycerides, and low HDL-cholesterol levels (Freedman et al. 1999b). In a recent German study, 45.8 % of obese children had an abnormal lipid profile: 18.9 % had low HDL-cholesterol combined with high triglycerides, 15.2 % had both high LDL-cholesterol and high triglycerides and 11.7 % had high LDL-cholesterol alone (Korsten-Reck et al. 2008).

2.3.3. Blood pressure

Adipocytes produce angiotensinogen, angiotensin-converting enzyme, and cathepsins. The excess production of these agents raises the blood pressure (Miranda et al. 2005). Insulin has effects on renal sodium reabsorption and on the activity of the

sympathetic nervous system, and hyperinsulinemia may raise the blood pressure of insulin-resistant individuals (Eckel et al. 2005).

Results from the Bogalusa Heart Study show that obese children (BMI $\geq 95^{th}$ percentile) have an increased risk of high systolic and diastolic blood pressure (Freedman et al. 1999b). A trend towards increased blood pressure with increasing BMI occurs through the entire BMI spectrum, not only in subjects with a BMI over specific cut-off points (Reich et al. 2003).

2.3.4. Clustering of overweight-related cardiometabolic risk factors

The association between childhood overweight and cardiovascular risk factors has been widely studied since the early 1970's (Martin and Martin 1973, Reilly et al. 2003). Cardiovascular risk factors tend to cluster in overweight children and adolescents, and the most accepted and unifying hypothesis to describe the pathophysiology of this clustering is insulin resistance (Reaven 1988, Raitakari et al. 1995). In 1998, the World Health Organization (WHO) proposed a first standard definition for the clustering which was also known as the insulin resistance syndrome, syndrome X, and the metabolic syndrome (Alberti and Zimmet 1998). Thereafter, various definitions for the metabolic syndrome in adult population have been proposed by the European Group for the Study of Insulin Resistance (EGIR), the National Cholesterol Education Program (NCEP), the American Association of Clinical Endocrinologists, and the International Diabetes Federation (IDF) (Balkau and Charles 1999, Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults 2001, Einhorn et al. 2003, Alberti et al. 2005). All definitions agree on the essential components (obesity, impaired glucose metabolism, dyslipidemia, and hypertension), but they differ with regard to the details of the criteria. Definitions based on these adult definitions and others have been applied to children and adolescents for the metabolic syndrome, but the agreement between the definitions is poor. Thus, the reported prevalence of the metabolic syndrome among young people, even in the same population, varies widely depending on the definition (Ford and Li 2008, Goodman et al. 2004, Golley et al. 2006).

Half of all overweight adolescents have at least one cardiometabolic risk factor and about 10 % have a cluster of two or more risk factors (I'Allemand et al. 2008). In North America, the prevalence of the metabolic syndrome varies from 4 % to 12 % in the general paediatric population but reaches 30 % among overweight individuals (Cook et al. 2003, Lambert et al. 2004, de Ferranti et al. 2004). The prevalence of the metabolic syndrome increases further as the degree of obesity increases: 39 % of moderately obese and 50 % of the severely obese children and adolescents have the metabolic syndrome (Weiss et al. 2004). In Finland, the prevalence of the metabolic syndrome is 1.2 % among girls and 3.5 % among boys aged 16 years (Pirkola et al. 2008). When cardiometabolic risk factors cluster in the same individual, the risk of type 2 diabetes and early changes of atherosclerotic disease, such as reduced arterial distensibility, increases, also among adolescents (Whincup et al. 2005).

2.3.5. Non-alcoholic fatty liver disease (NAFLD)

Lipid accumulation in the liver is caused by an excess of circulating free fatty acids, de novo lipogenesis within the liver, and by dietary factors that promote lipogenesis (Weiss and Caprio 2008). The spectrum of NAFLD ranges from steatosis to steatohepatitis and to fibrosis and, ultimately, cirrhosis. Measurement of the activity of serum alanine aminotransferase (ALAT) is used to screen for NAFLD. In a study on obese children and adolescents, high ALAT levels were recorded in 14 % of the participants; these levels were associated with reduced insulin sensitivity and glucose tolerance, and increased free fatty acid and triglyceride concentrations in the serum (Burgert et al. 2006).

2.3.6. Other short-term consequences of childhood overweight

Overweight in childhood and adolescence is associated with a risk of asthma. Also, young people with overweight and pre-existing asthma tend to have more asthma symptoms the heavier they are (Reilly et al. 2003). Overweight and the associated hyperinsulinemia contribute to the development of polycystic ovary syndrome (Stanley and Misra 2008). Furthermore, inflammatory factors, like TNF-α and IL-6, are secreted by adipocytes which contribute to subclinical inflammation associated with obesity (Ronti et al. 2006). Overweight children and adolescents have more orthopaedic complications (fractures, musculoskeletal discomfort, and knee pain) than their normal-weight peers, and they tend to have sleep apnea which may be associated with insulin resistance (Taylor et al. 2006, Verhulst et al. 2009). Overweight in childhood and adolescence is also associated with psychosocial problems, e.g., low self-esteem (Strauss 2000).

2.3.7. Tracking of overweight and associated morbidity into adulthood

Overweight and obesity in adolescence increase greatly the risk of overweight in adulthood (Guo et al. 2002). Whitaker and colleagues (1997) found that 75 % of overweight adolescents were overweight as adults. Also, overweight in adolescence associates with increased all cause mortality in adult men independently of weight status in adulthood (Must et al. 1992).

Tracking of overweight-related cardiometabolic risk factors from childhood to adulthood is not as strong as tracking of overweight itself, with tracking of risk factors mainly attributable to the persistence or increase in weight status over the same period (Freedman et al. 2001, Sinaiko et al. 1999). However, there is some evidence that high blood pressure in childhood and insulin resistance in adolescence may, independently of the BMI, predict the metabolic syndrome or insulin resistance in early adulthood (Sun et al. 2007, Sinaiko et al. 2006). The risk of the metabolic syndrome in adulthood is 9-fold higher among those who have the metabolic syndrome in childhood compared with those who do not (Morrison et al. 2008). However, changes in dietary and physical activity patterns affect the clustering of overweight-related cardiometabolic

risk factors, which suggests that tracking is affected by lifestyle changes (Raitakari et al. 1994, Pan and Pratt 2008).

2.4. Prevention of childhood overweight and related morbidity

2.4.1. Lifestyle prevention programs

Prevention of childhood overweight may be implemented at different levels: 1) individual level at primary health care, 2) school- and community-level, and 3) administrative level (Moya 2008). At the individual level, prevention of overweight may be implemented at every clinical encounter, so that height and weight as well as dietary and physical activity patterns are monitored routinely (Daniels et al. 2009). Preventive measures may be targeted at high-risk individuals, e.g., children from low SES families and/or children with parental overweight, high birth weight, early adiposity rebound, adverse dietary habits, or physical inactivity (Danielzik et al. 2004). Intervention studies in high-risk individuals have shown a marked improvement in nutrition knowledge, behaviours, and attitudes, but – regrettably – only a marginal reduction in body fat (Harrell et al. 1998, Caballero et al. 2003).

School- and community-based overweight prevention programs target the entire population and they may, in addition to classroom education, include nutrition guidance, modifications of school meals, and increase in the amount of physical activity during the school day. The data from the Child and Adolescent Trial for Cardiovascular Health (CATCH) and from the Eat Well and Keep Moving Study show that intervention including all these components has beneficial effects on the quality of diet and physical activity (Luepker et al. 1996, Gortmaker et al. 1999). However, there were no favourable changes for body size (Luepker et al. 1996). In a recent Swedish study, modification of school meals accompanied with increased physical activity during the school day led to a reduction in the prevalence of overweight and obesity in 6- to 10-year-old children (Marcus et al. 2009). A minor intervention of installing water fountains in schools resulted in a marked reduction in the risk of overweight, presumably due to reduced consumption of soft drinks (Muckelbauer et al. 2009). The Kiel Obesity Prevention Study (KOPS) is unique in that it combines a universal school-based intervention program with selective prevention measures within overweight families (Danielzik et al. 2005). The intervention in the KOPS resulted in increased remission of overweight but there was no effect on the incidence of overweight (Danielzik et al. 2007). The after-school physical activity program offered in the Medical College of Georgia FitKid Project resulted in a significant decrease in percentage of body fat (Yin et al. 2005, Gutin et al. 2008). Cost-effectiveness analysis of the FitKid project showed that an additional cost of $317 per student was needed to obtain these results (Wang et al. 2008). The results from the FitKid project as well as from other studies with long follow-up times suggest that the impact of a prevention program may last only for the time it is running (Gutin et al. 2008, Jaime and Lock 2009).

The administrative level of overweight prevention includes measures like building safe play grounds, building safe environments for walking and cycling, and legislation on school physical activity lessons and on food advertising (Moya 2008). City planning plays a role in overweight prevention. A neighbourhood in which walking and cycling are possible may protect against overweight (Frank et al. 2004). Also the location of supermarkets, i.e., the availability of affordable and high quality foods, affects the risk of overweight (Lopez 2007).

2.4.2. Challenges to overweight prevention programs

The effects of intervention programs depend on how receptive target individuals are to the intervention. The susceptibility of an individual may be, at least partly, genetically determined, as implied by the fact that the physical activity attenuates the effect of the FTO genotype on BMI (Rampersaud et al. 2008). Thus, overweight prevention programs including physical activity might be beneficial especially in those individuals with this genetic predisposition to obesity.

Prevention programs focus mainly on changes in dietary and physical activity patterns and less attention is paid on how to motivate an individual to adopt favourable behaviours (Livingstone et al. 2006). The children's dietary and physical activity patterns develop in a multidimensional context that involves the family, friends, school, and community. Preventive measures should be applied on all these levels (Davison and Birch 2001). Also, since rapid weight gain in infancy associates with obesity later in life, obesity prevention programs in school may be too late. Maybe preventive measures are needed not only in school but also during the years preceding the school years (Livingstone et al. 2006).

3. AIMS OF THE STUDY

The purpose of the present study was to examine possible predictors of childhood overweight and to evaluate the effect of infancy-onset, individualised dietary and lifestyle counselling, primarily aimed at reducing the serum concentration of LDL-cholesterol, on the development of overweight and related comorbidities among children and adolescents. The more specific aims were:

1. To study whether serum leptin concentration at age 2 years predicts changes in adiposity by age 8 years (I).

2. To study the predictive role of birth weight and parental weight status on childhood overweight and to evaluate the effect of repeated, individualised dietary and lifestyle counselling on the prevalence of overweight in prepubertal children (II).

3. To examine the effect of the FTO genotype and its interaction with the counselling on adiposity and cardiovascular risk factors in children followed up from 7 months to 15 years of age (III).

4. To evaluate the effect of dietary and lifestyle counselling on the prevalence of overweight and the number and clustering of overweight-related cardiometabolic risk factors in 5- to 15-year-old children (IV).

4. SUBJECTS AND METHODS

4.1. Study design of the Special Turku coronary Risk factor Intervention Project

The Special Turku coronary Risk factor Intervention Project (STRIP) is a long-term, prospective, randomised lifestyle intervention trial with onset in infancy. The aim of the intervention is to reduce the exposure of the children to the environmental risk factors of atherosclerosis. The study design and the intervention have been described in detail (Lapinleimu et al. 1995, Simell et al. 2009).

The recruitment of the study subjects and their families took place at the well-baby clinics of the city of Turku between February 1990 and June 1992. During the routine visits when the infants were 5 months old, the clinic nurses provided the parents of 1880 children with information about the STRIP trial. The families of 1105 children were interested in participating, and the design and goals of the project were explained to these families in more detail at the Research Centre of Applied and Preventive Cardiovascular Medicine (formerly the Cardiovascular Research Unit). At this point, the families of 43 children refused and the families of 1062 children volunteered to participate (56.5 % of the eligible cohort). The children were randomly assigned to an intervention group (N=540; 255 girls and 285 boys) or a control group (N=522; 256 girls and 266 boys). The cohort included eight pairs of twins, and they were randomised as pairs.

