DISSERTATIONS IN
HEALTH
SCIENCES

Anne Jääskeläinen

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The Role of Early-Life Risk Factors, Eating Patterns and Common Genetic Variants

Publications of the University of Eastern Finland
Dissertations in Health Sciences

UNIVERSITY OF
EASTERN FINLAND

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To be presented by permission of the Faculty of Health Sciences, University of Eastern Finland
for public examination in Auditorium L1, Canthia building, Kuopio,
on Saturday, September 28th 2013, at 12 noon

Publications of the University of Eastern Finland
Dissertations in Health Sciences
Number 189

Department of Clinical Nutrition, Institute of Public Health and Clinical Nutrition,
School of Medicine, Faculty of Health Sciences, University of Eastern Finland, Kuopio
and
Institute of Health Sciences, Faculty of Medicine, University of Oulu, Oulu

Kuopio
2013

Kopijyvä Oy
Kuopio, 2013

Distributor:
University of Eastern Finland
Kuopio Campus Library
P.O. Box 1627
FI-70211 Kuopio, Finland
http://www.uef.fi/kirjasto

ISBN (print): 978-952-61-1222-0
ISBN (pdf): 978-952-61-1223-7
ISSN (print): 1798-5706
ISSN (pdf): 1798-5714
ISSN-L: 1798-5706

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Jääskeläinen, Anne
Epidemiologic studies on overweight and obesity in adolescents: the role of early-life risk factors, eating patterns and common genetic variants
University of Eastern Finland, Faculty of Health Sciences
Publications of the University of Eastern Finland. Dissertations in Health Sciences 189. 2013. 81 p.

ISBN (print): 978-952-61-1222-0
ISBN (pdf): 978-952-61-1223-7
ISSN (print): 1798-5706
ISSN (pdf): 1798-5714
ISSN-L: 1798-5706

ABSTRACT

In recent decades, the prevalence of overweight and obesity in children and adolescents has increased worldwide, now reaching pandemic proportions. Identification of early risk factors is essential for the prevention of excessive weight gain in childhood. Weight development involves an intricate interplay between environmental and genetic factors; however, lifestyle choices, such as dietary habits, may significantly alter the risk for obesity.

The aims of the present study were 1) to identify early-life risk factors associated with adolescent overweight and obesity, 2) to investigate the association between meal frequencies and overweight, obesity and the features of the metabolic syndrome in adolescents and 3) to examine whether meal frequency could modulate the effect of common genetic variants on body mass index (BMI) in adolescence. The study population was derived from the prospective, population-based Northern Finland Birth Cohort 1986. Data collection began prenatally with the latest follow-up being conducted in 2001–2002 when the participants were 16 years old. The genetic data comprised eight single nucleotide polymorphisms at or near eight obesity-susceptibility loci including the variants *FTO* rs1421085 and *MC4R* rs17782313.

Paternal overweight and obesity before pregnancy were nearly as important as maternal pregravid overweight and obesity as risk factors for adolescent overweight in both genders. Regarding parental long-term BMI status, the risk for overweight was notably high in those boys and girls both of whose parents had BMI ≥25 from pre-pregnancy to 16-year follow-up.

After adjusting for potential confounders such as maternal education level and smoking in early pregnancy, it was found that the highest fourth of maternal weight gain (>7.0 kg) during the first 20 weeks of gestation was associated with offspring overweight/obesity and abdominal obesity but nonetheless maternal pregravid obesity was a relatively more important determinant of both outcomes.

Three different meal patterns were examined at age 16; a regular five-meal pattern was associated with reduced risks of overweight/obesity in both genders and abdominal obesity in boys after taking into account several early-life and later childhood factors. Moreover, the regular five-meal pattern attenuated the increasing effect of the common genetic variants studied on BMI.

These findings emphasise the importance of taking early on a whole-family approach to childhood obesity prevention. Furthermore, it is important to be aware that the effects of predisposing genotypes can be modified by lifestyle habits such as regular meal frequency.

National Library of Medicine Classification: WD 210, QU 500, WS 115, WS 460
Medical Subject Headings: Overweight/epidemiology; Obesity/epidemiology; Meals; Diet; Genetic Variation; Polymorphism, Single Nucleotide; Metabolic Syndrome X; Body Mass Index; Adolescent; Cohort Studies, Finland

Jääskeläinen, Anne
Väestötutkimuksia nuorten ylipainosta ja lihavuudesta: varhaisten vaaratekijöiden, ateriarytmin ja yleisten geenimuunnosten merkitys
Itä-Suomen yliopisto, terveystieteiden tiedekunta
Publications of the University of Eastern Finland. Dissertations in Health Sciences 189. 2013. 81 s.

ISBN (print): 978-952-61-1222-0
ISBN (pdf): 978-952-61-1223-7
ISSN (print): 1798-5706
ISSN (pdf): 1798-5714
ISSN-L: 1798-5706

TIIVISTELMÄ

Viime vuosikymmenten aikana lasten ja nuorten ylipaino ja lihavuus ovat yleistyneet maailmanlaajuisesti epidemian lailla. Lapsuusiän liiallisen painonnousun ennaltaehkäisy edellyttää varhaisten vaaratekijöiden tunnistamista. Painonkehitys on monitahoisen ulkoisten ja perinnöllisten tekijöiden yhteisvaikutuksen tulos. Elintavoilla, kuten ruokatottumuksilla, voidaan kuitenkin merkittävästi vaikuttaa lihavuuden vaaraan.

Tämän väitöskirjatyön tarkoituksena oli 1) tunnistaa varhaisia nuoruusiän ylipainon ja lihavuuden vaaratekijöitä, 2) tutkia ateriarytmien yhteyttä ylipainoon, lihavuuteen ja metabolisen oireyhtymän piirteisiin nuorilla ja 3) selvittää, voiko ateriarytmi muokata perimän vaikutusta nuoren kehon painoindeksiin. Tulokset perustuvat Pohjois-Suomen vuoden 1986 syntymäkohortin tutkimusaineistoon, jota on kerätty etenevästi raskausajalta lähtien. Viimeisin tiedonkeruu toteutettiin 2001–2002, kun tutkittavat olivat 16-vuotiaita. Genotyyppiaineistoon kuului kahdeksan yhden emäksen sekvenssimuunnosta kahdeksassa lapsuusiän painoindeksiin liittyvässä geenilokuksessa, mukaan lukien *FTO*- ja *MC4R*-geenien variantit.

Isän ylipaino ja lihavuus ennen raskausaikaa olivat sekä tytöillä että pojilla ylipainon ja lihavuuden vaaratekijöinä lähes samanveroiset kuin äidin raskautta edeltävä ylipaino ja lihavuus. Vanhempien painon pitkittäistarkastelu osoitti, että jälkeläisen ylipainon ja lihavuuden vaara oli huomattavan suuri, kun molemmat vanhemmat olivat ylipainoisia tai lihavia sekä ennen raskautta että 16-vuotisseurannassa.

Äidin painonnousun ylin neljännes (>7.0 kg) 20 ensimmäisellä raskausviikolla oli itsenäisesti yhteydessä nuoren ylipainon ja lihavuuden sekä vyötärölihavuuden suurentuneeseen vaaraan. Äidin lihavuus ennen raskautta oli kuitenkin painonnousua vahvemmin yhteydessä molempiin selitettäviin muuttujiin.

Kolmen ateriarytmin vertailu osoitti, että säännöllinen viiden aterian rytmi oli yhteydessä pienentyneeseen ylipainon ja lihavuuden vaaraan sekä pojilla että tytöillä ja vyötärölihavuuden vaaraan pojilla. Tuloksissa huomioitiin useita sekä varhaisia että myöhempiä lapsuusiän tekijöitä. Säännöllinen viiden aterian rytmi myös vähensi yhden emäksen sekvenssimuunnosten suurentavaa vaikutusta kehon painoindeksiin.

Tulokset korostavat koko perheen varhaisen ohjauksen tärkeyttä lasten lihavuuden ehkäisyssä sekä vahvistavat käsitystä, että altistavien perintötekijöiden vaikutuksia voidaan elintavoilla, esimerkiksi säännöllisellä ateriarytmillä, vähentää.

Luokitus: WD 210, QU 500, WS 115, WS 460
Yleinen suomalainen asiasanasto: ylipaino; lihavuus; epidemiologia; riskitekijät; ateriat; ruokavaliot; geneettiset tekijät; metabolinen oireyhtymä; painoindeksi; nuoret; kohorttitutkimus; Suomi

Acknowledgements

The present work was carried out in the Department of Clinical Nutrition, University of Eastern Finland in 2009-2012.

I owe my deepest gratitude to the supervisors of this thesis, Adjunct professor Marjukka Kolehmainen, Adjunct professor Jaana Laitinen and Associate professor Ursula Schwab, for their advice, encouragement and invaluable scientific contributions at all stages of my postgraduate studies.

I sincerely thank Professor Hannu Mykkänen, Professor Matti Uusitupa, Professor Jussi Pihlajamäki and Professor Emerita Helena Gylling for skillfully steering the ship of the Department of Clinical Nutrition over the years, teaching and guiding under- and postgraduate students, including myself, and allowing me to use department facilities during my PhD project.

I have been priviledged to study the Northern Finland Birth Cohort 1986 and I am most indebted to all the people behind this unique cohort. The late Professor Paula Rantakallio, whose determination led to the launching of the Northern Finland Birth Cohort studies in the 1960s, is remembered with admiration. Professor Marjo-Riitta Järvelin and Professor Anna-Liisa Hartikainen are acknowledged as the initiatiors and developers of the NFBC1986. I owe a great debt of gratitude to Marika Kaakinen, PhD, for her work in data management and delivery and prompt assistance in numerous practical issues throughout the study. I wish to recognise Ms Tuula Ylitalo for her indispensable contribution to the management of the cohort study project.

I thank the pre-examiners of the thesis, Professor Inga Thorsdottir and Adjunct professor Eero Kajantie, for their insightful comments and suggestions that helped me markedly improve the content. I thank Ewen MacDonald, PhD, for the careful language revision of the thesis.

I warmly thank all the co-authors for their excellent collaboration: Outi Nuutinen, PhD; Jatta Pirkola, MD; Anneli Pouta, MD, PhD; Johanna Pussinen, MSc; Professor Markku Savolainen; Ulla Sovio, PhD, and Marja Vääräsmäki, MD, PhD. In addition to the co-authorship, Professor Philippe Froguel and Stéphane Cauchi, PhD, are gratefully acknowledged for the management of genotyping and genetic data handling in the NFBC1986. I am very thankful to Marja-Leena Hannila, MSc, for sharing her expertise in statistical analysis.

I extend my special thanks to my colleagues and co-workers in the Department of Clinical Nutrition for pleasant company and help in countless situations. I also wish to thank the personnel at the Department of Epidemiology and Biostatistics, Imperial College London for welcoming me on my research visit and leaving me with fond memories.

My heartfelt thanks go to my parents for their continuous support. The same gratitude goes to my sister and her family. My dear friends near and far deserve equal appreciation for enriching my life. Above all, words fail to express my gratitude to Benjamin for showing immense patience throughout the years and providing priceless help with the graphs.

In appreciation of their financial support for this work, I would like to thank the Academy of Finland (Responding to Public Health Challenges Research Programme, SALVE) and the Finnish Graduate School on Applied Bioscience.