The families attended for the first study visit when the child was 7 months old. In the beginning of the trial, study visits of the families in the intervention and control groups were at 1- to 3-month and 4- to 6-month intervals, respectively. When the child was 2 – 7 years, the study visits of both study groups were at 6-month intervals, and after that the intervention group continued at 6-month intervals while the visits of the control group were at 12-month intervals. During each visit, a physician or registered nurse examined the child and recorded the child's health history. Further, a nutritionist met the family at each visit, and venous blood samples were drawn when the child was 7 and 13 months, and 2, 3, 4, 5, 7, and 9 years, and annually thereafter.

The flow-chart of the STRIP trial is shown in Figure 2. A total of 534 children still attended the study visit at 15 years (50.3 % of the original cohort). Logistic regression analysis was used to study the possible contributors to loss-to-follow-up, and it was found that the odds ratio for discontinuation was slightly higher among the children in the intervention group than the control group (Study IV). However, after adjustment for other possible contributors (percentage of visits with missing blood samples, various measures of the child's size, lipid values, nutrient intake, quality of diet, pubertal status, maternal BMI, familial SES and familial smoking habits) the effect of the study group on discontinuation was no longer significant.

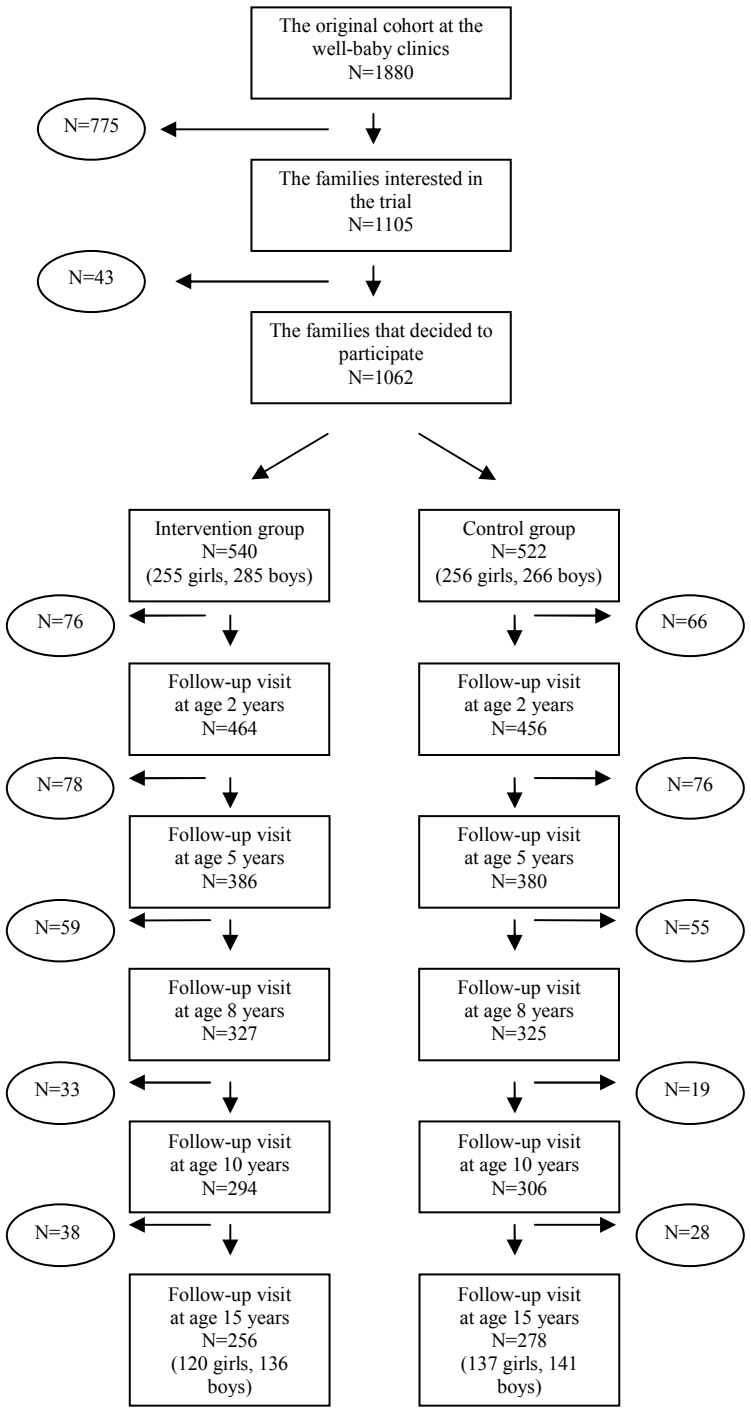


Figure 2. Flow-chart of STRIP trial.

4.2. Study design and subjects of the present study

4.2.1. Study I

To study the predictive power of serum leptin concentration for future weight gain, a group of 156 8-year-old children was selected according to the change in weight-for-height (relative weight in the original publication) during the preceding 6 years. The weight-for-height of 52 children had decreased between 7 and 20 %-units on growth curves of the Finnish children (Sorva et al. 1984), and the weight-for-height of 50 children had increased by 11 to 49 %-units. The weight-for-height of 54 children had been stable during follow-up (change in weight-for-height ≤ 2 %-units). The serum leptin concentrations of these children were analysed in serum samples which were drawn when the children were aged 2 years.

4.2.2. Study II

The possible predictors of childhood overweight and the effect of lifestyle intervention on the development of overweight in prepubertal children were studied in the entire STRIP study cohort. The analysis covered all follow-up visits until the child was 10 years. A total of 462 children discontinued participation before 10 years of age, and they were included in the longitudinal analyses until discontinuation. The few study children (N=15) with chronic diseases (e.g. chromosomal diseases, diabetes) that may influence body weight development were excluded from this analysis.

The possible predictors of childhood overweight included birth weight, age, parental BMIs, study group, and pubertal status. When the children were 7 months old, 1056 mothers and 983 fathers attended for the follow-up visit. The figures were 484 mothers and 331 fathers when the child was 10 years old.

4.2.3. Study III

The role of the FTO genotype for the development of overweight was studied in the children from whom blood samples for DNA analysis were available. Blood samples for DNA analysis were obtained when the children were 5 years old. Of the 766 children who attended for the follow-up visit, the parents of 665 children consented to DNA analysis. Three children with chromosomal diseases were excluded, and because of technical problems, the genotype of 22 children could not be determined. Genotyping of the FTO gene variant was successfully carried out in 640 children (299 girls; 324 in the intervention group). The growth of genotyped children was followed up from 7 months of age to the age of 15 years. Of these children, 196 discontinued participation between age 5 and 15 years, and these children were included in the longitudinal analyses until discontinuation. The children who developed type 1 diabetes during the follow-up were excluded.

4.2.4. Study IV

The effect of lifestyle intervention on the prevalence of overweight and on the number and clustering of overweight-related cardiometabolic risk factors was analysed in 5- to 15-year-old participants in the STRIP trial. This became possible as a fasting serum triglyceride concentration was available from the participants since the age of 5 years. Children (N=17 and N=9 at the ages of 5 and 15 years, respectively) with chronic diseases (e.g. chromosomal diseases, diabetes, familial hypercholesterolemia) were excluded from this analysis.

4.3. Lifestyle intervention and food records

The lifestyle intervention was given by a physician or registered nurse and a nutritionist. The child and the family had also an active role in counselling sessions. Counselling was individualised and it was based on the child's previous eating and physical activity habits, which the family were encouraged to gradually change in a healthier direction. During the first years of the trial, counselling was provided to the parents. From the age of 7.5 years onwards, the child was met alone without the parents and, consequently, more information and suggestions were given directly to the child.

The child's food consumption data were obtained from 4-day food records that the families filled in before each study visit. The food record was reviewed by a nutritionist for completeness and accuracy, and the nutrient composition of diet was analysed using the Micro-Nutrica PC Program (Research and Development Unit of the Social Insurance Institution, Turku, Finland), which was updated continuously. At the beginning of the trial, the main focus of the dietary intervention was on the reduction of saturated fat intake (Talvia et al. 2004). The optimal diet was defined as containing protein 10-15 % of daily energy (E%), carbohydrates 50-60 E%, and fat 30-35 E% until the child was 2 years. After this age, the recommended intake of fat was 30 E% with unsaturated to saturated fatty acid ratio of 2:1. The families were counselled to change from products containing large amounts of saturated fat to products with either less saturated fat or to products with more unsaturated fat instead of saturated fat. During the course of the trial, the families were also encouraged to consume more vegetables, fruits, berries, and whole-grain products, and to lower salt intake. The nutrition counselling was based on Nordic nutrition recommendations (2004).

Physical activity counselling was provided by a physician or registered nurse. At each visit, the hobbies of the child were recorded and especially the physically inactive participants were encouraged to increase the amount of everyday physical activity, like walking or cycling to school if possible. No specific physical activity programs were offered.

The children and families in the control group were met by the same counselling team as the children and families of the intervention group. However, the eating and physical activity habits of the child were discussed only superficially and no special suggestions were made. In other words, these families received similar basic health education as is routinely given at Finnish well-baby clinics and school health care.

4.4. Anthropometric measurements

The birth weights and relative birth weights [standard deviation (SD), birth weight adjusted for gestational age] were collected from the records of the delivery hospital and well-baby clinics. Anthropometric measurements were performed at every visit. When the children were younger than two years, supine lengths were recorded on a baby-board (Bekvil, Paljerakenne, Helsinki, Finland), and from the age of two years onwards, standing heights were measured to the nearest millimetre with a wall-mounted Harpenden stadiometer (Holtain, Crymych, the United Kingdom). Weights of the infants were measured on a baby scale until age 15 months (Seca 725, Hamburg, Germany). Thereafter, weights were measured to the nearest 0.1 kg with an electronic scale (S10, Soehnle, Murrhardt, Germany). Weights-for-height (deviation of weight as percentage from the mean weight of healthy Finnish children of the same gender and height) were determined from the Finnish growth charts (Sorva et al. 1984). The BMI was calculated as weight in kilograms divided by the square of height in meters, and the age- and gender-specific BMI Z-scores were calculated. The beginning of adiposity rebound was determined as the age at which the child's BMI started to increase again after an initial decrease. Heights of the parents were measured with a wall-mounted Harpenden stadiometer (Holtain, Crymych, UK) and their weights were measured with an electronic scale (S10, Soehnle, Murrhardt, Germany).

Two definitions of overweight were applied. In study II, children were classified as overweight if their weight-for-height was >20 % above the Finnish mean and as underweight if their weight-for-height was <15 % below the mean value. In studies III and IV, the definition of overweight was based on the age- and gender-specific BMI cut-off points of the IOTF (Cole et al. 2000).

Blood pressure was measured at each visit on the right arm with an automatic device (Dinamap Compact T, Criticon; Tampa, FL, USA) while the subject was seated and after a rest of at least 5 minutes. Waist circumferences were measured to the nearest 0.5 cm with a flexible tape at the mid-point between the lower costal border and the iliac crest. The pubertal development was rated according to Tanner staging (Tanner and Whitehouse 1976). Breast tissue diameter (M) and pubic hair development (P) were estimated visually and testicular length (G) was measured with a ruler. Stages M1/P1 in girls and G1/P1 in boys were considered prepubertal and all other stages pubertal.

4.5. Physical activity index

The leisure-time physical activity index (PAI) was assessed at age 15 years with a self-administered questionnaire that collected information on the frequency, duration, and intensity of habitual leisure-time physical activity (Pahkala et al. 2007). PAI was calculated as a multiple of the resting metabolic rate (MET; h/wk) by multiplying the frequency, mean duration in minutes, and mean intensity of weekly leisure-time physical activity (Raitakari et al. 1996).

4.6. Biochemical analyses

Venous blood samples were drawn from an antecubital vein, and cutaneous analgesia (EMLA®; Astra, Södertälje, Sweden) was used, if needed. Nonfasting blood samples were drawn between 8 AM and 4 PM when the participants were 4 years or younger and after that age, at ages 5, 7, and 9 years and annually thereafter, the samples were drawn in the morning after a 12-hour, overnight fast. After clotting at room temperature for 30 to 60 minutes and centrifugation at 3400 x G for 12 minutes, sera were separated. The sera were stored at -25ºC for up to a few weeks before lipid and lipoprotein measurements. Sera for later measurements were stored at -70ºC.

4.6.1. Leptin

Serum samples were stored at -70ºC until measurement of leptin concentration. The serum leptin concentration was determined in duplicate using a commercially available double-antibody radioimmunoassay kit (Human Leptin RIA Kit; Linco Research, St. Charles, MO, the United States). The detection limit of the assay was 0.5 ng/mL, when the sample size was 100 μL. The interassay (intraassay) coefficients of variation of the method were 6.2 % (8.3 %) and 3.0 % (4.7 %) at the levels of 4.9 ng/mL and 15.7 ng/mL, respectively.

4.6.2. Lipid, lipoprotein and apolipoprotein measurements

Serum total cholesterol concentration was measured with a fully enzymatic cholesterol oxidase-p-aminophenazone method (CHOD-PAP, Merck, Darmstadt, Germany) (Richmond 1973) either with an automatic Olympus AU 510 analyser (from November 20, 1990 to January 10, 2001) or with an AU 400 analyser (since January 11, 2001) (Olympus; Hamburg, Germany). The samples that were analysed before November 20, 1990 were measured with the Boehringer CHOD-PAP kit (Siedel et al. 1983) and an OLLI analyser (Kone, Helsinki, Finland). Serum HDL-cholesterol concentration was measured after precipitation of LDL and VLDL with dextran sulphate 500 000 (Kostner 1976). Calibration runs were carried out for the concentrations of total and HDL cholesterol measured with different reagents and/or analysers and the results were corrected to the latest level. ApoA-1 and apoB were determined immunoturbidimetrically using apoA-1 and apoB kits (Orion Diagnostica,

Helsinki, Finland) (Riepponen et al. 1987). The interassay (intraassay) coefficients of variation of the total cholesterol, HDL-cholesterol, apoA-1, and apoB determinations were 2.0 % (1.5 %), 1.9 % (1.2 %), 3.0 % (1.8 %), and 4.5 % (3.3 %), respectively.

Serum triglyceride concentrations were analysed using a colorimetric GPO-PAP method (Merck, Darmstadt, Germany) either in an automatic Olympus AU 510 analyser (before January 11, 2001) or in an AU 400 analyser (after January 11, 2001). The interassay coefficients of variation were 4.32 %, 4.46 %, and 4.42 %, when the mean serum triglyceride concentrations were 0.89, 1.43, and 2.26 mmol/L, respectively. The intraassay coefficients of variation were 3.10 %, 3.35 %, and 4.06 %, when the mean serum triglyceride concentrations were 2.35, 1.38, 0.98 mmol/L, respectively. Since the serum samples were taken in the nonfasting state when the participants were aged 4 years or below, the triglyceride concentration could not be determined in this age group. However, non-HDL cholesterol was calculated. The Friedewald formula was used to calculate the LDL-cholesterol concentration of participants aged 5 years and above as LDL cholesterol = total cholesterol – HDL cholesterol – 0.45 x triglycerides (Friedewald et al. 1972). All serum lipid, lipoprotein, and apolipoprotein analyses were done at the laboratory of the National Public Health Institute (formerly the Research and Development Unit of the Social Insurance Institution) in Turku, Finland.

4.6.3. Glucose and insulin measurements

Blood samples for the determination of serum glucose and insulin were centrifuged immediately, and 15 μL of the enzyme inhibitor Antagosan® was added to the 0.5 mL serum insulin sample. Samples were stored at -25ºC for a maximum of two months. Serum glucose was measured by the glucose dehydrogenase method (Merck Diagnostica, Darmstadt, Germany). Serum insulin was measured with radioimmunoassay (RIA; Pharmacia Diagnostics, Uppsala, Sweden). The interassay (intraassay) coefficient of variation for insulin was 3.89 % (2.89 %) at an average concentration of 16.5 mU/L and 3.91 % (3.12 %) at 142 mU/L. The homeostasis model assessment method (HOMA-index) was used to estimate insulin resistance and it was calculated as follows: fasting insulin (μU/mL) x fasting glucose (mmol/L) / 22.5 (Matthews et al. 1985).

4.7. FTO genotyping

Whole blood samples were dried on filter paper. Genomic DNA was extracted from these spots using a commercially available kit according to the manufacturer's instructions (Gentra Systems, Minneapolis, MN, USA). The TaqMan Genotyping Assay with the ABI Prism 7900HT Sequence Detection System (Applied Biosystems, Foster City, CA, the United States) was used to genotype the rs9939609 SNP in the FTO gene. The PCR reactions contained genomic DNA, 1 x TaqMan Genotyping Master Mix, 900 nM of each primer and 200 nM of each probe, and were performed in

384-well plates using a standard protocol. Known control samples and random blind duplicates were run in parallel with unknown samples as for quality control. The genotype frequencies were in Hardy-Weinberg equilibrium in our study population. Genotyping was performed in the Department of Clinical Chemistry at Tampere University Hospital and University of Tampere.

4.8. Definitions of overweight-related cardiometabolic risk factors and risk factor cluster

Age- and gender-specific (intervention and control groups combined) quintile cut-off points were determined for the 5- to 15-year-old children for BMI, triglycerides, HDL-cholesterol, systolic blood pressure, diastolic blood pressure, and serum glucose concentration (Table 1). The following four risk factors were included in the longitudinal analysis: being in the highest quintile for 1) BMI, 2) triglycerides, and 3) systolic or diastolic blood pressure or in the lowest quintile for 4) HDL-cholesterol. The data on serum glucose concentrations were available for the participants at age 15 years. The 15-year-old participants were defined as having a cluster of overweight-related cardiometabolic risk factors if they belonged to the highest BMI-quintile and had at least two other risk factors, e.g., being in the highest quintile for 1) triglycerides, 2) systolic or diastolic blood pressure or 3) serum glucose or in the lowest quintile for 4) HDL-cholesterol.

4.9. Socioeconomic status

The parents of the study children filled in a questionnaire on the socioeconomic status of the family when the study children were aged 15 to 16 years. Parental education was inquired, and the answers were categorised in three groups: 1) basic education, 2) occupational education, and 3) university education.

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Table 1. Age- and gender-specific (intervention and control groups combined) quintile cut-off points for cardiometabolic risk factors (Study IV).

	5 years		7 years		9 years		11 years		13 years		15 years	
	Cut off point	**N[1]**	**Cut off point**	**N[1]**	**Cut off point**	**N[1]**	**Cut off point**	**N[1]**	**Cut off point**	**N[1]**	**Cut off point**	**N[1]**
Girls												
Body mass index (kg/m^2)	16.45 (17.15)[2]	70	17.54 (17.75)[2]	62	18.98 (19.07)[2]	58	20.82 (20.74)[2]	54	21.95 (22.58)[2]	52	22.62 (23.94)[2]	50
Triglycerides (mmol/L)	0.94	60	1.04	48	1.15	41	1.15	50	1.20	46	1.30	43
HDL-cholesterol (mmol/L)	1.01	65	1.13	61	1.11	57	1.07	53	1.04	57	1.03	51
Systolic blood pressure (mmHg)	105	62	109	59	108	55	116	54	117	52	124	48
Diastolic blood pressure (mmHg)	63	68	66	51	64	52	63	53	66	51	67	48
Glucose (mmol/L)											5.1	50
Boys												
Body mass index (kg/m^2)	16.13 (17.42)[2]	79	16.85 (17.92)[2]	71	18.32 (19.10)[2]	63	20.05 (20.55)[2]	60	21.06 (21.91)[2]	58	22.22 (23.29)[2]	54
Triglycerides (mmol/L)	0.94	59	0.94	66	0.94	58	1.00	58	1.10	52	1.20	51
HDL-cholesterol (mmol/L)	1.04	75	1.09	67	1.15	67	1.09	59	1.00	62	0.90	55
Systolic blood pressure (mmHg)	104	70	107	69	107	62	114	59	118	53	133	53
Diastolic blood pressure (mmHg)	63	73	65	63	63	56	64	55	66	56	67	52
Glucose (mmol/L)											5.3	46

[1]Number of children in the respective quintile.
[2]Cut-off point for overweight of the IOTF (Cole et al. 2000)

4.10. Statistical analyses

SAS for Windows (SAS Institute, Cary, NC, the United States) software, releases 8.0 (I) and 9.1 (II-IV), were used for statistical analyses. The results are presented as means and standard errors of mean (SEM) or SD, odds ratios with 95 % confidence intervals (95% CI), or as percentages. The differences were considered statistically significant at $p<0.05$.

Study I: Because the distribution of leptin was skewed, the data were double log ($\log_{10}\log_{10}$) transformed. Log_{10} transformation was used to normalize the skewness of the BMI-adjusted leptin values. The analyses were run for girls and boys separately. Analysis of variance (ANOVA) models were used to compare the three groups with different weight-change patterns. Pairwise comparisons were carried out with T-tests using Tukey-Kramer's adjustment.

Study II: The proportions of overweight and underweight 10-year-old children in the intervention and control groups were compared using Fisher's Exact Test. Logistic regression analysis with the generalised estimating equations methodology was used to study the possible predictors of childhood overweight. For this analysis, children were divided into those whose weight-for-height exceeded the Finnish mean by more than 20 % at any age point and into those whose weight-for-height was constantly +20 % or less. The pre hoc predictors included in the model were birth weight, age, study group, maternal BMI, paternal BMI, and pubertal status at age 10 years.

Study III: Both additive and recessive models were fitted for the FTO genotype. However, BMIs of the children with the TT and TA genotype were almost identical during follow-up, and thus the assumptions of the additive model were not fulfilled. Therefore, the results only of the recessive model are presented. All p-values were multiplied by two to correct for multiple testing. Longitudinal data were analysed using general linear models [repeated measures analysis of variance (RM ANOVA)] with age as a repeated measurement factor and with first order autoregressive covariance structure. Gender and the STRIP study group (intervention and control) together with their interactions with the FTO genotype were included in the models. Backward selection with exclusion criteria $p>0.1$ was used. The analyses of blood pressure values were adjusted for BMI Z-score and height, and the analyses of serum lipid values were adjusted for BMI Z-score. The effect of the FTO genotype on the proportion of overweight children was analysed with logistic regression and age, gender, and study group and their interactions with the FTO genotype as covariates. Cross-sectional data on birth weight, adiposity rebound, and different phenotypes at the age of 15 years were analysed with linear models (ANOVA) using backward selection ($p>0.1$).

Study IV: Longitudinal data on the proportions of overweight children were analysed using general linear models (RM ANOVA) with age as a repeated measurement factor. The analyses were run for both genders separately because an age-by-gender

interaction was identified. An age-by-study group (intervention and control) interaction was included in the models. The numbers of risk factors in the intervention and control children were compared using Cochran-Mantel-Haenszel's statistics for row mean score difference, stratified by age. Linear models (ANOVA) with backward selection ($p>0.1$) were used to analyse the characteristics of the 15-year-old participants in the intervention and control groups. Logarithmic transformation was used for BMI, serum triglycerides, glucose, and insulin as well as for the HOMA-index, because of the skewness of the distributions. The ANOVA models were adjusted for gender and study group.