Kuopio, August 2013

Anne Jääskeläinen

List of the original publications

This dissertation is based on the following original publications which will be referred to by their Roman numerals (I-IV) in the text:

I Jääskeläinen A, Pussinen J, Nuutinen O, Schwab U, Pirkola J, Kolehmainen M, Järvelin M-R and Laitinen J. Intergenerational transmission of overweight among Finnish adolescents and their parents: a 16-year follow-up study. *Int J Obes 35: 1289-1294, 2011.*

II Laitinen J, Jääskeläinen A, Hartikainen A-L, Sovio U, Vääräsmäki M, Pouta A, Kaakinen M and Järvelin M-R. Maternal weight gain during the first half of pregnancy and offspring obesity at 16 years – a prospective cohort study. *BJOG 119: 716-723, 2012.*

III Jääskeläinen A, Schwab U, Kolehmainen M, Pirkola J, Järvelin M-R and Laitinen J. Associations of meal frequency and breakfast with obesity and metabolic syndrome traits in adolescents of Northern Finland Birth Cohort 1986. *Nutr Metab Cardiovasc Dis doi: 10.1016/j.numecd.2012.07.006.* In press.

IV Jääskeläinen A, Schwab U, Kolehmainen M, Kaakinen M, Savolainen M, Froguel P, Cauchi S, Järvelin M-R and Laitinen J. Meal frequencies modify the effect of common genetic variants on body mass index in adolescents of the Northern Finland Birth Cohort 1986. *PLOS ONE 8: e73802, 2013.*

The publications were adapted with the permission of the copyright owners. In addition, some previously unpublished data are presented.

Contents

Abbreviations

ANOVA	Analysis of variance
BMI	Body mass index
CI	Confidence interval
DBP	Diastolic blood pressure
DNA	Deoxyribonucleic acid
FPG	Fasting plasma glucose
FTO	Fat mass- and obesity-associated
GDM	Gestational diabetes mellitus
GRS	Genetic risk score
GWAS	Genome-wide association study
GWG	Gestational weight gain
HDL	High-density lipoprotein
HWE	Hardy-Weinberg equilibrium
IDF	International Diabetes Federation
IOTF	Intenational Obesity Task Force
MAF	Minor allele frequency
MC4R	Melanocortin 4 receptor
MetS	Metabolic syndrome
MWC	Maternity welfare clinic
NFBC1986	Northern Finland Birth Cohort 1986
NPC1	Niemann-Pick C1
OGTT	Oral glucose tolerance test
OR	Odds ratio
RTEC	Ready-to-eat cereal
SBP	Systolic blood pressure
SD	Standard deviation
SES	Socioeconomic status
SNP	Single nucleotide polymorphism
SSB	Sugar-sweetened beverages
TG	Triacylglycerol concentration
USA	The United States of America
WC	Waist circumference
WHO	World Health Organization

1 Introduction

An epidemic of obesity has affected all age groups in both the developed and developing worlds in recent years. As with adult-onset obesity, the possible co-morbidities and complications of childhood obesity are many and diverse, including chronic inflammation, impaired glucose metabolism, psychiatric ill-health, asthma, orthopaedic abnormalities and liver disease (Reilly and Wilson 2006; Daniels 2009). From a public health perspective, a major concern is the impact of obesity on cardiovascular and metabolic health. While complications of obesity occur more frequently in adults, the metabolic consequences of obesity are increasingly evident among young individuals as the incidence of childhood obesity continues to increase (Dietz 1998; Weiss and Kaufman 2008).

There is a significant tracking of childhood overweight and obesity into adulthood (Singh et al. 2008). In addition to the strong tendency to persist, overweight and obesity in youth *per se* may contribute to the risk of later morbidity and premature mortality, i.e. adverse long-term effects have been seen even after adjusting for adult body mass index (Al Mamun et al. 2009). It has been speculated that the current trends in obesity could negatively affect life expectancy of today's youth (Olshansky et al. 2005). Inevitably, childhood obesity is a major threat to national economies due to the growth in obesity-related health care expenditures (Wang and Dietz 2002; Kirk et al. 2012).

Obesity is a strong, but fortunately modifiable risk factor for type 2 diabetes and cardiovascular disease. In adults, it has been shown convincingly that changes in lifestyle can prevent or delay the progression of overweight, insulin resistance and related cardiometabolic disease (Tuomilehto et al. 2001). Even children can benefit from lifestyle modifications. For example, there is evidence suggesting that the number of daily meals and breakfast consumption are inversely related to the risk of obesity in children and adolescents (Koletzko and Toschke 2010; Patro and Szajewska 2010; Szajewska and Ruszczynski 2010).

If one wishes to combat the problem, then it is important to identify early-life predictors of overweight and obesity. On the other hand, it is crucial to elucidate factors that could protect from excessive weight gain. This study focuses first on parental body mass index and maternal gestational weight gain with a view to assessing their importance as early-life risk factors of adolescent overweight and obesity. The second half of the study deals with meal frequencies; their association with obesity and metabolic syndrome (MetS) traits and the potential modifying effect on genetic predisposition to increased body mass index in adolescence.

2 Review of the literature

2.1 OVERWEIGHT AND OBESITY IN CHILDHOOD AND ADOLESCENCE

Several approaches can be used to determine obesity in children and adolescents. Although these approaches yield differing estimates of the extent of the phenomenon they have unequivocally demonstrated a dramatic worldwide increase in the proportion of children and adolesecents affected. The next two chapters provide an overview of the methods available for measuring and defining childhood obesity and estimates of its prevalence.

2.1.1 Definitions

Obesity, also called adiposity, is a state of excess body fat. Body mass index (BMI) expresses the relationship between weight and height (weight in kilograms divided by the square of height in meters, kg/m^2) and is a widely accepted surrogate measure of general adiposity in adults and 2- to 19-year-old children and adolescents (Krebs et al. 2007; Okorodudu et al. 2010). BMI has become the preferred measure for evaluating obesity since it has several advantages: it can be determined easily, it correlates strongly with body fat percentage but only weakly with height and it identifies the fattest individuals correctly, with acceptable accuracy at the upper end of the distribution (Krebs et al. 2007).

On the basis of adult BMI, the World Health Organization (WHO) has defined overweight as BMI greater than or equal to 25 (but less than 30) and obesity as BMI greater than or equal to 30 (World Health Organization 2000). These cutoff points are also related to health risks. Since children's body composition varies according to age and gender, a child's weight status is determined using an age- and sex-specific percentile for BMI rather than the BMI categories used for adults. In 2000, Cole and co-workers presented cut-off points i.e. the International Obesity Task Force (IOTF) criteria for BMI in childhood that were based on international data and linked to the adult BMI cut-off points of 25 and 30 (Cole et al. 2000). However, due to differences in body composition between races and ethnicities, the usage of child growth references based on multiethnic data at national level has been criticised (Wang 2004). In 2011, Saari and co-workers introduced contemporary weight references (weight-for-length/height and body mass index-for-age) for Finnish children and adolescents aged 0 to 20 years (Saari et al. 2011). These new growth references were constructed using a large Finnish population-based sample. Similarly to Cole et al. (2000), Saari et al. (2011) formulated cut-off curves for defining BMI-for-age cut-off points for childhood thinness, overweight and obesity based on adult BMI values.

In addition to BMI, skinfold thickness, waist (i.e. abdominal) circumference, waist-to-height ratio and waist-to-hip ratio may be used as simple anthropometric measurements to define obesity and assess body fat distribution (Duren et al. 2008). There are more accurate but also more complex and costly methods for body composition assessment, e.g. bioelectrical impedance analysis, dual energy X-ray absorptiometry, magnetic resonance imaging, quantitative magnetic resonance, computed tomography, air displacement plethysmography and hydrodensitometry (i.e. underwater weighing) (Duren et al. 2008; Lee and Gallagher 2008).

2.1.2 Prevalence

Since the prevalence of overweight and obesity in children and adolescents has increased substantially and rapidly in most regions of the world, the problem is no longer limited to industrialised nations; some developing countries now have prevalence levels of childhood obesity even higher than those of the USA (Sinha and Kling 2009). In Europe, the prevalence of childhood obesity is higher in the western and southern countries than in northern Europe (Lobstein and Frelut 2003).

It is difficult to accurately estimate the extent of the problem since different definitions of childhood obesity have been employed in prevalence studies (Wang and Lobstein 2006). Using the IOTF definitions, Kautiainen and colleagues reported steep rises in the prevalence of overweight and obesity in Finnish 12, 14, 16 and 18-year-old adolescents between 1977 and 1999. Age-standardised prevalence of overweight increased in boys from 7.2% to 16.7% and in girls from 4.0% to 9.8% and, furthermore, the prevalence of obesity increased in boys from 1.1% to 2.7% and in girls from 0.4% to 1.4%. The largest increase in BMI was observed at the upper end of the BMI distribution which suggests that some individuals are more susceptible to an obesogenic (obesity-promoting) environment than others (Kautiainen et al. 2002). Vuorela and colleagues (2011) analysed longitudinally the BMI distribution of Finnish children and adolescents in five birth cohorts and found that from the 1970s to the 1990s, the respective proportions of boys over the 85th and 95th percentiles of BMI increased from 9% to 19% and from 3% to 6% in 12-year-olds and from 11% to 22% and from 2% to 9% in 15-year-olds; conversely, toddlers had become markedly slimmer.

More recent data have pointed to a levelling off in childhood and adolescent obesity prevalence in some, primarily Western, nations (Rokholm et al. 2010; Olds et al. 2011). However, current prevalence estimates are still high and possibly conservative: a large number of excessively fat children and adolescents may not be identified as obese since BMI, despite high specificity for detecting excess fatness (low false-positive rate), has only modest sensitivity (moderate to high false-negative rate) (Reilly and Wilson 2006; Reilly et al. 2010).

2.1.3 Risk factors

When one evaluates the aetiology of both childhood and adult obesity, then it seems that numerous environmental, behavioural, and genetic factors influence the susceptibility to excessive weight gain and due to their synergistic effects, it is difficult to assess the relative importance of a single factor. The current obesity pandemic could be seen as a result of a gene-environment interaction where human genotype is exposed to environmental influences that affect the balance between energy intake and energy expenditure. Fundamentally, an accumulation of excess body fat is caused by a chronic positive energy balance (Hall et al. 2012).

Unhealthful dietary habits

Dietary habits play a key role in the development of obesity although the dietary causes of obesity are complex and incompletely understood. Nutritional habits are established in childhood and the stability of food choices from childhood into adulthood could explain the persistence of childhood obesity into later life (Mikkilä et al. 2005; Craigie et al. 2011).

Several studies have revealed a positive association between intake of sugar-sweetened beverages (SSBs) and weight gain and obesity in children, adolescents and adults. The postulated explanations for the association include lower satiety levels and increased caloric intake, and decreased insulin sensitivity (Berkey et al. 2004; Malik et al. 2006; Libuda and Kersting 2009). However, the effect of SSB consumption seems to be rather small except in predisposed individuals or at high levels of intake (Gibson 2008).

In their first review on the association between childhood obesity and different aspects of dietary intake, Rodríquez and Moreno stated that cross-sectional and longitudinal studies did not reveal any clear relationships between energy intake or diet composition and the development of obesity in children and adolescents (Rodríquez and Moreno 2006). Nevertheless, in their second review they did mention that a lack of breastfeeding, high early energy intake and high intake of SSBs seemed to be the main dietary factors contributing to body fatness at a young age (Moreno and Rodríquez 2007). Several other features of the diet, such as large portion sizes, fast food consumption and low fruit and vegetable intake, have been tentatively linked to the risk of obesity in youth but their contributions have not been established. With respect to childhood and adolescent obesity, it has been proposed that the impact of overall eating patterns may be more significant than that of single foods or nutrients (Nicklas et al. 2001).

Parental obesity

BMI is correlated within families, i.e. between parents and offspring, and siblings. The effect of parental BMI on offspring BMI probably includes both genetic and environmental components (Burke et al. 2001; Bouchard 2009). Children both of whose parents are overweight or obese are at a higher risk of being overweight than children with only one overweight or obese parent (Whitaker et al. 1997; Fuentes et al. 2002). Since data on paternal BMI have been less often available for analyses, its effects have been less studied than those of maternal BMI. Based on the studies that were able to analyse data from both parents, maternal BMI seems to show a stronger association with offspring BMI than paternal BMI in both genders (Fuentes et al. 2002; Lawlor et al. 2007; Mihas et al. 2009; Whitaker et al. 2010); however, not all studies have confirmed this difference (Davey-Smith et al. 2007; Kivimäki et al. 2007). Maternal weight is also known to be more influential than paternal weight in offspring birthweight (Griffiths et al. 2007; Kivimäki et al. 2007).

Based on longitudinal data, Mamun and co-workers (2005) found that children whose parents were overweight or obese were more likely to change from being non-overweight at age 5 y to being overweight at age 14 y and were more likely to be overweight at both ages; these transitions showed stronger association with mothers' than with fathers' overweight or obesity. Another prospective study in pre-pubertal children found a gender-assortative relationship between parental BMI and offspring weight gain, i.e. the BMI of the daughter was associated with that of her mother, and the BMI of the son with that of his father (Perez-Pastor et al. 2009). However, a larger cohort data did not confirm these differences in parent-offspring BMI associations (Leary et al. 2010). In Finnish populations, there are no prospective studies on gender-specific associations between parental and offspring BMI.

Unfavourable intrauterine environment

Evidence is accumulating to support the importance of early-life environment *in utero* on many long-term health outcomes, such as obesity, type 2 diabetes and cardiovascular disease. Maternal obesity in early pregnancy has been observed to increase the risk of offspring obesity in childhood, adolescence and adulthood (Whitaker 2004; Salsberry and Reagan 2007; Pirkola et al. 2010; Reynolds et al. 2010). In addition to high maternal BMI, gestational diabetes mellitus (GDM) has been associated with the risk of overweight in the offspring. In a Finnish cohort study, overweight and metabolic syndrome manifestations were more prevalent in the adolescent offspring of mothers with GDM compared with a non-GDM group (Vääräsmäki et al. 2009). A multi-ethnic cohort study found a relationship between an increasing maternal glycaemic level in pregnancy and an increased risk of childhood obesity (Hillier et al. 2007). However, the association of GDM with offspring overweight might be explained by other factors, particularly maternal obesity and high birth weight (Gillman et al. 2003; Pirkola et al. 2010).

Birth weight is a strong indicator of maternal health and nutrition status and a predictor of the future health of the mother and the child (Stephenson and Symonds 2002; Stein et al. 2006; Walsh and McAuliffe 2012). Intriguingly, both low (<2500 g) and high (≥4000 g) birth weight have been linked to the development of excess body weight in childhood and adolescence (Pietiläinen et al. 2001; Walker et al. 2002; Reilly et al. 2005). In addition, maternal gestational weight gain (GWG) has been associated with both birthweight and BMI from childhood to adulthood (Oken et al. 2008a; Ludwig and Currie 2010; Schack-Nielsen et al. 2010), although not all studies have detected these associations (Koupil and Toivanen 2008). Prenatal smoking exposure, maternal haemoglobin levels and parity may also influence offspring body size and fat distribution, and these effects could be mediated by birth size (Steer 2000; Salsberry and Reagan 2007; Oken et al. 2008b; Reynolds et al. 2010; Syme et al. 2010).

In addition to intrauterine environmental influences, genetic factors, i.e. maternal and fetal genotypes, are known to regulate fetal growth and size at birth (Lunde et al. 2007; Yaghootkar and Freathy 2012). Furthermore, epigenetic programming (metabolic imprinting) has been proposed to explain associations between fetal environment and later metabolic health (Cutfield et al. 2007).

Lack of breastfeeding

Some studies have suggested that breastfeeding exerts a protective effect on childhood obesity while early introduction of infant formula or solid foods increases the risk of obesity (Gillman et al. 2001; Mayer-Davis et al. 2006; Gibbs and Forste 2013). Among adolescent sibling pairs, in which only one sibling was breastfed, the difference in weight was approximately 6 kg, favouring the breastfed sibling (Metzger and McDade 2010). A dose-dependent relationship between longer duration of breastfeeding and decreased risk of obesity has also been reported (Harder et al. 2005). The underlying mechanisms may be metabolic or behavioural and probably based on the differences in the compositions of human milk and infant formulas (Bartok and Ventura 2009; Oddy 2012). The higher protein content of infant formula can increase postnatal growth velocity and induce earlier adiposity rebound whereas breastmilk prevents early-life adiposity via lower plasma insulin levels (Oddy 2012). This view was supported by the work of Koletzko and

colleagues who reported that a lower protein content of infant formula normalised infant growth to the level of a breastfed reference group and the WHO growth reference (Koletzko et al. 2009). Interestingly, compared to bottle-feeding (human milk or formula), direct breastfeeding has been associated with greater appetite regulation, i.e. higher satiety responsiveness, in childhood (Disantis et al. 2011). In addition, differences in gut microbiota composition between lean and obese children have been observed and it has been suggested that early exposure to maternal microbiota and prebiotics, i.e. bacteria and galactooligosaccharides in breast milk and skin-derived microbes, constitutes the link between breastfeeding and weight development (Kalliomäki et al. 2008; Bervoets et al. 2013).

However, the overall evidence seems inconsistent and, if the association is causal, the effect of breastfeeding on future obesity risk is probably modest (Ryan 2007; Beyerlein and von Kries 2011). In a recent large randomised trial, the intervention which succeeded in improving the duration and exclusivity of breastfeeding did not prevent overweight or obesity at age 11.5 years (Martin et al. 2013). It should be noted that family's socioeconomic status and maternal level of education are important determinants of feeding practices (Ummarino et al. 2003; Gibbs and Forste 2013). Moreover, due to the fact that breastfeeding seems to protect against paediatric underweight, it could have a less marked effect on mean BMI (Grummer-Strawn et al. 2004).

Early adiposity rebound

Adiposity rebound is the phase when BMI begins to increase after reaching a nadir in early childhood (4–7 years). An early rebound (before 5.5 years) has been found to be followed by a significantly higher adiposity level than a later rebound (after 7 years) (Rolland-Cachera et al. 1984; Taylor et al. 2005; Rolland-Cachera et al. 2006; Lagström et al. 2008; Chivers et al. 2009). However, the reasons for early adiposity rebound are unclear and whether rapid early growth reflects a cause of later obesity or whether it is simply an early marker of an energy balance trajectory leading to later obesity. Although some have argued that the timing of the adiposity rebound in early childhood could accurately predict up to 30% of later obesity (Rolland-Cachera et al. 2006; Chivers et al. 2009), the predictive value of early adiposity rebound has also been criticised. According to Cole (2004), the connection between early rebound and later obesity is not physiological but statistical and BMI centile crossing would be a more direct indicator of the underlying drive to fatness.

Low physical activity and increased sedentary behaviour

Sedentary pastimes, such as TV viewing, computer use and playing video games, in childhood seem to have a disadvantegous effect on body composition (Tremblay et al. 2011) that could be due to lower energy expenditure (less time for physical activity, lower resting metabolic rate) or increased energy intake. In a crossover trial in normal-weight male adolescents, a single session of video game play was associated with an increased food intake that was not compensated for during the rest of the day; no increase in appetite sensations or in profiles of appetite-related hormones were observed (Chaput et al. 2011). In preschoolers, the relationship between TV viewing and fatness was not found to be mediated by physical activity but is more likely explained by an effect on food intake (Jackson et al. 2009). Among non-overweight children and adolescents, experimental

changes in the amount of sedentary behaviour resulted in changes in energy intake and energy expenditure: increased sedentary behaviour was linked to increased energy intake and decreased energy expenditure (Epstein et al. 2002), whereas reduced sedentary behaviour led to a decreased energy intake and increased physical activity (Epstein et al. 2005).

With regard to the dominant recreational pastime at all ages, TV viewing, in 1985 Dietz and Gortmaker reported that in 12-17-year-old adolescents, the increase in the prevalence of obesity was 2% for each additional hour of television viewed. In a more recent review, Swinburn and Shelly (2008) concluded that the effect size estimated from observational studies was small, i.e. TV viewing accounted for very little of the variance in BMI, even though the results of intervention studies showed fairly large effect sizes. Regarding physical activity as a determinant of adolescent adiposity, the data on the issue are still too sparse and weakened by methodological limitations in order to generate evidence-based recommendations, albeit the majority of studies have shown protective effects (Reichert et al. 2009).

Inequalities in built environment

The built environment refers to the many forms of surroundings that influence human activity. In recent years, there has been an upsurge of research on the effect of the built environment on obesity and obesity-related behaviour (Galvez et al. 2010). For instance, physical activity may depend on environmental features that encourage or discourage physical activity, such as access to recreational facilities, walkability or bikeability of the environment, and low neighbourhood crime rates (Davison and Lawson 2006; Ferreira et al. 2007). The built environment can also affect dietary intake: access to healthy food resources is related to lower obesity rates whereas proximity to high-caloric foods and convenience stores might increase the risk of overweight and obesity (Morland et al. 2006). Furthermore, the school environment, including the availability of healthy foods and professionally led physical activity classes, has an important role in childhood and adolescent obesity (Kubik et al. 2003; Fox et al. 2009; Story et al. 2009). In the comprehensive review of Dunton and colleagues, school play space, road safety, proximity to supermarkets, and lower population density were found to be related to lower obesity rates in younger children, whereas in adolescents, the number of recreational facilities was the only built environment attribute that could be clearly associated with obesity (Dunton et al. 2009).

Short sleep duration

There is a considerable amount of data revealing an association between inadequate amounts of sleep and the risk of obesity in children and adolescents (Garaulet et al. 2011; Hart et al. 2011; Nielsen at al. 2011). However, in a recent 2-year longitudinal study, no statistically significant relationships between change in total sleep and change in BMI or percent body fat were seen in adolescent boys and girls (Lytle et al. 2012).

Low socioeconomic status

In 1989, Sobal and Stunkard reviewed 34 studies published after 1941 on the relationship between socioeconomic status (SES) and childhood obesity in the developed countries; they found inverse associations (36%), no associations (38%), as well as positive associations

(26%). Nearly two decades later, Shrewsbury and Wardle (2008) carried out a similar analysis of 45 cross-sectional studies published between 1990 and 2005 and observed predominantly inverse associations whereas positive associations were nearly non-existent. They also concluded that parental education was more consistently inversely associated with adiposity than other SES indicators (parental occupation or income) and the children whose parents, particularly mothers, had a low level of education seemed to be at a higher than average risk. SES-adiposity associations were also more common in studies of children (5-11 years) compared with adolescents (12-18 years). Although differences in child feeding and physical activity have been identified in some studies, more research is needed to understand the mechanisms that explain the SES-adiposity associations (Shrewsbury and Wardle 2008).

2.2 MEAL CONSUMPTION PATTERNS: ASSOCIATION WITH CHILDHOOD OBESITY

In the 1960s, Fábry and co-workers brought out the inverse relationship between habitual frequency of eating and body weight in human subjects (Fábry et al. 1964; Fábry et al. 1966). In recent years, meal consumption patterns, that is, meal frequency, meal timing and breakfast consumption, have re-emerged in nutrition research as potential contributors to the obesity epidemic. Observational studies have shown a fairly consistent association between skipping meals, especially breakfast, and an increased risk of obesity in both children and adults. The next chapters cover the association between obesity and the consumption of meals, snacks and breakfast.