Predictors of overweight (unpublished data): Logistic regression was used to assess the effect of the following possible predictors of overweight: gender, FTO-genotype, birth weight, STRIP study group, change in weight from birth to 2 years of age, serum leptin concentration at the age 2 years, age at beginning of the adiposity rebound, parental BMI at the child's age of 7 months and the change in parental BMI between the child's ages of 7 months and 15 years, parental education, participant's diet (energy intake and energy nutrient intakes), and participant's physical activity level at the age 15 years. All predictors with a considerable effect on the risk of overweight in the single predictors models were combined into a multivariate model, and excluded by backward selection if the exclusion criteria were fulfilled (inclusion/exclusion criteria $p>0.15$).

4.11. Ethics

The STRIP study was approved by the Joint Commission on Ethics of the Turku University and the Turku University Hospital. At the beginning of the study, parents of the children signed informed consent for the study itself and later, another informed consent was obtained for gene analysis. When the study participants had reached age 15 years, they provided informed written consent.

5. RESULTS

5.1. Predictors of overweight

5.1.1. Serum leptin (Study I)

Serum leptin concentrations were measured in 156 2-year-old children, who were selected on the basis of their change in weight-for-height (relative weight in the original publication) between 2 and 8 years of age (Table 2). At the age of 2 years, the girls whose weight-for-height decreased during the follow-up had a higher weight-for-height and BMI compared with the girls whose weight-for-height remained stable or increased by age 8 years ($p<0.03$ for weight-for-height and BMI). Furthermore, 2-year-old girls whose weight-for-height subsequently decreased had a higher mean serum leptin concentration than the girls whose weight-for-height remained stable ($p=0.019$). The statistical significance of this difference was slightly reduced when the serum leptin values were adjusted for BMI ($p=0.07$ for the overall comparison). The girls whose weight-for-height remained stable during the follow-up did not differ in weight-for-height, BMI, or mean serum leptin concentration at the age of 2 years from the girls who had an increase in weight-for-height by age 8 years.

Consistent with the data for the girls, the 2-year-old boys whose weight-for-height decreased during the follow-up had higher weight-for-height and BMI compared with boys, whose weight-for-height remained stable or increased by the age of 8 years ($p<0.01$ for weight-for-height and BMI). The boys whose weight-for-height remained stable during the follow-up did not differ in weight-for-height or BMI at the age of 2 years from the boys whose weight-for-height increased by the age of 8 years. The mean serum leptin concentrations and BMI-adjusted leptin concentrations were similar in the three groups at the age of 2 years.

Table 2. Anthropometric measures and serum leptin concentrations of 52, 54, and 50 2-year-old children in the STRIP study whose weight-for-height decreased, remained stable, or increased during follow-up until age 8 years (modified from Study I).

	Weight-for- height decreased (1)	Weight-for- height stable (2)	Weight-for- height increased (3)	Overall p	Group comparisons[1]
Girls	N=27	N=26	N=24		
Weight-for-height at 2 y (%)[2]	6.5 (1.1)	-0.1 (1.5)	0.3 (2.0)	0.004	1 vs 2 0.008 1 vs 3 0.016
BMI at 2 y (kg/m^2)	17.2 (0.2)	16.2 (0.2)	16.3 (0.3)	0.004	1 vs 2 0.006 1 vs 3 0.023
Change in weight-for- height from 2 to 8 y (% units)	-11.4 (0.7)	+0.2 (0.2)	+23.3 (1.6)	<0.001	1 vs 2 <0.001 1 vs 3 <0.001 2 vs 3 <0.001
Serum leptin at 2 y (ng/mL)	4.2 (0.3)	3.2 (0.2)	3.4 (0.3)	0.016	1 vs 2 0.019
BMI-adjusted leptin at 2 y	0.24 (0.02)	0.20 (0.01)	0.21 (0.02)	0.072	
Boys	N=25	N=28	N=26		
Weight-for-height at 2 y (%)[2]	6.1 (1.5)	-1.0 (1.1)	-1.7 (1.6)	<0.001	1 vs 2 0.002 1 vs 3 <0.001
BMI at 2 y (kg/m^2)	17.3 (0.3)	16.2 (0.2)	16.2 (0.3)	0.002	1 vs 2 0.008 1 vs 3 0.005
Change in weight-for- height from 2 to 8 y (% units)	-11.4 (0.6)	0.0 (0.2)	+17.7 (1.2)	<0.001	1 vs 2 <0.001 1 vs 3 <0.001 2 vs 3 <0.001
Serum leptin at 2 y (ng/mL)	2.9 (0.2)	3.3 (0.3)	3.2 (0.2)	0.73	
BMI-adjusted leptin at 2 y	0.17 (0.01)	0.20 (0.01)	0.20 (0.01)	0.28	

Values are mean (SEM).
[1]Pairwise comparisons were carried out with T-tests using Tukey-Kramer's adjustment.
[2]Deviation of weight as percentage from mean weight of healthy Finnish children of the same gender and height.

5.1.2. Birth weight and parental weight status (Study II)

The effects of birth weight and parental BMI on the child's risk of becoming overweight were analysed during the first 10 years of life. In girls, a one unit increase in their mother's BMI increased the risk of becoming overweight by 16 % (p=0.025, 95% CI 6 to 26 %) and a one unit increase in their father's BMI increased the risk by 10 % (p=0.017, 95% CI 5 to 14 %). In boys, a one unit increase in their father's BMI increased the risk of becoming overweight by 14 % (p=0.040, 95% CI 1 to 30 %) but the mother's BMI was not a significant predictor of the risk of becoming overweight. Birth weight, study group and pubertal status at age 10 years did not predict of the risk of becoming overweight in our study population.

5.1.3. FTO genotype (Study III)

The rs9939609 SNP in the FTO gene was genotyped in 640 children. The FTO genotype was not associated with birth weight or relative birth weight (Table 3). During follow-up from age 7 months to age 15 years, the effect of the FTO genotype on BMI changed over time (p=0.004 for FTO-by-age interaction) (Fig. 3). Gender and study group were dropped out of the model by backward selection, because they had neither an interaction with the FTO genotype nor a main effect on BMI. The FTO genotype was not associated with the age at the beginning of the adiposity rebound (Table 3), and therefore, we analysed the effect of the FTO genotype on BMI before or during the adiposity rebound (in children aged 7 months to 6 years) and after the adiposity rebound (in children aged 7 to 15 years). The FTO genotype did not associate with BMI in children younger than 7 years (FTO-by-age interaction was dropped out of the model by backward selection and p>0.99 for the main effect of the FTO). In children aged 7 years or older, the effect of the FTO genotype on BMI changed over time: the AA genotype was associated with a progressively higher BMI compared with the TA or TT genotype (p=0.029 for FTO-by-age interaction). The FTO genotype was further associated with increased risk of overweight in children aged 7 years or older but not in the younger age (Fig. 4). The odds ratio of overweight was 1.67 (95% CI 1.36-2.04) in the group of children with the AA genotype compared with the children with TA/TT genotype (p<0.001). Gender and study group did not modify the effect of FTO genotype on the risk of overweight.

Table 3. Associations of rs9939609 variants in the FTO gene with phenotype characteristics at birth and at the beginning of the adiposity rebound (Study III).

	Mean (SEM) by FTO genotype			
	TT	**TA**	**AA**	**P for the recessive model[1]**
N (Proportion of boys)	211 (58 %)	325 (50 %)	104 (53 %)	
Birth weight (g)	3598.2 (34.2)	3524.8 (30.8)	3537.3 (55.5)	p>0.99
Relative birth weight (SD)[2]	0.13 (0.07)	0.06 (0.06)	0.07 (0.11)	p>0.99
Age at the beginning of the adiposity rebound (yrs)[3,4,5]	5.4 (0.13)	5.4 (0.10)	5.2 (0.19)	p>0.99

[1]The P values were multiplied by two because both the additive and recessive models were fitted.
[2]Birth weight adjusted for gestational age.
[3]The beginning of the adiposity rebound was determined as the age at which the child's BMI started to increase again after an initial decrease.
[4]The data on the age at the beginning of the adiposity rebound were available from 166, 255 and 72 children with TT, TA, and AA genotype, respectively.
[5]75 % of the children with TT, TA, and AA genotype had reached the adiposity rebound by the ages 6.1, 6.5 and 6.3 years, respectively.

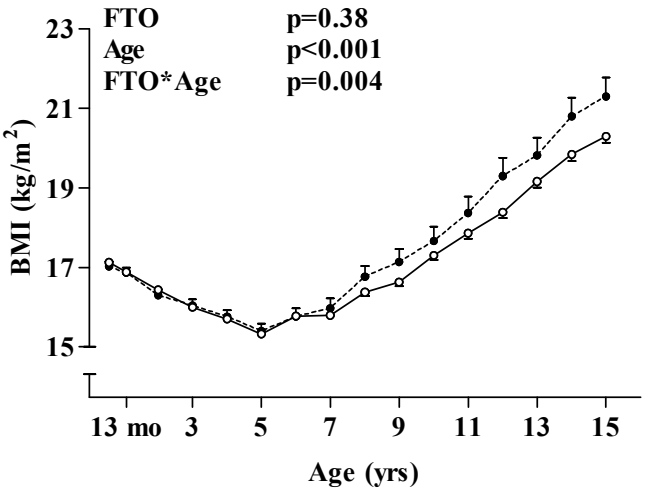

Figure 3. Mean (SEM) BMI of the children with AA genotype (black circle with broken line) and the children with TT or TA genotype (open circle with solid line) in rs9939609 of the FTO gene. FTO-by-gender and FTO-by-study group interactions were not significant. (Study III).

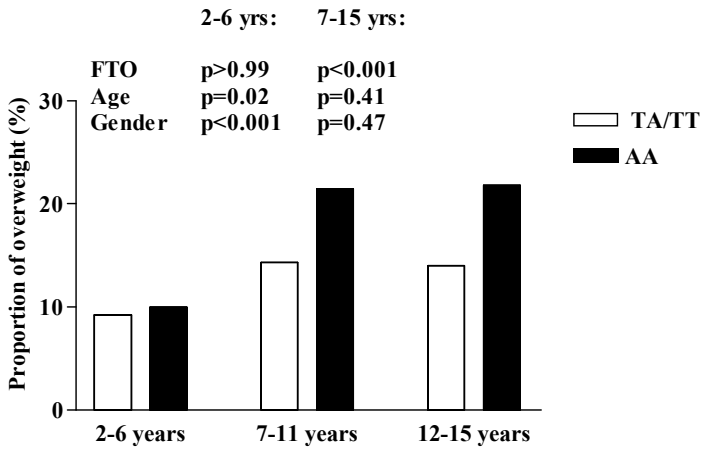

Figure 4. The proportion of overweight (according to IOTF cut-off points, Cole et al. 2000) children with AA or AT/TT genotype. FTO-by-gender and FTO-by-study group interactions were not significant. (Study III).

5.1.4. Predictors of overweight at age 15 years (unpublished data)

At age 15 years, 11.9 % of girls and 13.7 % of boys were overweight (according to the BMI cut-off points of the IOTF, Cole et al. 2000). To assess the impact of the possible predictors of weight status at age 15 years, a multivariate model was constructed. First, univariate associations with $p<0.15$ were identified for the following factors: change in weight from birth to 2 years of age ($p<0.0001$), serum leptin concentration at age 2 years ($p=0.10$), age at the beginning of the adiposity rebound ($p<0.0001$), mother's BMI at the child's age of 7 months ($p<0.0001$), father's BMI at the child's age of 7 months ($p<0.0001$), mother's education ($p=0.08$), total energy intake at age 15 years ($p=0.002$), protein intake at age 15 years ($p=0.03$), and the level of physical activity at age 15 years ($p=0.006$). These factors were included in the multivariate model, the final results of which are shown in Table 4. Three predictors of the overweight status at age 15 were identified and they were: 1) change in weight between birth and age 2 years, 2) age at beginning of the adiposity rebound, and 3) paternal BMI when the child was 7 months old.