2.2.1 Definition of meal, breakfast, snack and snacking

There are several published definitions of eating occasions. According to Gatenby (1997), the definition of a 'meal' and a 'snack' is most often based on the criteria of time of consumption and/or nutrient composition of the eating occasions. In general, a 'meal' is described colloquially as one of the main eating occasions of the day, nominally occurring at morning ('breakfast'), mid-day ('lunch') or evening ('dinner'), whereas a 'snack' has come to refer to other eating episodes, generally smaller and less structured than a 'meal' (Gatenby 1997). In their review on eating frequency in terms of weight control, Drummond and colleagues define a 'snack' as "any food taken outwith a regular mealtime (namely breakfast, lunch and dinner) or snack item taken in place of such meal" (Drummond et al. 1996). Furthermore, 'snacking' refers to the patterns of frequency of 'snacks' consumed at times other than recognised 'meal' times (Gatenby 1997). Some investigators have used the type, quantity or energy content of food consumed - in some cases, combined with an added time constraint - as the basis for the definition of eating occasions. Eating occasions could also be defined on the basis of the presence or absence of fellow diners, i.e. a 'meal' could be seen as a planned social interaction centred on food, whereas a 'snack' would imply an eating event conducted individually (Gatenby 1997). Evidently, the type of definition may significantly influence the outcome and interpretation of studies in which they have been used.

There is no consensus on what constitutes a breakfast and in fact the varying definitions used in the studies seriously hamper the comparison of the findings. Generally, breakfast is defined as the first eating occasion after waking. In some studies, to qualify as a breakfast consumer, breakfast must be eaten on a certain number of days a week. Some studies have assessed breakfast eating using single day recall methods. In some cases, any food intake was accepted as breakfast while others required a minimum proportion of daily energy for morning intake to qualify as a meal. Differences in definition of breakfast may explain the discrepancies between findings: Dialektakou and Vranas (2008) demonstrated that whether there was an association between breakfast skipping and BMI depended on how breakfast was defined.

2.2.2 Meal frequency

There is evidence for an inverse association between the number of daily eating occasions and the risk of excessive weight gain in childhood and adolescence (Koletzko and Toschke 2010; Patro and Szajewska 2010; Ritchie et al. 2012) although not all studies have confirmed this association (Nicklas et al. 2003; Nicklas et al. 2004) and the results of a recent meta-analysis showed that the effect of eating frequency was significant only in boys (Kaisari et al. 2013). The majority of studies have been cross-sectional and there have been variations in the categorisation of the number of eating occasions (Table 1). With respect to the findings from longitudinal studies, in a ten-year follow-up of black and white girls, lower eating frequency at 9-10 years of age predicted greater increases in BMI and waist circumference while the percentage of girls eating > 3 meals a day (snacks not included) was reduced from 15% to 6% over the course of the study (Franko et al. 2008; Ritchie et al. 2012).

Meal frequency has also been associated with other indicators of metabolic health. Eating meals regularly was inversely associated with the prevalence of metabolic syndrome and insulin resistance in 60-year-old men and women living in Sweden (Sierra-Johnson et al. 2008). In 50-89-year-old white men and women, those reporting higher eating frequency (≥ 4 meals a day) had lower total and LDL cholesterol concentrations than those who ate infrequently (1-2 meals a day); the HDL cholesterol level did not vary according to meal frequency (Edelstein et al. 1992). Moreover, Farshchi and colleagues reported higher fasting lipid profiles after a 14-day period of irregular eating compared with measurements after a regular eating phase in a randomised cross-over trial in lean women (Farshchi et al. 2004b). There is a lack of similar studies for children and adolescents.

Experimental studies conducted in adults have shed some light on potential biological mechanisms explaining the inverse association. The suggested explanations include effects on appetite control and food intake regulation, thermogenic effect of food, and glucose and insulin responses (Farshchi et al. 2004a; Toschke et al. 2005; Leidy and Campbell 2011). However, the limited number of published studies and conflicting findings makes it impossible to draw any definitive conclusions.

Table 1. Studies on meal frequencies and obesity outcomes in children and adolescents

Reference	Gender (total *n*) and age in years	Meal frequency (daily unless otherwise specified)	Obesity measure	Association
Fábry et al. (1966)	M + F (226) 6-16	3, 5, 7	Body weight Skinfold thickness	Negative* Negative*
Summerbell et al. (1996)	M + F (33) 13-14	1-3, 4-6	BMI	Negative, $p < 0.05$
Nicklas et al. (2003)	M + F (1562) 10	Total eating episodes	Overweight	NS, $p \geq 0.05$
Nicklas et al. (2004)	M + F (1584) 10	<3 yes vs no Total eating episodes	Overweight	NS, OR 1.25 (CI 0.92,1.70) NS, OR 0.97 (CI 0.90,1.05)
Toschke et al. (2005)	M + F (4370) 5-6	≤3, 4, ≥5	Overweight Obesity	≥5 meals: negative, OR 0.56 (CI 0.42,0.75) ≥5 meals: negative, OR 0.51 (CI 0.29,0.89)
Barba et al. (2006)	M + F (3668) 6-11	≤3, 4, ≥5	BMI Waist circumference	Negative, $p < 0.001$ Negative, $p < 0.001$
Thompson et al. (2006)	F (101) 8-19	0.0-3.9, 4.0-5.9 vs ≥6.0 (weekdays)	Change in BMI z-score	0.0-3.9: NS, $p \geq 0.05$ 4.0-5.9: negative, $p = 0.002$
Kosti et al. (2007)	M + F (2008) 12-17	Total eating episodes;<3 vs ≥3	Overweight/obesity	Negative, $p = 0.01$ (boys) and NS, $p = 0.28$ (girls)
Franko et al. (2008)	F (2375) 9-19	Number of days eating ≥3 meals	BMI-for-age z-score Overweight	Negative, $p < 0.0001$ Main effect: NS, $p \geq 0.05$ Days with ≥3 meals x race: negative, $p < 0.05$
Lagiou and Parava (2008)	M + F (633) 10-12	Total eating episodes	Overweight (≥85th centile)	Negative, $p < 0.001$
Lioret et al. (2008)	M + F (748) 3-11	Tertiles of weekly eating episodes	Overweight	Negative, $p = 0.009$
Mota et al. (2008)	M + F (886) 13-17	≤3, 4, ≥5	Overweight/obesity	Negative, $p = 0.04$ (girls) and $p = 0.001$ (boys)
Barbiero et al. (2009)	M + F (511) 10-18	Total number of meals	Normal weight, overweight, obesity	Negative, $p = 0.005$
Toschke et al. (2009)	M + F (4642) 5-6	≤3, 4, ≥5	Obesity	Negative, $p < 0.05$
Kontogianni et al. (2010)	M + F (1305) 3-18	Total eating episodes	Normal weight, overweight, obesity BMI	NS, $p = 0.83$ (3-12 y) and $p = 0.038$ (13-18 y) Negative, $p < 0.001$
Vik et al. (2010)	M + F (2870) 15.5	0-1, 2, 3, 4	Overweight	Inverted U-shaped, $p \leq 0.001$
Cassimos et al. (2011)	M + F (335) 11-12	≤3 yes vs no	Overweight/obesity	Negative, $p = 0.030$ (unadjusted) and $p = 0.037$ (adjusted)
Antonogeorgos et al. (2012)	M + F (700) 10-12	1-3, >3 and breakfast skipping yes / no	Overweight/obesity	Negative in breakfast eaters, OR 0.49 (CI 0.27,0.88)
Ritchie et al. (2012)	F (2372) 9-10, 19-20	1-3, 3.1-4, 4.1-6, >6	Change in BMI Change in WC	Negative, $p = 0.012$ (whites) Negative, $p = 0.015$ (whites) and $p = 0.010$ (blacks)

BMI, body mass index; CI, confidence interval, F, females; M, males; NS, not significant; OR, odds ratio; WC, waist circumference.

*Actual level of significance not given.

2.2.3 Snacking

Although increased eating frequency has been associated with a lower prevalence of obesity, it has been suspected that snacking has a deleterious influence on the energy balance and weight control. In 1988, Booth hypothesised that "the growing trend for 'grazing' rather than of the traditional pattern of three proper meals a day is a major factor in the aetiology of obesity". In the USA, the prevalence of snacking and the average daily energy from snacks increased in all age groups of children from 1977 to 1996 (Jahns et al. 2001). However, epidemiologic studies and trials on snacking behaviour in youth have provided little support for the claims presented by Booth. A prospective trial in children aged 9-14 years suggested that snacks are not an important determinant of weight gain although snack foods may be of low nutritional value (Field et al. 2004). Among 12-18 year-old adolescents, the prevalence of overweight or obesity and of abdominal obesity were found to decrease with increasing snacking frequency and increasing percentage of energy from snacks (Keast et al. 2010). According to Chapelot (2011), the problem in the studies has been the lack of any clear definition of a snack and an accurate distinction between meals and snacks. Nonetheless, Chapelot has claimed that recent data actually support the view that snacking promotes overweight and obesity and emphasises the importance of the nutritional quality and macronutrient content of snacks for satiety and energy balance (Chapelot 2011).

2.2.4 Breakfast consumption

A number of studies have investigated the association between breakfast consumption and overweight or obesity in children and adolescents. The majority of the studies have been cross-sectional and only a few studies have longitudinally assessed weight change and breakfast intake. Some studies have aimed to establish the type and content of breakfast; however, of those studies that have looked at ready-to-eat cereal (RTEC) consumption, many have been carried out by or have been funded by cereal manufacturers. A few studies have examined participation in breakfast promoting programmes in schools but no randomised trials or other experimental studies in children have been reported in this area.

In several studies, regular breakfast consumption has been associated with lower BMI and reduced risks of overweight and obesity in children and adolescents (Rampersaud et al. 2005; Szajewska and Ruszczynski 2010; Veltsista et al. 2010; Duncan et al. 2011; Lehto et al. 2011). The relationship has been detected in Western countries as well as in the Asian and Pacific regions (Horikawa et al. 2011). Nonetheless, some cross-sectional studies have failed to detect any association (Abalkhail and Shawky 2002; Kim and So 2012). Based on longitudinal analyses, Berkey and colleagues reported that in overweight adolescents, skipping breakfast was associated with a decline in BMI over the following year whereas among normal weight breakfast skipping adolescents, there was a non-significant tendency to gain weight; however, skipping breakfast was associated with overweight in a cross-sectional evaluation (Berkey et al. 2003). Another prospective analysis in adolescents showed that the frequency of breakfast was inversely associated with 5-year change in BMI in a dose-response manner (Timlin et al. 2008). In 12-17-year-old Greek adolescents, consumption of breakfast cereals was associated with lower BMI in both genders and the results were more prominent for more than two daily servings consumed for breakfast

(Kosti et al. 2008). In 9-13-year-old children and adolescents, the prevalence of obesity was lower among RTEC consumers than in breakfast skippers or other breakfast consumers (Deshmukh-Tashkar et al. 2010). The effect of school breakfast participation on obesity has also been investigated. In the USA, participation in the School Breakfast Program reduced breakfast skipping and was associated with lower BMI (Gleason and Dodd 2009). In Spain, a school-based nutrition education programme including provision of a daily breakfast resulted in a decreased prevalence of metabolic syndrome, overweight and obesity in adolescent boys and girls (Campos Pastor et al. 2012). In contrast, there is no evidence to suggest that breakfast programme participation would increase the risk of obesity.