Table 4. Predictors of overweight at age 15 years (overweight was defined according to the IOTF cut-off points for BMI, Cole et al. 2000) (Unpublished data).

The predictor	Mean (SD) in normal-weight adolescents (N=457)	Mean (SD) in overweight adolescents (N=67)	Odds ratio[1] (95% CI)	p-value[2]
Change in weight from birth to 2 y (kg)	9.2 (1.2)	10.1 (1.5)	2.2 (1.6-2.9)	<0.0001
Age at beginning of adiposity rebound (yrs)	5.5 (1.6)	4.1 (1.4)	0.58 (0.45-0.75)	<0.0001
Paternal BMI when child was 7 months old (kg/m^2)	24.6 (3.0)	26.9 (3.7)	1.2 (1.1-1.3)	<0.001

[1]Odds ratio for being overweight at age 15 years per one unit increase of the predictor.
[2]Main effect p-value (multivariate model).

5.2. Effect of lifestyle intervention on the prevalence of overweight

5.2.1. Effect of lifestyle intervention in prepubertal children (Study II)

During the first ten years of life, the study children were classified as overweight if their weight-for-height was >20 % above the Finnish mean. At the age of 10 years, 10.2 % of girls in the intervention group and 18.8 % of girls in the control group were overweight (p=0.044) (Fig. 5). In the group of 10-year-old boys, there was no difference between the intervention and control groups in the prevalence of overweight with 11.6 % of boys in the intervention group and 12.1 % of boys in the control group being overweight (p>0.99) (Fig. 5).

On the other hand, the children were classified as underweight if their weight-for-height was more than 15 % below the mean value on the Finnish growth charts. The proportions of underweight children were similar in the intervention and control groups (Fig. 5). At the age of 10 years, 2.9 % and 3.5 % of the girls in the intervention and control groups, respectively, were underweight (p>0.99). In the 10-year-old boys the figures were 4.1 % and 8.3 % for the intervention and control groups, respectively (p=0.16).

5.2.2. Effect of lifestyle intervention in 5- to 15-year-old children (Study IV)

The 5- to 15-year-old children and adolescents were classified as normal-weight or overweight according to the age- and gender-specific BMI cut-off points of the IOTF (Cole et al. 2000) (Fig. 6). At age 15 years, 10.4 % of girls in the intervention group and 13.1 % of girls in the control group were overweight and of boys 11.4 % and 15.8 %, respectively. During follow-up from age 5 years to age 15 years, the intervention given in the STRIP trial had no effect on the proportion of overweight girls and boys (p=0.71 and p=0.09 for age-by-study group interaction in girls and boys, respectively; and p=0.49 and p=0.33 for the main effect of study group in girls and boys, respectively).

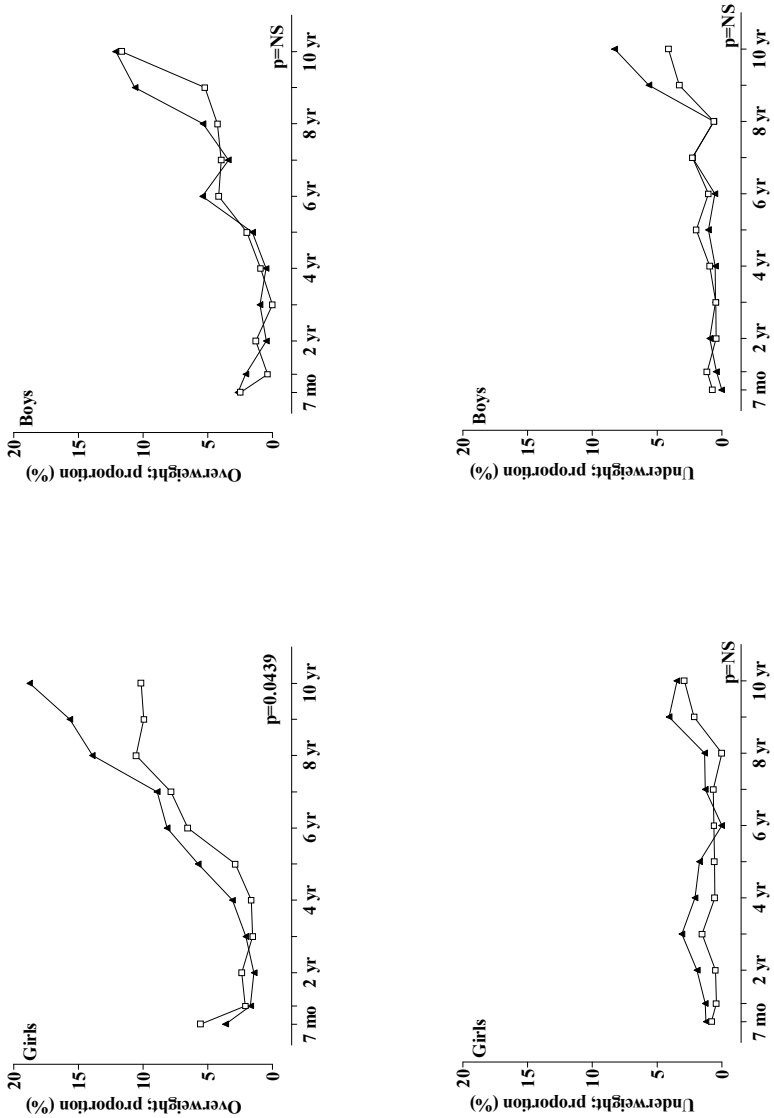

Figure 5. The proportions of overweight and underweight children (according to the Finnish growth charts, Sorva et al. 1984) in the intervention (□) and control (▲) groups. P-values are presented only at the age of 10 years. The girls, left panel; the boys, right panel. (Study II).

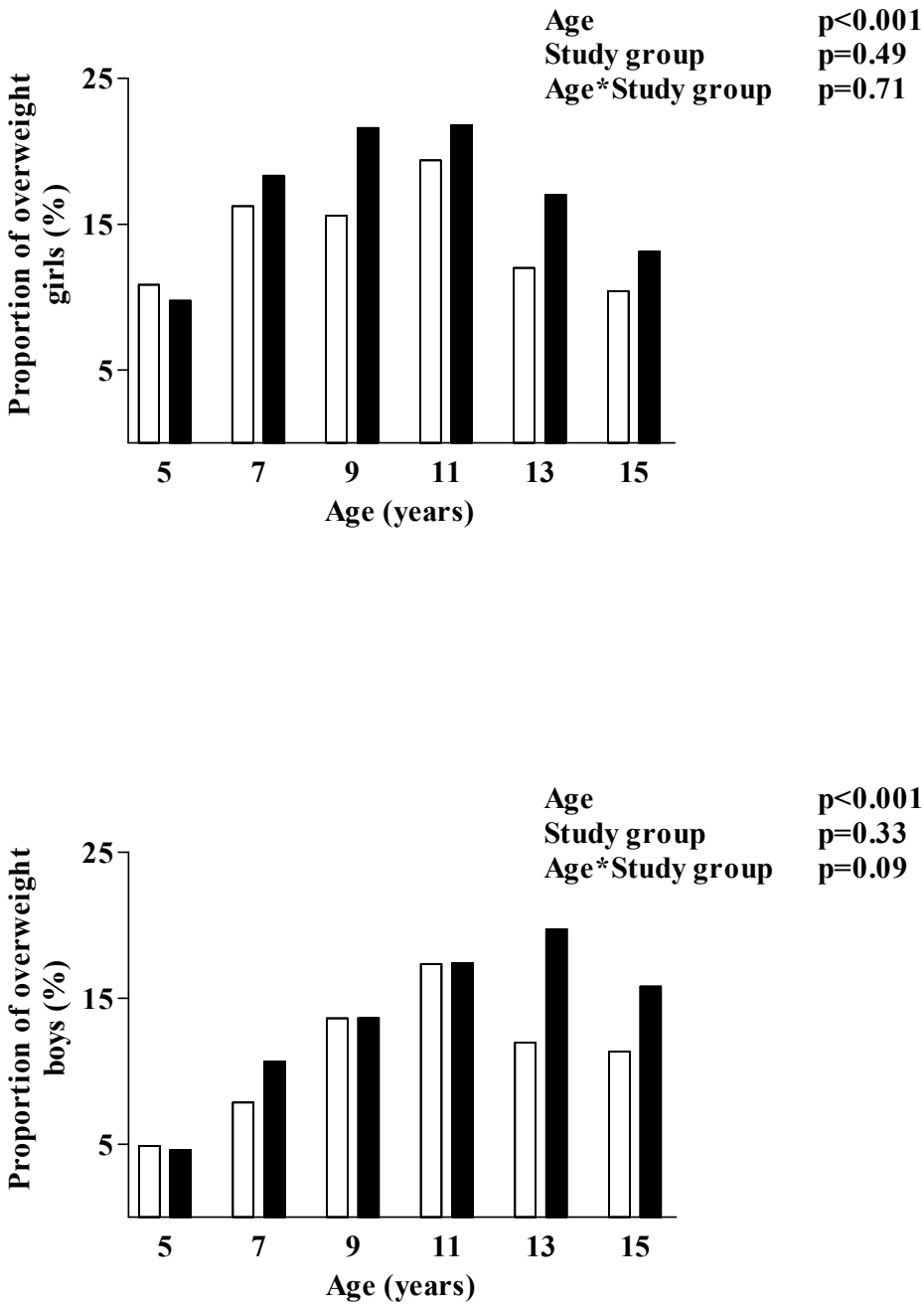

Figure 6. The proportions of overweight children (according to the IOTF cut-off points, Cole et al. 2000) in the intervention (open bars) and control (black bars) groups of the STRIP trial (Study IV).

5.3. Role of the FTO genotype (Study III)

5.3.1. Energy intake and physical activity

The function of the FTO gene is largely unknown at present, and therefore the associations between the FTO genotype and energy intake and physical activity among 15-year-old adolescents were studied. 148, 220, and 71 adolescents with TT, TA and AA genotype, respectively, attended the 15-year-old follow-up visit and the phenotypes of these adolescents are shown in Table 5. Adolescents with the AA genotype had a 1.0 unit higher BMI than the children with TA or TT genotype ($p=0.04$). Furthermore, the adolescents with AA genotype had a mean waist circumference of 75.2 cm compared with 72.5 cm in adolescents with at least one T allele ($p=0.05$). However, there were no associations between the FTO genotype and dietary variables analysed from the 4-day food records [mean daily energy intake, the daily energy intake per kilogram of weight, or fat, protein and carbohydrate intakes (as percentage of daily energy intake)] (Table 5). Nor was there any association between the FTO genotype and leisure-time physical activity index (Table 5). Gender and study group were included in the analyses, but still no interactions emerged between gender or study group and the FTO genotype with regard to dietary or physical activity variables.

Table 5. Associations of rs9939609 variants in the FTO gene with phenotype characteristics at the age of 15 years. FTO-by-study group and FTO-by-gender interactions were not significant. (Study III).