The association between breakfast consumption and reduced risk of obesity could stem from the effect of breakfast on total energy intake. However, studies attempting to quantify this relationship have not consistently shown any lower daily energy intake (compensatory undereating) among breakfast eaters; quite the contrary, breakfast eaters have often reported higher energy intakes than non-eaters (Berkey et al. 2003; Rampersaud et al. 2005). On the other hand, breakfast eating has been associated with greater total physical activity (Aarnio et al. 2002; Cohen at al. 2003; Keski-Rahkonen et al. 2003) and decreased time spent watching television (Magnusson et al. 2005), both of which may promote a desirable energy balance.

As with daily meal frequency, breakfast habits might exert metabolic effects beyond obesity; however, studies in children and adolescents are lacking. In a cross-sectional study in young adults, Deshmukh-Taskar and colleagues found that breakfast consumption was associated with an improved cardiometabolic risk profile and the RTEC consumers had an even more favourable risk factor profile than other breakfast consumers (Deshmukh-Taskar et al. 2012). No difference in the prevalence of metabolic syndrome was seen with breakfast skipping or type of breakfast consumed. In an Australian 20-year longitudinal study, continual breakfast skipping since childhood was related to poor cardiometabolic health in later life (Smith et al. 2010). Conversely, an 18-year follow-up study revealed recuced risks for several metabolic risk markers and conditions (obesity, abdominal obesity, hypertension, metabolic syndrome) among daily breakfast consumers (Odegaard et al. 2013).

Some studies have assessed the joint effect of breakfast consumption and the number of daily meals on childhood obesity risk. Antonogeorgos and colleagues examined the possible interaction between meal frequency and breakfast consumption in children aged 10-12 years and found that consuming four or more meals a day was associated with a lower likelihood of overweight/obesity in breakfast eaters but not in breakfast skippers (Antonogeorgos et al. 2012). Thus, the negative association of higher meal frequency with obesity risk was dependent upon breakfast consumption. In contrast, Toschke and colleagues observed that the impact of frequent daily meals on childhood obesity was independent of breakfast eating; the inclusion of regular breakfast in the analysis had only a marginal effect on the inverse association between meal frequency and obesity (Toschke et al. 2009). Whether the benefits of regular breakfast consumption could outweigh the disadvantages of otherwise irregular daily meal pattern remains to be clarified.

2.3 GENETICS OF COMMON CHILDHOOD OBESITY

2.3.1 Overview and basic concepts

In most individuals, the genetic predisposition to obesity has a polygenic basis, in fact, the cases of monogenic obesity are rare (Hinney and Hebebrand 2008; Hinney et al. 2010). Monogenic (single-gene) forms of obesity are usually early onset, very severe and caused by functional mutations, i.e. changes in DNA sequence, especially in genes encoding appetite regulating proteins. The most commonly known forms of monogenic obesity in humans are due to mutations in the genes coding for leptin, the leptin receptor, pro-opiomelanocortin and melanocortin 4 receptor (Farooqi and O'Rahilly 2006). In addition, obesity can be a characteristic feature of several pleiotropic (multi-system) congenital disorders caused by mutations or chromosomal aberrations, e.g. Prader-Willi and Bardet-Biedl syndromes (Stefan and Nicholls 2004; Chung and Leibel 2005).

Studies of polygenic obesity have been primarily based on the analysis of single nucleotide polymorphisms (SNPs), i.e. alterations of a single nucleotide (A, C, G or T) in the DNA sequence. SNPs represent the most common source of genetic variablity in the human genome; approximately 90% of all human genetic variation (differences between unrelated individuals) is due to SNPs (International HapMap Consortium et al. 2007). The cut-off value of prevalence for a variation to be classified as a polymorphism is usually either 1% or 5%; if the minor allele frequency (MAF) in the population is below this arbitrary threshold, then the allele is typically regarded simply as a mutation (Arias et al. 1991; International HapMap Consortium et al. 2007).

Twin, adoption and family studies have found evidence for high genetic influences on obesity and obesity-related traits (Loos and Bouchard 2003; Yang et al. 2007; Wardle et al. 2008; Silventoinen et al. 2010; Dubois et al. 2012). For example, Sørensen and colleagues found stronger associations of adopted offspring BMI with the BMI of their biological parents than with that of their adoptive parents, even when the adopted offspring had shared their environment with their adoptive family from very early in life (Sørensen et al. 1992; Sørensen et al. 1998). For BMI, the reported heritability estimates (i.e. proportion of genetic influences on the variation of a trait within a population) range from 16 to as high as 85% (Yang et al. 2007). The wide range of estimates reflects the fact that heritability depends on many population-specific factors, such as variations in environmental factors and allele frequencies.

Regarding the heritability of BMI at different ages, paediatric twin studies have yielded higher estimates than adult twin studies. This could be due to the fact that adults are more likely than children to make deliberate attempts at weight control and may thus limit the observed genetic effect (Llewellyn et al. 2013). In a systematic review including mainly Caucasian populations up to the age of 18 years, BMI showed moderate-to-high heritability and age patterning, i.e. the estimates were lowest in mid-childhood and increased in adolescence (Silventoinen et al. 2010). Likewise, a more recent systematic review and meta-regression indicated that the genetic contribution to BMI varies by age and could be stronger during childhood than in adulthood (Elks et al. 2012). The meta-analysis reported nearly equal overall heritability estimates for men (0.73) and women (0.75). Among children, heritability estimates were on average 0.07 higher compared with adults, rising by 0.012/year throughout childhood (age ≤ 18 years) (Elks et al. 2012). In

regard to adolescents, heritability estimates ranged from 0.81 in males to 0.84 in females among 13-15 year-old Caucasians whereas in another twin study, heritability of BMI at 12-14 years was estimated to be 0.46-0.61 (Hur et al. 2008; Salsberry and Reagan 2010).

GWAS-identified obesity-related SNPs

In the search of obesity-susceptibility genes, early studies used candidate gene, biologic pathway and genome-wide linkage approaches with limited success. The advent of genome-wide association studies (GWAS) in the early 2000s revolutionised the discovery of genes for common traits and diseases, including obesity and obesity-related conditions (Day and Loos 2011). By 2012, more than 50 obesity-related genetic loci, i.e. regions of the chromosome at which genes or certain DNA sequences are located, had been identified through GWAS (Loos 2012). However, the established loci exert fairly small effects on obesity-susceptibility: they explain only a fraction of the inter-individual variation in BMI and their ability to predict a risk of obesity is lower than that of traditional risk factors (Loos 2012). In 2010, Speliotes and colleagues estimated that the confirmed 32 BMI loci explained only 1.45% of the inter-individual variation in BMI (Speliotes et al. 2010). On the other hand, as the risk alleles are common in populations, the population-attributable risk for obesity may be highly significant (Bouchard 2009). In addition, their cumulative contribution to the risk of obesity could be considerable and thus they could improve the prediction of complex traits and diseases. Speliotes and colleagues also estimated the cumulative effect of the 32 variants on BMI and reported a difference in average BMI between individuals with the highest genetic susceptibility (≥ 38 BMI-increasing alleles) and those with the lowest (≤ 21 BMI-increasing alleles) of 2.73 kg/m^2, equivalent to 7.9 kg body weight in individuals 170 cm in height (Speliotes et al. 2010).

Although most of the GWAS for obesity have focused on adult BMI, several adult-discovered genetic determinants have also been found to contribute to common childhood obesity. Loci identified through GWAS and associated with BMI in paediatric populations are presented in Table 2, including the widely replicated obesity-susceptibility loci harbouring the fat mass- and obesity-associated (*FTO*) gene and the melanocortin 4 receptor (*MC4R*) gene.

Table 2. Genes near/in which variants have been associated with increased BMI among children and adolescents (Zhao and Grant 2011; Fernandez et al. 2012; Manco and Dallapiccola 2012)

Gene abbreviation	Locus	Full gene name
BDNF	11p4	Brain-derived neurotrophic factor encoding gene
ETV5	3q27	Ets variant gene 5
FAIM2	12q13	Fas apoptotic inhibitory molecule 2 encoding gene
FTO	16q12	Fat mass- and obesity-associated gene
GNDPA2	4p12	Glucosamine-6-phosphate deaminase 2 encoding gene
KCTD15	19q13	Potassium channel tetramerisation domain containing 15 encoding gene
MAF	16q23	V-maf musculoaponeurotic fibrosarcoma oncogene homolog (avian) encoding gene
MC4R	18q21	Melanocortin 4 receptor encoding gene
MTCH2	11p11.2	Mitochondrial carrier homolog 2 encoding gene
NEGR1	1p31	Neuronal growth regulator 1 encoding gene
NPC1	18q11.2	Niemann-Pick disease type C1 gene
PTER	10p12	Phosphotriesterase-related gene
SDCCAG8	1q43	Serologically defined colon cancer antigen 8 encoding gene
SEC16B	1q25	SEC16 homolog B (*Saccharomyces cerevisiae*) encoding gene
SH2B1	16p11.2	Scr-homology-2 domain containing putative adapter protein 1 encoding gene **or** SH2B adaptor protein 1 encoding gene
TFAP2B	6p12	Transcription factor AP-2 β encoding gene **or** Activating enhancer-binding protein 2 β encoding gene
TMEM18	2p25	Transmembrane protein 18 encoding gene
TNJK/MSRA	8p23.1	Peptide methionine sulfoxide reductase encoding gene

2.3.2 *FTO* gene

FTO is a large gene with nine exons and more than 400 kilo base pairs in length located on chromosome 16. In 2007, GWAS led to the discovery of *FTO* rs9939609, the first SNP robustly associated with increased BMI (Dina et al. 2007; Frayling et al. 2007). Since then, a number of SNPs in tight linkage disequilibrium (LD) - i.e. non-random association of alleles at different loci or genes, usually on the same chromosome - with rs9939609 and residing in the first intron of the *FTO* gene have been associated with BMI in adults and children from different ethnicities. On average, the individuals who are homozygous for the risk allele weigh 3-4 kg more and have a 1.67-fold increased risk of obesity compared with those homozygous for the protective allele (Frayling et al. 2007; Loos and Bouchard 2008). In addition to BMI and the risk of obesity, the association of *FTO* locus has been demonstrated

with other adiposity traits such as fat mass, body fat percentage and waist circumference (Frayling et al. 2007; Xi et al. 2010). The *FTO* variants have also been shown to be associated with type 2 diabetes - both in a BMI-dependent and -independent manner - and metabolic syndrome (Frayling 2007; Li et al. 2012; Wang et al. 2012).

With regard to the association between *FTO* variants and BMI or adiposity in children and adolescents, age-dependent relations have been found. Hakanen et al. (2009) reported that in children followed from the age of 7 months, the effect of the *FTO* variant rs9939609 on BMI became evident only after the age of 7 years. Similarly, Frayling and colleagues observed the association from the age of 7 onwards (Frayling et al. 2007). In an analysis of eight cohorts of European ancestry, Sovio and colleagues found a positive association between carriage of *FTO* rs9939609 minor alleles and BMI from 5.5 years onwards and an inverse association below the age of 2.5 years (Sovio et al. 2011). Longitudinal twin analyses indicated that the increasing expression of *FTO* parallels increasing heritability of BMI between ages 4 and 11 (Haworth et al. 2008). In non-Hispanic whites, the carriers of two risk alleles of *FTO* rs9939609 had BMI 0.7 kg/m^2 higher at age 8 and 1.6 kg/m^2 higher at age 17 than those those with no or one risk allele (Hallman et al. 2012). *FTO* SNPs have also been related to increased ponderal index, weight, total fat mass and abdominal fat in 2-week-old neonates but no association with birth weight has been found (López-Bermejo et al. 2008; Andersson et al. 2010).