	Mean (SEM) by FTO genotype			
	TT	**TA**	**AA**	**P for the recessive model[1]**
N at the age of 15 years (Proportion of boys)	148 (57 %)	220 (48 %)	71 (58 %)	
Height (cm)	170.1 (0.6)	170.1 (0.6)	170.3 (1.0)	>0.99
Weight (kg)	58.8 (0.9)	59.1 (0.7)	61.9 (1.6)	0.13
BMI (kg/m^2)	20.3 (0.3)	20.3 (0.2)	21.3 (0.5)	0.04
Waist (cm)	72.3 (0.7)	72.7 (0.6)	75.2 (1.2)	0.05
Energy intake[2] (kcal)	2028.3 (47.9)	1989.0 (40.3)	2010.0 (64.3)	>0.99
Energy / weight (kcal/kg)	35.5 (0.9)	34.6 (0.8)	34.0 (1.4)	0.69
Fat intake (E%)	31.1 (0.5)	31.7 (0.4)	30.6 (0.7)	0.27
Protein intake (E%)	17.7 (0.3)	17.4 (0.2)	17.9 (0.4)	0.81
Carbohydrate intake (E%)	51.3 (0.5)	50.9 (0.4)	51.5 (0.7)	0.97
Physical activity index (PAI)[3] (MET h/wk)	31.9 (2.1)	26.4 (1.6)	28.5 (2.9)	>0.99

[1]The P values were multiplied by two because both the additive and recessive models were fitted.
[2]Food record was available from 127, 190 and 65 children with TT, TA and AA genotype, respectively.
[3]PAI was available from 129, 193 and 61 children with TT, TA and AA genotype, respectively.

5.3.2. Cardiometabolic risk factors

The associations between the FTO genotype and cardiometabolic risk factors were studied with longitudinal, BMI Z-score-adjusted analyses. The blood pressure analyses were further adjusted for height. During follow-up from age 7 months to age 15 years, the AA genotype was associated with higher systolic and diastolic blood pressure ($p=0.01$ and $p<0.001$ for systolic and diastolic blood pressure, respectively) (Fig. 7) and with elevated serum total and LDL-cholesterol concentrations ($p=0.05$ and $p=0.04$ for the total cholesterol and LDL-cholesterol, respectively) (Fig. 8). Gender and study group did not interact with the FTO genotype with respect to blood pressure or serum lipid values. Gender had a main effect on systolic blood pressure, serum total cholesterol, and LDL-cholesterol ($p\leq0.02$ for all main effects). Furthermore, the study group had a main effect on systolic blood pressure, diastolic blood pressure, serum total cholesterol, and LDL-cholesterol ($p<0.001$ for all main effects). The FTO genotype did not associate with HDL-cholesterol, non-HDL-cholesterol, triglycerides, ApoA-1 or ApoB after adjustment for BMI Z-score (data not shown).

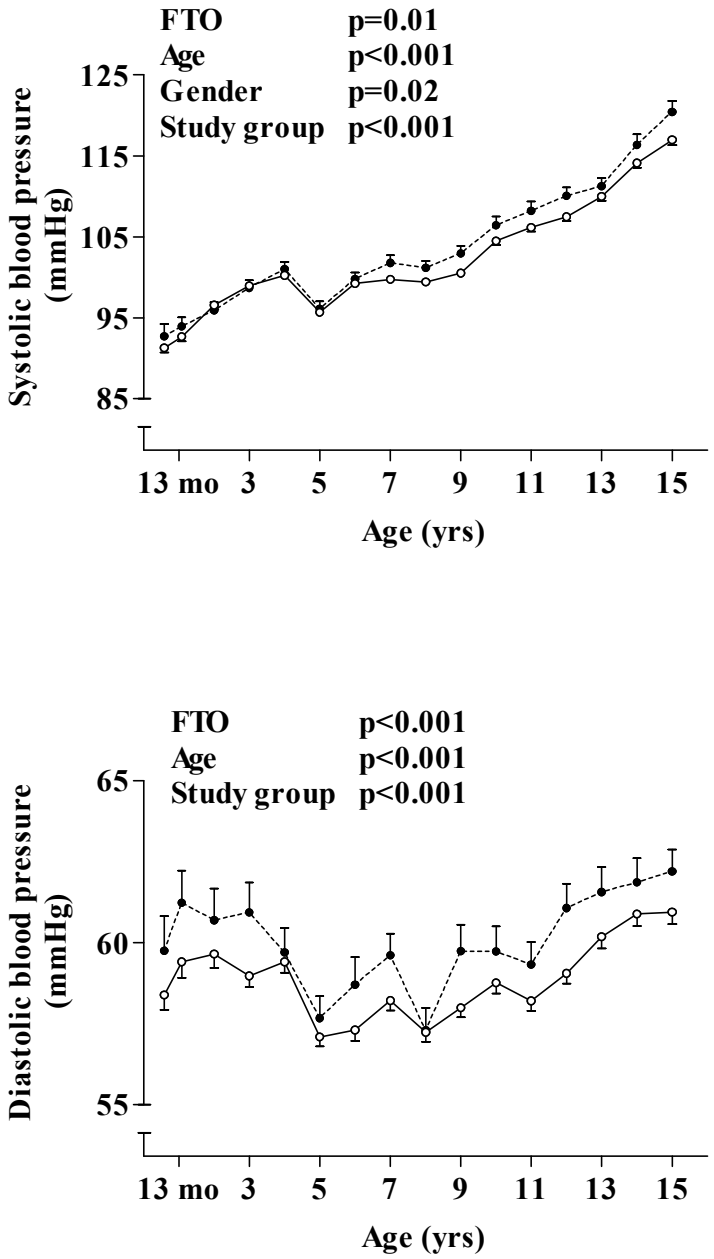

Figure 7. Mean (SEM) systolic and diastolic blood pressure of the children with AA genotype (black circle with broken line) and the children with TT or TA genotype (open circle with solid line) in rs9939609 of the FTO gene. The p-values are from the RM ANOVA model adjusted for BMI Z-score and height. FTO-by-gender and FTO-by-study group interactions were not significant. (Study III).

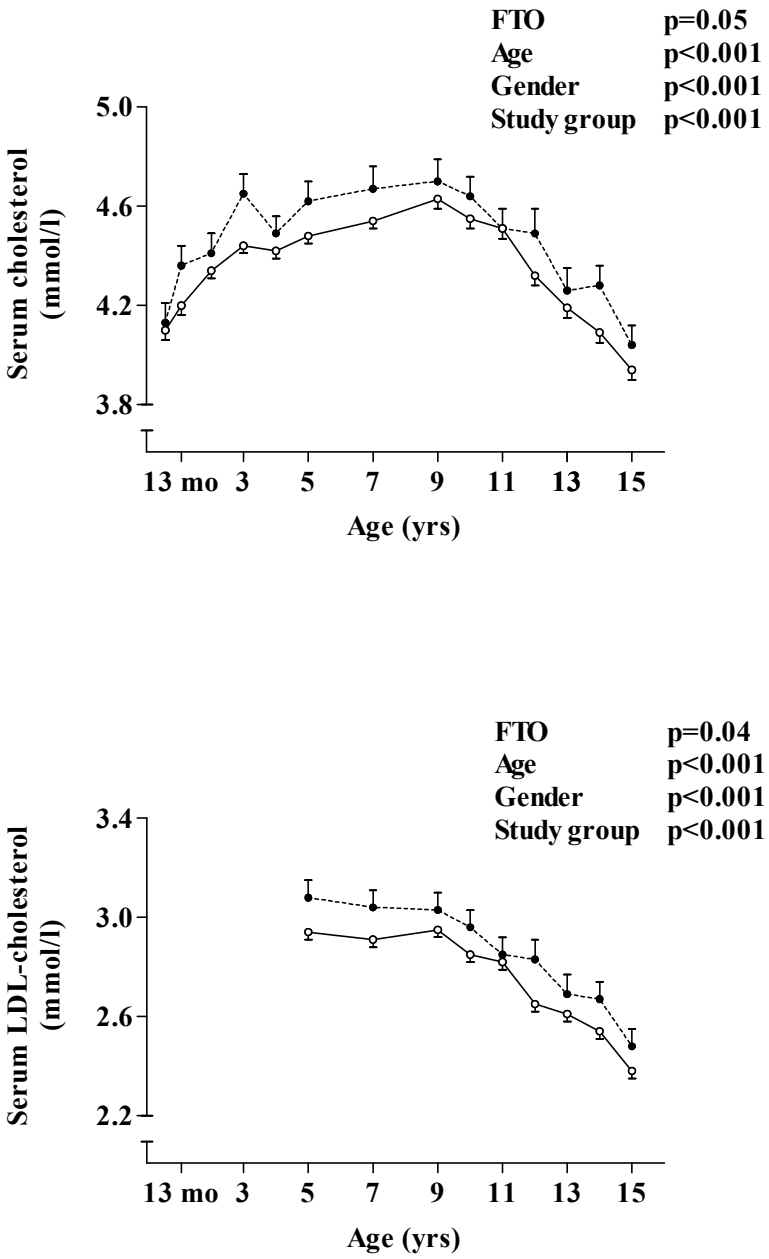

Figure 8. Mean (SEM) serum cholesterol and LDL-cholesterol concentrations of the children with AA genotype (black circle with broken line) and the children with TT or TA genotype (open circle with solid line) in rs9939609 of the FTO gene. The p-values are from the RM ANOVA model adjusted for BMI Z-score. FTO-by-gender and FTO-by-study group interactions were not significant. (Study III).

5.4. Effect of lifestyle intervention on clustering of overweight-related cardiometabolic risk factors (Study IV)

The effect of the dietary and lifestyle intervention provided to the participants in the STRIP trial on overweight-related cardiometabolic risk factors was studied in 5- to 15-year-old children and adolescents. The four risk factors included in the longitudinal analyses were: being in the highest quintile of 1) BMI, 2) triglycerides, and 3) systolic or diastolic blood pressure or in the lowest quintile of 4) HDL-cholesterol. During the study period, the proportion of children with none of these risk factors ranged from 38.1 % to 50.2 % in the intervention group and from 39.0 % to 46.0 % in the control group (Table 6). From the age of 7 years onwards, the proportion of children with 2 or more risk factors was constantly lower in the intervention group than in the control group (p=0.005).

At age 15 years, the participants in the intervention group had slightly lower diastolic blood pressure than the ones in the control group, but there was no difference between the groups with regard to BMI, serum triglycerides, HDL cholesterol, or the indexes of glucose metabolism (serum glucose, insulin, or HOMA-index) (Table 7). The study participants at 15 years of age were classified as having a cluster of overweight-related cardiometabolic risk factors if they belonged to the highest quintile in BMI and had at least 2 additional risk factors (being in the highest quintile in triglycerides, systolic or diastolic blood pressure or serum glucose or in the lowest quintile in HDL-cholesterol). The prevalence of the risk factor cluster was lower in the intervention group than in the control group (13.0 % vs. 17.5 % in girls and 10.8 % vs. 18.8 % in boys, p=0.046 for the main effect of the study goup) (Table 7).

Table 6. The proportion (%) of children having 0, 1, 2, 3, or 4 cardiometabolic risk factors at different age points in the intervention (I) and control (C) groups of the STRIP trial (Study IV).

Age in yrs	Number of children		Percentage of children with various numbers of the risk factors[1,2]									
			0 risk factors		1 risk factor		2 risk factors		3 risk factors		4 risk factors	
	I	C	I	C	I	C	I	C	I	C	I	C
5	**352**	**335**	38.1	42.4	38.9	39.7	18.5	14.3	4.0	2.1	0.6	1.5
7	**313**	**320**	47.3	39.4	32.3	37.5	14.7	16.6	4.8	5.6	1.0	0.9
9	**281**	**294**	50.2	41.5	28.1	32.6	17.4	19.4	3.2	5.4	1.1	1.0
11	**270**	**291**	45.6	46.0	31.1	27.5	15.9	16.8	6.7	7.2	0.7	2.4
13	**264**	**282**	49.2	42.5	29.2	32.3	14.8	15.2	5.3	6.4	1.5	3.5
15	**245**	**274**	47.8	39.0	34.7	34.7	11.8	18.6	4.9	6.6	0.8	1.1

[1]The risk factors included were: being in the highest quintile of the study population in 1) BMI, 2) triglycerides, 3) systolic or diastolic blood pressure, and in the lowest quintile in 4) HDL-cholesterol.