Although ubiquitously expressed in human central and peripheral tissues, *FTO* is most highly expressed in brain tissues (Frayling et al. 2007). While it seems that *FTO* polymorphisms are not involved in the regulation of energy expenditure, *FTO* genotype has been suggested to affect energy balance by influencing central control of food intake (Speakman et al. 2008; Cecil et al. 2012). Cecil and colleagues observed that the A allele of *FTO* rs9939609 was associated with increased energy intake independently of body weight among 4- to 10-year-olds (Cecil et al. 2008). In addition to increased energy intake, Timpson and colleagues reported that children carrying minor variants at rs9939609 consumed more fat (Timpson et al. 2008). According to Tanofsky-Kraff and colleagues, children and adolescents with one or two *FTO* rs9939609 obesity-risk alleles reported more frequent loss of control eating episodes and selected foods higher in fat at a buffet meal; however, their total energy intake at the test meal did not differ significantly by genotype (Tanofsky-Kraff et al. 2009). Likewise, Hakanen et al. (2009) and Liu et al. (2010) did not find an association between *FTO* rs9939609 and energy intake in Finnish 15-year-old adolescents and European- and African-American youth (mean age 16.5 years).

2.3.3 *MC4R* gene

In 2008, the variant rs17782313 near the *MC4R* gene was identified to be associated with common obesity by a genome-wide analysis (Loos et al. 2008). Long before this finding, mutations in the *MC4R* gene were known to cause severe early-onset obesity on the basis of human studies and animal models (Vaisse et al. 1998; Yeo et al. 1998). Thus, *MC4R* is an example of the overlap in the genetic determinants of monogenic and polygenic forms of obesity. Subsequently, rs17782313 has been associated with both childhood and adult adiposity in Europeans and East Asians (Xi et al. 2012). The two published studies in subjects of African ancestry reported discrepant results (Grant et al. 2009; Hester et al. 2012). In a meta-analysis based on 61 studies, the effect size (pooled odds ratio) of

rs17782313 on obesity was 1.26 (95% CI 1.19, 1.33) in children and 1.15 (95% CI 1.12, 1.17) in adults (Xi et al. 2012). Several other SNPs near the *MC4R* gene in high LD with rs17782313 have also been investigated but the associations have been less consistent.

Like *FTO, MC4R* is highly expressed in hypothalamus, and in that respect it has a key role in the control of appetite (Fan et al. 1997; Walley et al. 2009). Indeed, the rs17782313 variant has been linked to obesity-related eating behaviours, e.g. the CC genotype was associated with low satiety responsiveness and increased enjoyment of food in obese children (Valladares et al. 2010). Moreover, the rs17782313 C allele was related to increased snacking and food intake in European children and adolescents (Stutzmann et al. 2009; Cole et al. 2010).

2.3.4 Gene-lifestyle interactions in childhood obesity

In the complex aetiology of obesity, genetic variation and gene-environment interactions might explain why some individuals gain more weight than others in the current obesogenic environment. As illustrated in Figure 1, under conditions of normal energy intake and expenditure, the BMI of a genetically susceptible subpopulation barely differs from that of a non-susceptible subpopulation (Hofbauer 2002). As energy intake increases, BMI distribution curves shift to the right; this shift is more marked in the genetically susceptible subpopulation. A combination of high energy intake and low energy expenditure results in further increases in BMI and a more pronounced separation of the subpopulations. In individuals with rare forms of obesity caused by monogenic mutations, BMI will be increased irrespective of the environmental conditions; however, even these subjects with monogenic forms of obesity have been shown to respond to lifestyle modifications (hypocaloric dietary or multidisciplinary interventions) to a similar degree as non-monogenic obese individuals (Santoro et al. 2006; Reinehr et al. 2009).

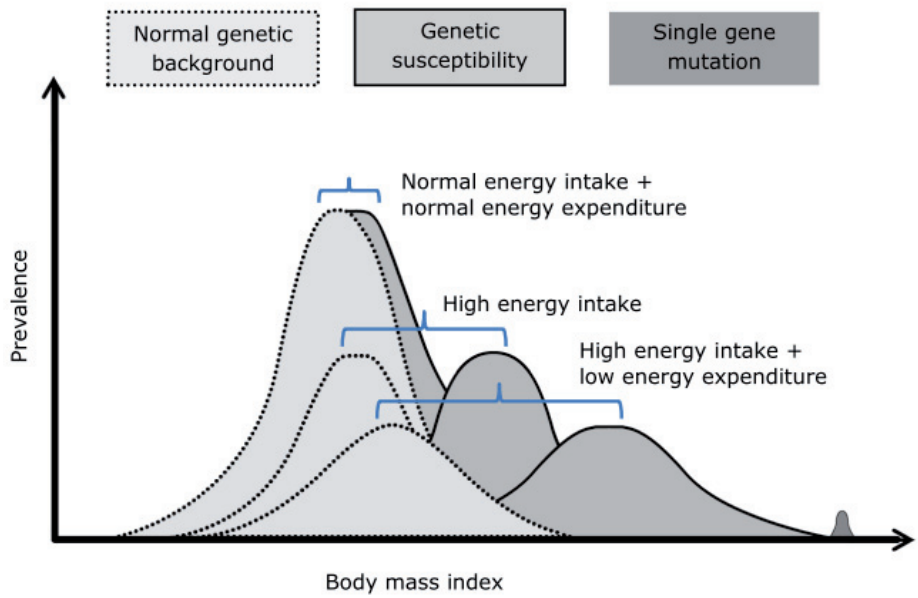

Figure 1. Interaction of genetic background, energy intake and energy expenditure on body mass index (modified from Hofbauer 2002)

Recently, studies have begun to emerge unravelling the interactions between genetic and lifestyle factors on obesity in paediatric and adolescent populations. In a recent meta-analysis including both adults and children, physical activity was found to attenuate the effect of *FTO* variants on the obesity risk in adults but not in children (Kilpeläinen et al. 2011). However, a study examining variation in the *FTO* gene in Finnish adolescents indicated that the genetic effect can be blunted through physical activity: the values of BMI in highly physically active subjects with one or two risk alleles were comparable to those without risk alleles (Cauchi et al. 2009). In Spanish children, dietary fat composition was found to interact with the *FTO* gene variant rs9939609 on the obesity risk: risk allele carriers consuming high proportions of saturated fat of total energy or having a low polyunsaturated fat/saturated fat ratio were at a higher risk of developing obesity compared with non-carriers with similar fat intakes (Moleres et al. 2012). Accordingly, Riedel and colleagues reported an interaction between a low intake of unsaturated fatty acids and an obesity-risk-allele score in relation to BMI among 7-year-olds (Riedel et al. 2013). In adults, it has also been shown that high fat intakes can amplify the effect of the *FTO* genotype on the risk of obesity (Sonestedt et al. 2009; Corella et al. 2011).

With regard to gene-lifestyle interactions reported in experimental studies, genetic variation in *SDCCAG8* was associated with a reduced weight loss after a 1-year lifestyle intervention among overweight children and adolescents (Scherag et al. 2012). Among the adult participants of the Finnish Diabetes Prevention Study, no association was observed between the *FTO* rs9939609 or other obesity-susceptibility variants and the magnitude of weight reduction achieved by lifestyle intervention (Lappalainen et al. 2009; Jääskeläinen et al. 2013); on the other hand, there was a trend for higher BMI by a genetic risk score in those who reported a diet low in fibre (Jääskeläinen et al. 2013). Thus, there is equivocal evidence as to whether the effect of lifestyle intervention targeting weight loss is modulated by genetic background. Nevertheless, the results from observational and experimental studies suggest that the effect of common SNPs in obesity-susceptibility genes could be modified by environmental conditions, including dietary and other lifestyle factors.

2.4 SUMMARY OF THE LITERATURE REVIEW

The common form of obesity in childhood and adolescence is multifactorial in origin, i.e. it is a result of complex interactions between genotype and environment. In a broad sense, environmental risk factors include a wide spectrum of social, behavioural and personal factors. In rare cases, obesity among other traits is linked to a monogenic (Mendelian) disorder or it is due to a single gene mutation with obesity as an isolated or predominant feature. In the common polygenic forms of obesity, it is impossible to fully disentagle the contribution of inherited and environmental factors. Figure 2 is a schematic presentation of potential determinants of overweight and obesity in children and adolescents as well as consequences which may occur over the life course after the onset of obesity (Must and Strauss 1999).

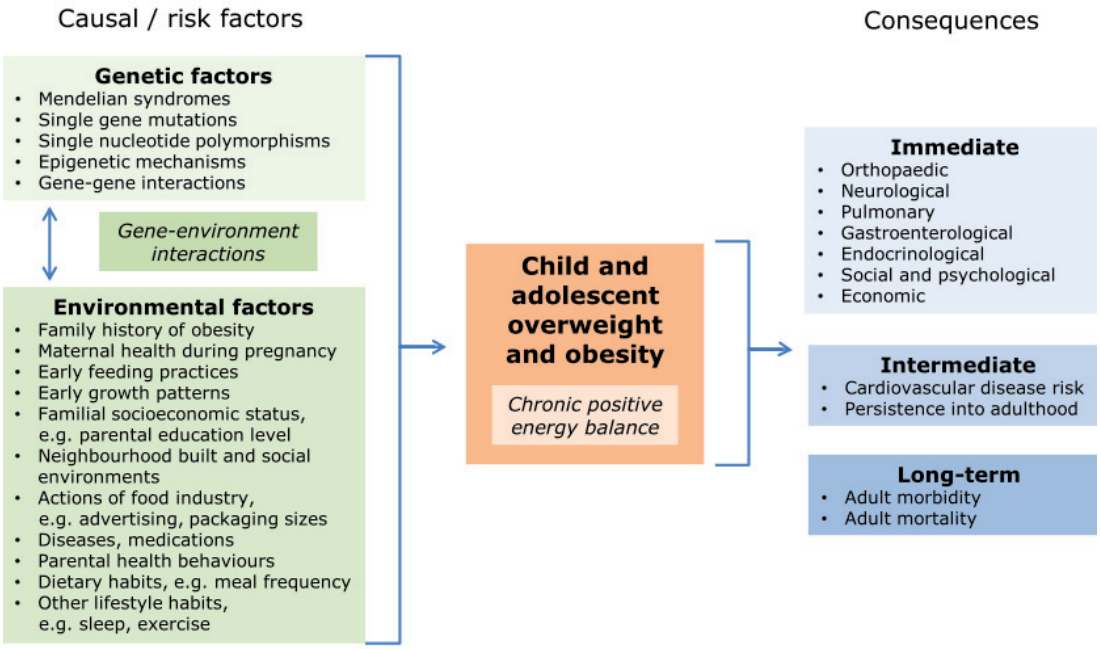

Figure 2. Causes or determinants and consequences of child and adolescent overweight and obesity

3 Aims of the Study

This study was carried out to identify early-life risk factors associated with adolescent overweight and obesity and to investigate whether meal frequencies (the number of meals on weekdays) could modulate the effect of genetic susceptibility on obesity in 16-year-old adolescents from a Finnish, population-based birth cohort.

The specific aims were:

1. to investigate associations of maternal and paternal pre-pregnancy BMI, weight change, BMI, and BMI class change 16 years after pregnancy with adolescent offspring overweight/obesity (*Study I*),

2. to evaluate the effect of maternal gestational weight gain on the overweight/obesity and abdominal obesity of adolescent offspring, taking into account possible confounding factors such as maternal pre-pregnancy BMI and glucose metabolism (*Study II*),

3. to examine associations of a regular five-meal-a-day pattern and two other meal patterns differing in breakfast regularity with overweight/obesity and the components of the metabolic syndrome including abdominal obesity in adolescents (*Study III*) and

4. to evaluate the effect of two meal frequency patterns i.e. five meals including breakfast (regular) and ≤four meals with or without breakfast (meal skipping) on the association between obesity-related common genetic variants and BMI in adolescents (*Study IV*).

4 Study Population and Study Designs

The present study is based on data from the Northern Finland Birth Cohort 1986 (NFBC1986). NFBC1986 is an ongoing, population-based study which at the baseline comprised 9432 infants born alive in the two northernmost provinces of Finland to women with expected delivery dates between July 1, 1985 and June 30, 1986, covering 99% of all eligible births in the region (mothers n = 9362, all births n = 9479). Data have been collected prospectively since gestation week 12. The latest follow-up, in 2001-2002 when the children were aged 16 years, consisted of questionnaires for adolescents (response rate 80%, n = 7344) and their parents (response rate 76%, n = 6985) and a clinical examination of these adolescents (participation rate 74%, n = 6798) (Figure 3).

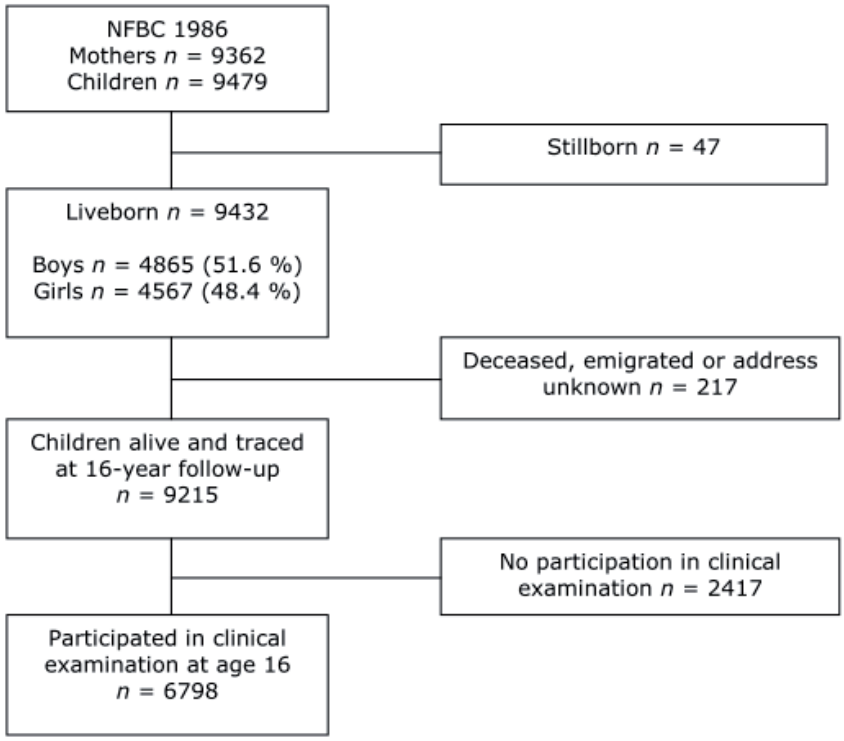

Figure 3. Flow chart of the Northern Finland Birth Cohort 1986 study population

The adolescents and their parents were asked to sign a written informed consent form for their data to be used for scientific research. The participants could either refuse the use of their data totally or forbid only the delivery of their data to collaborating units. Only those participants who provided informed consent and gave permission to use their data in the scientific study were included in the analyses. The study was approved by the ethics

committees of the Northern Osthrobothnia Hospital District and the Faculty of Medicine of the University of Oulu.

4.1 INTERGENERATIONAL TRANSMISSION OF OVERWEIGHT (*STUDY I*)

Longitudinal data were utilised to investigate associations of maternal and paternal pre-pregnancy BMI, present BMI, weight change and BMI class change 16 years after pregnancy with offspring overweight at the age of 16. A total of 4788 mother-father-child trios (2325 boys and 2463 girls) were included in the analyses. Exclusion criteria were as follows: refusal to provide informed consent (n = 153), missing values for age or clinically measured height or weight (n = 40) and adolescent not living with both of his/her biological parents at 16-y follow-up (self-reported by adolescents; n = 1341 and data missing n = 476).

BMI (kg/m^2) of the adolescents was calculated from measured height and weight and classified according to the International Obesity Task Force (IOTF) age- and gender-specific criteria (Cole at al. 2000). For 16-year-old males and females, BMI cut-off points for overweight (corresponding to an adult BMI of 25.0 kg/m^2) were 23.90 kg/m^2 and 24.37 kg/m^2, respectively.

The equivalent BMI categories for the parents were normal weight/underweight < 25.0 kg/m^2, overweight ≥ 25.0 and < 30.0 kg/m^2, and obese ≥ 30.0 kg/m^2 according to the World Health Organization (2000) international classification of adult BMI. Parental weight change over the 16-year follow-up was categorized as ≤ -3.0 kg, -2.9 - +2.9 kg (no change), +3.0 - +7.9 kg, +8.0 - +17.9 kg, and ≥ +18.0 kg. Parental BMI status change was defined as

1) remained normal weight,
2) gained weight from normal weight to overweight/obese or
3) remained overweight/obese.

These three classes were then combined into seven categories to obtain the parental BMI class change variable:

1) mother and father had remained normal weight,
2) mother had remained normal weight, father had become overweight/obese
3) one parent had remained normal weight, the other had remained overweight/obese,
4) mother had become overweight/obese, father had remained normal weight,
5) mother and father had become overweight/obese,
6) one parent had become overweight/obese, the other had remained overweight/obese, and
7) mother and father had remained overweight/obese.

Possible confounders of associations between the outcome and explanatory variables considered were maternal and paternal age and education level (serving as a proxy for socioeconomic status), and, for parental weight change, also pre-pregnancy BMI. Parental education was classified according to the modified International Standard Classification of Education definition as ≤ 9 years (basic), 10-12 years (upper secondary), or ≥ 13 years (tertiary) (Isohanni 2000). Parental pre-pregnancy BMI was categorised into three classes as described above whereas age was used as a continuous variable.

4.2 GESTATIONAL WEIGHT GAIN AND THE RISK OF OFFSPRING OBESITY (*STUDY II*)

Purpose was to evaluate the effect of maternal gestational weight gain on obesity and abdominal obesity of offspring, taking into account potential confounding factors such as maternal pre-pregnancy BMI and glucose metabolism. A total of 6637 mother-child pairs were included in the analyses. Participants who refused permission to the use of their data (n = 3) and twins and triplets (n = 158) were excluded.

Maternal weight gain during the first 20 gestational weeks was based on the difference between weight at the 20th gestational week and self-reported pre-pregnancy weight and classified into quartiles. The quartile cut-off values for GWG were as follows: Q1 ≤ 3.0 kg; Q2 > 3.0 kg and ≤ 5.0 kg; Q3 > 5.0 kg and ≤ 7.0 kg; Q4 > 7.0 kg. Maternal pre-pregnancy BMI (kg/m^2) was calculated from self-reported weight and height and classified using the World Health Organization (2000) criteria as follows: underweight < 18.5 kg/m^2, normal weight ≥ 18.5 and < 25.0 kg/m^2, overweight ≥ 25.0 and < 30.0 kg/m^2, and obese ≥ 30.0 kg/m^2.

BMI was calculated and IOTF age- and gender-specific BMI cut-off values were applied similarly as in *Studies I* and *III* (Cole et al. 2000). Adolescents with a waist circumference of ≥85th percentile for gender within the cohort were considered abdominally obese.

The association of maternal GWG with the risk of adolescent overall overweight/obesity and abdominal obesity was examined using univariable and multivariable logistic regression. The regression model was built in two stages to observe changes in risk estimates. The initial model included GWG as an exposure and the following covariates: maternal pre-pregnancy BMI class (underweight, normal weight, overweight, obese); level of haemoglobin in early pregnancy (< 120 g/l, 120-137 g/l, > 137 g/l); smoking during early pregnancy (no smoking, 1-10 cigarettes/day, > 10 cigarettes/day); offspring gender, parity (0, 1-3 or > 3 previous deliveries) and level of education (comprehensive school, vocational school, secondary school graduate). The fully adjusted model also included maternal glucose metabolism divided into six categories as follows: pre-pregnancy diabetes, GDM, OGTT not performed despite indications, no OGTT or indications, OGTT normal, not known.

4.3 ASSOCIATION OF MEAL FREQUENCIES WITH OVERWEIGHT AND MetS TRAITS (*STUDY III*)

Associations of three meal patterns with overweight or obesity and the components of metabolic syndrome including abdominal obesity were examined. After exclusion of ineligible subjects (refused to provide permission for the use of their data n = 154, born preterm i.e. before 37 weeks gestation n = 331, born from multiple-birth pregnancies n = 90), 6247 adolescents (3066 boys and 3181 girls) participated in the analyses.

For the analyses, dietary data on meal consumption on weekdays were categorised as follows: five meals a day including breakfast (regular meal pattern), ≤ four meals a day including breakfast (semi-regular meal pattern) and ≤ four meals a day not including breakfast (breakfast skippers). The semi-regular meal pattern comprised 15 subcategories all characterised by the regular consumption of breakfast and skipping at least one meal,

whereas the breakfast skipping pattern consisted of 15 possible combinations of meals excluding breakfast. The numerous combinations of daily meals were collapsed into three meal frequency categories in order to provide adequate statistical power in the analyses.

BMI was calculated and IOTF age- and gender-specific BMI cut-off values were applied similarly as in *Studies I* and *II* (Cole at al. 2000). The features of the metabolic syndrome were defined according to the International Diabetes Federation (IDF) paediatric criteria: 1) central obesity (waist circumference ≥ 90th percentile or adult cut-off if lower); 2) high serum triglyceride concentration (TG ≥ 1.7 mmol/L); 3) low serum high-density lipoprotein cholesterol concentration (HDL < 1.03 mmol/L); 4) high systolic or diastolic blood pressure (SBP ≥ 130 mm Hg or DBP ≥ 85 mm Hg); 5) elevated fasting plasma glucose level (FPG ≥ 5.6 mmol/L) (Zimmet et al. 2007). Metabolic syndrome is defined by the presence of central obesity plus at least two other risk features. In the NFBC1986 data, the waist circumference 90th percentile in girls was 82.0 cm, and therefore the IDF adult cut-off (80 cm for European women) was used to define abdominal obesity in females.

Associations of meal patterns with obesity and MetS traits were assessed using logistic regression stratified by gender. To take potential confounders into account, two multivariable regression models were constructed. The first model included early life factors: birth weight for gestational age, maternal weight gain during the first 20 weeks of gestation, maternal pre-pregnancy BMI, maternal level of education before pregnancy, maternal smoking during pregnancy, maternal gestational glucose metabolism and parity. The second model consisted of factors related to health behaviour, social conditions and physical development at the age of 16: sleep duration, tobacco use, time spent in sedentary activities outside school hours, physical activity outside school hours, Tanner stage of puberty, maternal and paternal education level and, for abdominal obesity and other MetS traits, also BMI. All the variables in the regression models were categorical.