[2]From the age of 7 years onwards, the proportion of children with 2 or more risk factors was constantly lower in the intervention group than in the control group (p=0.005 for Cochran-Mantel-Haenszel's statistics for row mean score difference, stratified by age).

Table 7. Cardiometabolic risk factors [mean (SD)] among 15-year-old adolescents in the intervention and control groups of the STRIP trial (Study IV).

	Intervention group (N=249)		Control group (N=276)		P[1]
	Girls (N=116)	Boys (N=133)	Girls (N=137)	Boys (N=139)	
Body mass index (kg/m^2)	20.6 (2.5)	20.1 (3.2)	20.7 (3.6)	20.6 (3.5)	0.31
Serum triglycerides (mmol/L)	0.93 (0.41)	0.85 (0.49)	0.92 (0.54)	0.96 (0.48)	0.25
Serum HDL cholesterol (mmol/L)	1.23 (0.21)	1.08 (0.22)	1.21 (0.24)	1.08 (0.22)	0.43
Systolic blood pressure (mmHg)	114 (10)	121 (13)	115 (12)	122 (12)	0.25
Diastolic blood pressure (mmHg)	60 (6.0)	61 (7.1)	62 (6.9)	63 (7.5)	0.005
Serum glucose (mmol/L)	4.8 (0.3)	5.0 (0.4)	4.8 (0.3)	5.0 (0.4)	0.20
Serum insulin (mU/L)	8.7 (4.5)	8.2 (4.0)	8.3 (3.4)	9.2 (4.6)	0.21
HOMA-index	1.9 (1.1)	1.8 (1.0)	1.8 (0.8)	2.1 (1.1)	0.18
Percentage of adolescents having risk factor cluster[2]	13.0	10.8	17.5	18.8	0.046
Percentage of adolescents with completed pubertal development	39.7	24.8	32.1	17.3	0.21/0.13[3]

[1]P for the main effect of the study group; all gender by study group interactions were insignificant.
[2] The cluster was defined as follows: belonging to the highest quintile in BMI and having at least two other risk factors, e.g., being in the highest quintile in 1) triglycerides, 2) systolic or diastolic blood pressure or 3) serum glucose or in the lowest quintile in 4) HDL-cholesterol.
[3]Cochran-Mantel-Haenszel's statistics for row mean score difference in girls and boys, respectively.

The number of risk factors at age 5 years predicted the presence of risk factor cluster at age 15 years (Table 8). Of the children with no risk factors at age 5 years, 4.9 % had the risk factor cluster at age 15 years. For a 5-year-old child with one risk factor, the odds ratio (95% CI) of having the risk factor cluster at age 15 was 3.8 (1.8-8.1) ($p<0.001$). The odds ratio further increased to 5.5 and to 28.8 in those 5-year-old children with 2 and 3 or more risk factors, respectively. Of the analysed variables, BMI was the strongest predictor of the risk factor clustering. Of the 5-year-old children with a BMI in quintiles 1-4, 7.7 % had the cluster of risk factors at age 15 whereas 42.7 % of the children with BMI in the highest quintile at age 5 had the risk factor cluster at age 15 years ($p<0.001$). On the other hand, only 9.6 % of the children having any other risk factor than high BMI at age 5 had the cluster of risk factors at age 15 ($p<0.001$ for comparison with children in the highest BMI quintile). The study group did not modify the predictive value of the risk factor profile at age 5 years, because the study group-by-risk factor interaction was dropped out of the model by backward selection.

Table 8. The proportion of children (girls and boys combined) having the cluster of overweight-related cardiometabolic risk factors at the age of 15 among those who had 0, 1, 2, or 3-4 risk factors at the age of 5 years (Study IV).

No. of risk factors at age 5 years[1]	Proportion of children with the cluster at age 15 years[2]	Point estimate (95% CI)[3]	P[3]
0	4.9		
1	16.7	3.8 (1.8-8.1)	<0.001
2	22.4	5.5 (2.4-12.7)	<0.001
≥3	60.0	28.8 (8.6-96.9)	<0.001

[1]The risk factors included were: being in the highest quintile of the study population in 1) BMI, 2) triglycerides, 3) systolic or diastolic blood pressure, and in the lowest quintile in 4) HDL-cholesterol.
[2]The cluster was defined as follows: belonging to the highest quintile in BMI and having at least two other risk factors, i.e., being in the highest quintile in 1) triglycerides, 2) systolic or diastolic blood pressure or 3) serum glucose or in the lowest quintile in 4) HDL-cholesterol.
[3]Point estimate (95 % CI) and P for the comparison with those having no risk factors.

6. DISCUSSION

6.1. Subjects

In a long follow-up study like the present one, the representativeness of the initial study population and the loss-to-follow-up need to be carefully taken into account. In the STRIP trial, the representativeness of the initial cohort was evaluated by a questionnaire which was sent to a random sample of 442 families of those 775 families who refused to participate at the first phase (Kukkamäki et al. 1993). The reasons for not participating were most often related to attitudes (unwillingness to change the child's diet and lifestyle habits) and to difficulties in arranging the study visits. A random sample of 412 non-participating families were also contacted by phone and their socioeconomic status and health beliefs (attitudes towards food and dietary counselling) were asked (Boström et al. 1992). The participating and non-participating families were not different from each other in these respects. It may, thus, be assumed that the original STRIP study population was representative of the whole age cohort in Turku.

Loss-to-follow-up is inevitable in a study with very long duration like the STRIP trial. At the age of 15 years, 534 adolescents attended for follow-up (50.3 % of the original study population). The odds ratio of discontinuation was slightly higher for the participants in the intervention group than the control group (Study IV). However, after adjustment for other contributors (of which the number of visits with missing blood samples was the most important) the effect of the study group was no longer significant. Other common reasons for withdrawal from the STRIP study were family situation (e.g., divorce, lack of time, illness with frequent visits to physicians), moving to a remote area, experienced excess effort (e.g., in keeping food records), and school attendance (Anttila 2003).

6.2. Methods

In the STRIP trial, the primary goal of the intervention was to reduce serum total and LDL-cholesterol by reducing the intake of saturated fatty acids. Consequently, the physical activity intervention played only a minor role. The hobbies and everyday physical activity, e.g., walking or cycling to school, were discussed with the families and the children but no specific physical activity programs were offered. It is well established that physical activity has beneficial effects on weight management and cardiometabolic risk factors (Must and Tybor 2005, Raitakari et al. 1997, Borghouts and Keizer 2000). Physical activity may also protect against overweight by attenuating the effect of the FTO genotype on BMI (Rampersaud et al. 2008). These data strongly suggest that the overweight prevention programs should include physical activity interventions. The results on prevention of overweight and related cardiometabolic risk factors might have improved in our study if more attention had been paid to physical activity.

In the STRIP trial, the children in the control group were followed up along with the children in the intervention group. They met the counselling team twice yearly until age 7 years and once yearly thereafter. Diet and physical activity matters were discussed only superficially. However, the children in the control group and their parents were weighed at every visit and they got information on their blood pressure and serum lipid values which might have affected their behaviours. It may, thus, be assumed that the close follow-up of the control group ultimately diluted the intervention effect.

BMI was used as an estimate of adiposity in studies III and IV. It is well known that BMI has its limitations because it does not distinguish fat mass from fat-free mass (Prentice and Jebb 2001). Increase in fat free mass as well as in fat mass contribute to the increase in BMI in overweight and obese children but the increase in fat mass is substantially greater than that in the fat free mass (Wells et al. 2006). A high BMI in childhood predicts an adverse CVD risk profile and may be considered as a reliable estimate of adiposity (Freedman et al. 2007, Baker et al. 2007). However, assessment of waist circumference or skinfolds thickness might be equally important, especially in overweight prevention studies including physical activity intervention, since increased physical activity may lead to no change or even to increase in BMI due to increase in fat free mass even though fat mass and consequently also waist circumference decrease. Measurement of the waist circumference might also help to differentiate the children and adolescents with high BMI into those with higher amount of visceral fat and consequently an increased risk of comorbidities and to those with lesser amount of visceral fat (Janssen et al. 2005). However, as long as we do not have age- and gender-specific cut-off points for the waist circumference, the clinical utility of the measurement is low. In the present study, waist circumference was used in study III. The results were essentially similar to those applying BMI as a measure of adiposity.

Dietary intake data were obtained from the food records, and physical activity data were obtained from self-administered questionnaires in the present study. However, these self-reported measures of both dietary and physical activity variables are imprecise (Livingstone et al. 2004), and especially in the context of nutritional and physical activity interventions, these measures are vulnerable to bias through under-reporting and over-reporting (Byers 2003). Therefore, studies with more objective measures of energy homeostasis are needed, e.g., to study the role of the FTO genotype in regulating energy expenditure.

Several attempts have been made to define insulin resistance or metabolic syndrome in children but the agreement between these definitions is poor (Goodman et al. 2004, Golley et al. 2006). In this study, the population-specific cut-off points were used to define the overweight-related cardiometabolic risk factors. Data on serum glucose concentration were available of the participants only at age 15 years, and thus serum glucose could be included in the definition only in that age. Furthermore, the dichotomous definition of the risk factors is problematic because the risk associated with these factors is usually of continuous nature.

6.3. Role of leptin in childhood overweight

Leptin plays a key role in the regulation of energy homeostasis both in adults and children. This is clearly seen in the individuals who have congenital leptin deficiency, and who consequently develop severe obesity at an early age (Farooqi et al. 2002). Administration of recombinant leptin to these individuals results in normalization of hyperphagia and in weight reduction. In contrast to these rare cases of extreme obesity, most overweight and obese adults and children have high serum leptin concentrations (Maffei et al. 1995, Considine et al. 1996, Hassink et al. 1996, Argente et al. 1997), which suggests that these individuals are insensitive to leptin.

Serum leptin concentrations change during growth and a gender difference becomes evident with advancing puberty (Argente et al. 1997, Horlick et al. 2000). By the end of puberty, girls have higher serum leptin concentrations than boys mostly reflecting the difference in the amount of body fat. Both in prepubertal and pubertal children, the serum leptin concentrations correlate strongly with BMI or percentage of body fat (Salbe et al. 1997, Hassink et al. 1996, Argente et al. 1997, Arslanian et al. 1998). In obese children, a high serum leptin concentration does not reduce appetite but seems to predict weight gain (Lahlou et al. 1997, Savoye et al. 2002). In normal-weight children, as the children in the present study, the serum leptin concentration does not predict the future weight gain but reflects the amount of adipose tissue.

6.4. Lifestyle interventions in the prevention of overweight and obesity

Primary prevention of overweight and obesity should be implemented throughout the environment the children live in. Primary health care, schools, and the community with its administrators should be incorporated into prevention programs which must support each other.

At the individual level, a healthy lifestyle may be promoted during each clinical encounter. In Finland, health care providers regularly meet all families with infants and children at well-baby clinics. In addition to growth and development follow-up, health education is delivered to both parents and children. One aim of the STRIP trial is to develop tools which may be applied in the well-baby clinic and school health care settings to provide all families with basic information on a healthy diet and on physical activity patterns and to promote lifestyle changes. Previous data from the STRIP trial suggest that the tools developed are effective in promoting lifestyle changes and in reducing the levels of CVD risk factors, such as serum lipid values (Talvia et al. 2004, Niinikoski et al. 2007). However, the results of the present study indicate that individualised, biannual counselling is not intense enough to prevent the development of overweight. One explanation for this lack of effect might be the fact that during the first years of the trial, the main aim of the intervention was to reduce serum LDL-cholesterol by reducing the intake of saturated fat. No special emphasis was put on total energy intake. Now that we acknowledge the importance of early weight gain for the future development of overweight it seems apparent that the energy balance should receive

more attention during the first years of life (Ong and Loos 2006). Another explanation for the lack of effect for overweight prevention might be the fact that no physical activity programs were offered to the children of the intervention group. It has been previously shown that, in fact, there was no difference in the level of physical activity in the 13-year-old participants of the intervention and control groups (Pahkala et al. 2007).

Physical activity may be more effectively promoted in the school-setting than in the clinical setting. During the first school-years, physical activity of children may be increased with environmental changes that provide more opportunities for physical activity during the school breaks (van Sluijs et al. 2007). In adolescents, a multicomponent approach including classroom, family, physical education, and environmental components seems to be the most effective way to increase physical activity (van Sluijs et al. 2007). In addition to promoting physical activity, the school-setting may be used as a platform to promote other aspects of a healthy lifestyle, e.g., sedentary behaviour like television viewing may be reduced by classroom lessons (Robinson 1999). Furthermore, modification of school meals and promotion of drinking water instead of soft drinks have been shown to be effective in overweight prevention (Marcus et al. 2009, Muckelbauer et al. 2009). Because the results from studies with long follow-ups suggest that the impact of these preventive measures is retained only for as long as they are maintained, it seems obvious that the changes made in school curriculum or environment should be of a permanent nature (Gutin et al. 2008, Jaime and Lock 2009).

Lifestyle interventions both on the individual level and in school target the entire population. An additional way to prevent overweight should be to target the individuals who are at increased risk of becoming overweight. Previous studies and the present study show that the parental weight status is one of the strongest predictors of childhood overweight (Danielzik et al. 2004, Reilly et al. 2005, Kleiser et al. 2009). This finding has two potential implications. First, the children of overweight parents should be considered to be at an increased risk of becoming overweight, and thus they should be followed carefully. Especially if other risk factors are present, intensive preventive measures should be initiated. Another implication of parental overweight is the role of the parents in weight management. The parents provide both the food and the possibilities for physical activity for their children, not to mention their importance as a role model. It is noteworthy that the weight status of the father was even a stronger predictor of overweight than the weight status of the mother in our study. In previous studies, the maternal weight status has been a stronger predictor (Sorensen et al. 1992, Danielzik et al. 2002). Our result, thus, further strengthens the previous guidelines on involving both parents in weight management programs (August et al. 2008). Other well established risk factors for childhood overweight include low and high birth weight, rapid weight gain in infancy, early adiposity rebound, low SES, high energy and fat intake, physical inactivity, and low physical activity (Danielzik et al. 2004, Oken and Gillman 2003, Ong and Loos 2006, Rolland-Cachera et al. 2006, Berkey et al. 2000, Klesges et al. 1995, Must and Tybor 2005). By multivariate analysis of the present study, the most important predictors of overweight during adolescence were rapid weight gain during the first two years, early adiposity rebound, and paternal weight status. These findings further highlight the need for early prevention starting in infancy.

6.5. FTO genotype and weight development

Common overweight is of polygenic origin. FTO was the first obesity-susceptibility gene identified by genome-wide association and opened a new area in the field of obesity genetics. The effect of the FTO genotype on BMI and risk of obesity is modest but consistent, at least in Caucasian adults and children (Frayling et al. 2007, Peeters et al. 2007, Price et al. 2008, Hunt et al. 2008, González-Sánchez et al. 2009, Hinney et al. 2007, Jacobsson et al. 2008). The results of the present study indicate that this association starts to develop after the adiposity rebound. The reason for this is not known but one explanation might be that the expression of the FTO gene changes during the adiposity rebound. The results further indicate that the effect of the FTO genotype on BMI and risk of overweight is so strong that the intervention given in the STRIP trial is not intense enough to abolish it. This suggests that more intensive overweight prevention programs are needed, especially for individuals with genetic susceptibility to overweight.

The function of the FTO gene is unknown. A peripheral role was suggested in a study in which the carriers of the risk allele had reduced lipolytic activity (Wahlen et al. 2007). On the other hand, recent studies suggest that the FTO gene has a role in central regulation of appetite: the high risk variant associates with reduced satiety responsiveness and increased energy intake from highly palatable foods (Wardle et al. 2008b, Wardle et al. 2009). In the present study, the FTO genotype did not associate with the daily energy intake obtained from 4-day food records. However, it is possible that keeping food record affects the diet and especially the consumption of highly palatable foods (Livingstone et al. 2004).

The FTO genotype also associates with various obesity-related traits, e.g., insulin sensitivity, fasting insulin, glucose, triglycerides, and HDL cholesterol (Andreasen et al. 2008, Freathy et al. 2008). In the present study, the associations between the FTO genotype and systolic and diastolic blood pressure as well as with serum total and LDL-cholesterol remained significant after adjustment for the BMI Z-score, which suggests that the effect of the FTO genotype is mediated not only through weight but also through other metabolic pathways. This result is contradictory to the findings of previous studies and needs to be confirmed (Andreasen et al. 2008, Freathy et al. 2008). If it proves to be correct, determining an individual's FTO genotype might help to identify those who are at risk of overweight and to identify those who are at risk of developing the cardiometabolic comorbidities of overweight.

The FTO variants explain only 1-1.3 % of the variance of the BMI (Frayling et al. 2007, Scuteri et a. 2007). After the discovery of the FTO variants, genome-wide association studies revealed a locus near the melanocortin 4 receptor gene that associates with risk of obesity in Caucasian adults and children (Loos et al. 2008, Grant et al. 2009). A recent study identified six additional loci associated with BMI (Willer et al. 2009). The loci uncovered so far explain only a fraction of the common obesity (Willer et al. 2009). Thus, there are many other overweight-susceptibility loci to be uncovered.

6.6. Prevention of overweight-related cardiometabolic risk in children

The ultimate objective of weight management interventions should be the prevention of overweight-related comorbidities rather than the prevention of overweight or obesity as such. The data from the previous studies and this study show that overweight is the most important correlate of cardiometabolic risk (Weiss et al. 2004, Goodman et al. 2005). Thus, it is obvious that early prevention of overweight should be considered as the most effective way to reduce cardiometabolic risk. On the other hand, overweight children who manage to reduce weight and change body composition as a result of lifestyle changes show a remarkable improvement in their cardiometabolic risk factors (Nemet at al. 2005).

Cardiometabolic risk may also be modified without changes in overweight status. A better overall quality of diet reduces the risk of clustering of overweight-related cardiometabolic risk factors regardless of change in weight (Pan and Pratt 2008). In the STRIP trial, it was previously reported that the counselling given to half of the study children led to favourable changes in diet, e.g., the intakes of total fat and saturated fat were lower in the intervention group than in the control group (Talvia et al. 2004, Niinikoski et al. 2007). These favourable changes in diet led to favourable changes in serum total cholesterol, LDL-cholesterol, and triglyceride concentrations (Niinikoski et al. 2007). The results of the present study indicate that implementation of healthy dietary patterns is further associated with a reduced number and clustering of overweight-related cardiometabolic risk factors despite an unchanged prevalence of overweight. These results indicate that not only the quantity of food ingested but also the quality of the diet should be the target of intervention programs that aim at reducing the comorbidities of overweight.

Physical activity reduces the clustering of overweight-related cardiometabolic risk factors and improves vascular endothelial function independent of change in body weight (Ekelund et al. 2009, Kelly et al. 2004). In the STRIP trial, no physical activity programs were offered to the children and adolescents in the intervention group. Consequently, no difference was observed in the level of leisure-time physical activity of the 13-year-old adolescents in the intervention and control groups (Pahkala et al. 2007). More intensive physical activity counselling or offering of exercise programs might have resulted in more pronounced effects for the prevention of cardiometabolic risk.

Overweight-related cardiometabolic risk has been defined in several ways and is most often referred to as the metabolic syndrome. However, during the past years, strong criticism has been presented against the concept of the metabolic syndrome and its clinical utility (Reilly and Rader 2003, Kahn et al. 2005, Reaven 2006, Brambilla et al. 2007). The role of the metabolic syndrome in predicting future risk of CVD may be questioned, as the risk associated with a diagnosis of the metabolic syndrome does not seem to add to the sum of the individual risk factors (Reaven 2006). Furthermore, other CVD risk factors convey a risk that is as high or even higher than the risk conveyed by the metabolic syndrome. The importance of a diagnosis of metabolic syndrome may

also be questioned, because, with the exception of weight loss, there is no uniform treatment for the syndrome. However, the concept of the metabolic syndrome may be useful in helping to understand the complex nature of cardiometabolic risk associated with overweight and to study the underlying mechanism.

6.7. Clinical implications

In Finnish well-baby clinics and school health care, all children are followed up very closely. The results of the present study show that dietary counselling given to the families, and later to the children themselves, has beneficial effects on cardiometabolic risk factors, and should be provided to all families. However, the results might be better if more intensive physical activity counselling was added. Therefore, it appears important that the health care providers in schools also advocate increased physical activity during school days.

The growth charts are carefully reviewed during every clinical encounter, and this enables the health care providers to recognise the children who are at increased risk of becoming overweight. The results of the present study further strengthen previous knowledge that children with rapid weight gain in infancy and/or with early adiposity rebound should be recognised and referred for more intensive lifestyle intervention, e.g., to a nutritionist.

6.8. Future research needs

BMI is widely used as a surrogate measure of adiposity. However, it is well known that insulin resistance and associated cardiometabolic risk factors correlate more strongly with visceral fat as reflected, for example, in the waist circumference. Therefore, there is a need for national and international cut-off points for waist circumference in children and adolescents to facilitate both clinical and research use.

Now that the importance of rapid weight gain in early childhood for the future risk of overweight and obesity is recognised, there is a need for intervention studies aiming at healthy diet based on nutrition recommendations and at physically active lifestyle starting from the early childhood. The intervention should include promotion of breast feeding as well as practical guidance on healthy choices in important turning points, like introduction of solid foods. Parents should be counselled to pay attention to both the quality and quantity of their child's diet after weaning. These studies should also include weight management programs for the parents. In addition to health outcomes, the cost-effectiveness of such a program should be evaluated.

7. CONCLUSIONS

1. Serum leptin concentrations measured in normal-weight 2-year-old children do not predict future development of overweight but rather reflect the current amount of adipose tissue.

2. Rapid increase in weight between birth and age of 2 years, early adiposity rebound, and parental weight status are strong predictors of future weight gain of prepubertal and pubertal children. Thus these markers should be carefully monitored in the Finnish well-baby clinics.

3. Individualised, repeated dietary counselling since infancy with the primary aim at reducing serum LDL-cholesterol by reducing saturated fat intake, is not intensive enough to prevent overweight to any significant degree.

4. The FTO genotype is a strong predictor of overweight development, and the effect of the FTO genotype on BMI and risk of overweight starts to develop after the adiposity rebound. The effect of the FTO genotype may not be abolished with individualised dietary counselling which is not primarily aimed at preventing overweight. The FTO genotype associates, independently of BMI, with systolic and diastolic blood pressure as well as with serum total- and LDL-cholesterol.

5. The individualised, repeated dietary counselling that leads to favourable changes in the quality of diet may reduce the cardiometabolic risk associated with overweight.

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"Regrets, I've had a few; But then again, too few to mention.
I did what I had to do; And saw it through without exemption.

I planned each charted course; Each careful step along the byway,
And more, much more than this, I did it my way."

-Paul Anka-

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