Offspring size at birth was classified as appropriate, small and large for gestational age, defined respectively as birth weight between the 10th and 90th, below the 10th and over the 90th percentile of the gender- and gestational age-specific cohort distributions. Maternal pre-pregnancy BMI, gestational weight gain, smoking behaviour, glucose metabolism, education level and parity were categorised as in *Study II*.

Adequate sleep duration was defined as sleeping at least 8 hours per night. Tobacco use was categorised as follows: never smoked or taken snuff, experimented with cigarettes or snuff, smoking or taking snuff regularly. The total time spent on sedentary activities (TV viewing, reading books or magazines, playing or working on a computer/playing video games, other sedentary activities) was calculated and then classified into four categories: < 3 h/d, 3-4.9 h/d, 5-7.9 h/d, ≥ 8 h/d. Regular physical activity was defined as at least 20 minutes of moderate to vigorous-intensity exercise outside school hours 4-7 days a week. The five categories of Tanner stages of puberty were used. Maternal and paternal level of education were classified as in *Study I*. Adolescent BMI was coded into three categories (normal weight/underweight, overweight, obese) to be used as an adjusting variable for the MetS components along with other later childhood factors.

4.4 INTERACTION OF MEAL FREQUENCIES AND GENETIC PREDISPOSITION ON BMI (*STUDY IV*)

The aim was to evaluate the effect of the two meal frequency patterns (regular and meal skipping) on the association between obesity-related genotypes and BMI among adolescents. The meal pattern variable used in *Study III* was re-categorised by combining the semi-regular pattern and the breakfast skipping pattern into one category characterised as meal skipping. After filtering the dataset for individuals with missing data on key variables (height, weight, stage of puberty, meal frequency on weekdays at 16 years, and all chosen BMI-related SNPs), the analyses included 4664 individuals (2215 boys and 2449 girls).

A genetic risk score (GRS) was created using eight SNPs representing eight early-life obesity-susceptibility loci, including *FTO* rs1421085 and *MC4R* rs17782313. SNP genotypes were recoded as 0, 1, or 2 BMI-increasing alleles, and the GRS was calculated for each individual by summing up the number of these alleles. The sample was divided into high-risk and low-risk groups using the median value of the GRS (8) as the cutoff point. The GRS was used as both a continuous and a categorical variable. Under an additive model of inheritance, the genotype-meal frequency interaction was also analysed separately for the *FTO* and *MC4R* variants. BMI was treated as a continuous variable and results were adjusted for gender and stage of puberty based on the five-point Tanner scale.

5 Methods

5.1 PRE- AND PERINATAL DATA COLLECTION

In Finland, health care is offered free of charge to all pregnant women in municipal maternity welfare clinics (MWCs). In the NFBC 1986, data were acquired prospectively from the mothers' first antenatal clinic visit onwards according to cohort study protocol (Järvelin et al. 1993; Vääräsmäki et al. 2009).

Data on parents' height, weight and level of eduation before pregnancy were collected using a self-completed questionnaire provided to all mothers on their first antenatal clinic visit and returned by the 24th gestation week. Maternal height and weight were measured at the first MWC visit and weight was also measured at every subsequent check-up at the MWCs. During the course of pregnancy, data on maternal wellbeing, health behaviours and socioeconomic status were collected via questionnaires that the mothers filled at MWCs with the help of trained nurses. Maternal data included e.g. smoking behaviour (the number of cigarettes smoked per day at the end of the second gestational month), haemoglobin at the first maternity clinic visit, parity, and level of education.

Gestational diabetes screening using oral glucose tolerance testing (OGTT) was performed in the MWCs based on the assessment of risk factors for GDM. Indications for screening were prior GDM, maternal pre-pregnancy BMI > 25 kg/m^2, maternal age > 40 years, glucosuria in the current pregnancy, suspected fetal macrosomia in the current pregnancy and previous macrosomic infant (weight > 4500 g). At between 26 and 28 weeks of gestation, 1228 pregnant women with risk factors for GDM underwent a diagnostic 2-hour OGTT, conducted by administering a 75-gram glucose load after an overnight fast. The upper ranges of the normal venous blood glucose values were 5.5, 11.0 and 8.0 mmol/l at fasting, one hour and two hours after the initial load, respectively, and the diagnosis of GDM was made after one abnormal value in the OGTT according to prevailing national guidelines (Österlund et al. 1978). Despite indications, 1987 women did not undergo the OGTT.

After delivery, gestational age and weight at birth were recorded by the attending midwives at the delivery hospital.

5.2 16-YEAR FOLLOW-UP DATA COLLECTION

5.2.1 Anthropometrics and blood pressure

At the age of 16 years, adolescents participated in a clinical examination carried out in all municipalities of Northern Finland and also in major cities elsewhere in Finland. The examinations took place primarily in municipal health centres and were performed by trained study personnel (three teams each consisting of one laboratory analyst and two study nurses) according to a standardised protocol. The accuracy of the measuring instruments was continuously assessed.

Height was measured in centimetres to one decimal place. Body weight was measured using a calibrated scale to the nearest 0.1 kg with subjects in their underwear. Waist circumference was measured at the level midway between the lowest rib margin and the iliac crest. At the clinical examination, the participants were also asked to assess their pubertal development using the Tanner staging drawings.

Systolic and diastolic blood pressures (SBD, DBP) were measured on the right upper arm with the participant in a sitting posture using an oscillometric pressure meter, Omron 705 CP, or, if this failed, a mercury sphygmomanometer. The participants were advised to sit and rest for at least 15 minutes before the measurement. The average of two readings taken two minutes apart was used.

5.2.2 Glucose and lipid measurements

At the clinical examination of the adolescents, venous blood samples were drawn after a 12-hour overnight fast. Fasting plasma glucose and serum lipid concentrations (HDL, TG) were analysed using Cobas Integra 700 automatic analyser (Roche Diagnostics, Basel, Switzerland) at Oulu University Hospital laboratory within 24 hours of sampling.

5.2.3 Questionnaires for adolescents and their parents

At the 16-year follow-up, adolescents filled in a postal questionnaire concerning their sociodemographic characteristics, wellbeing and health behaviours, e.g. tobacco use, physical activity, sedentary behaviours and sleeping habits. The postal questionnaire also included a five-item subquestionnaire on meal patterns on weekdays. Meal consumption was assessed using the question 'Do you usually have the following meals (breakfast, lunch, snack, dinner, evening snack) on weekdays?' The response categories were dichotomous (yes/no). In addition, self-reported data on parents' height, weight and level of education in 2001-2002 were obtained from responses to a postal questionnaire.

5.2.4 DNA extraction and genotyping

DNA was extracted from the venous blood samples drawn at the clinical examination according to standard protocols. Subsequently, the variants rs1421085, rs17782313, rs6265, rs10938397, rs1424233, rs6548238, rs11084753, and rs2815752, representing the respective early-life obesity-susceptibility loci at or near the *FTO*, *MC4R*, *BDNF*, *GNPDA2*, *MAF*, *TMEM18*, *KCTD15*, and *NEGR1* genes, were genotyped. Genotyping was performed by the TaqMan single nucleotide polymorphism assay (Applied Biosystems, Foster City, CA).

5.3 STATISTICAL ANALYSES

Data were analysed using SPSS for Windows, version 17.0 (SPSS Inc., Chicago, IL, USA) and SAS 9.2 (SAS Institute Inc., Cary, NC, USA). In *Studies I-III*, logistic regression analysis was used to evaluate independent associations of exposure variables with binary outcome variables. To adjust for potential confounding effects, covariates were entered simultaneously into the regression models. These results are presented as odds ratios along with their 95% confidence intervals (CIs). In *Studies I* and *III*, the analyses were stratified by offspring gender. In *Study IV*, analysis of variance (ANOVA) was used for comparisons

between groups and linear regression analysis to investigate per allele effects. Hardy-Weinberg equilibrium (HWE) and associations between genotypes and meal frequencies were tested using the chi-squared test. The distributions of BMI are presented as means and 95% CIs or standard deviations (SD) whereas categorical data are presented as percentages (%).

6 Results

6.1 INTERGENERATIONAL TRANSMISSION OF OVERWEIGHT (*STUDY I*)

During the follow-up period of 16 years, the proportion of obese (BMI ≥ 30) parents increased by four-fold. In their 16-year-old offspring, the combined prevalence of overweight and obesity was 15.1% for boys and 12.8% for girls. Compared with their peers living in intact families, girls coming from non-intact families had greater BMI (p = 0.025, Mann-Whitney U-test) while no difference was found in boys. The difference in the mean BMI between singletons and twins was also non-significant.

Maternal pre-pregnancy overweight was associated with a significant risk of being overweight/obese at the age of 16 years in boys OR 2.03 (95% CI 1.46, 2.81) and girls OR 2.73 (95% CI 1.97, 3.77). The risk was exacerbated when the mother was obese (Tables 3 and 4). Likewise, paternal overweight and obesity were significant predictors of adolescent overweight/obesity (Tables 3 and 4). The association of paternal pre-pregnancy overweight and obesity with overweight/obesity of the offspring was stronger in girls than in boys.

The maternal weight change over 16 years was a significant predictor for offspring overweight/obesity in both genders at the two highest levels of weight gain (8.0-17.9 kg and ≥ 18.0 kg) (Tables 3 and 4). With regard to paternal weight gain (≥ 18.0 kg), the odds ratio was statistically significant only for girls.

Among the seven parental BMI change patterns, the prevalence of offspring overweight/obesity was lowest (8.7% for sons, 4.1% for daughters) in those parents who remained normal weight at the follow-up. The highest proportions of overweight/obese offspring (33.3% for sons, 34.0% for daughters) were in the category of parents who were overweight or obese (BMI ≥ 25) from pre-pregnancy to the 16-year follow-up. Long-term overweight in both parents was a particularly strong predictor for the risk of overweight/obesity in girls. In addition, when one parent was overweight/obese from pre-pregnancy to follow-up and the other either remained normal weight or became overweight/obese, girls were at a higher risk for becoming overweight/obese than boys (Tables 3 and 4).

Table 3. Adjusted odds ratios and their 95% confidence intervals for overweight/obesity in boys by maternal and paternal predictors

Parental predictor	Boys overweight/obesity			
	n	%	OR	95% CI
Maternal pre-pregnancy BMI class[a,b]				
Normal weight/underweight	1911	12.8	Ref.	
Overweight	299	23.4	**2.03**	**1.46, 2.81**
Obese	74	39.2	**4.36**	**2.50, 7.59**
Maternal BMI class 16 y after pregnancy[a,b]				
Normal weight/underweight	1181	9.7	Ref.	
Overweight	643	18.2	**2.10**	**1.59, 2.80**
Obese	226	33.2	**4.60**	**3.24, 6.53**
Maternal weight change over 16 y of follow-up[c]				
≤ -3.0 kg	81	14.8	1.07	0.52, 2.22
-2.9 - +2.9 kg	375	10.7	Ref.	
+3.0 - +7.9 kg	695	13.4	1.49	0.99, 2.25
+8.0 - +17.9 kg	726	16.4	**1.83**	**1.23, 2.72**
≥ +18.0	156	26.3	**2.79**	**1.68, 4.64**
Paternal pre-pregnancy BMI class[a,b]				
Normal weight/underweight	1345	12.1	Ref.	
Overweight	585	22.4	**1.95**	**1.48, 2.58**
Obese	52	30.8	**3.17**	**1.70, 5.92**
Paternal BMI class 16 y after pregnancy[a,b]				
Normal weight/underweight	764	9.2	Ref.	
Overweight	1036	16.8	**1.93**	**1.43, 2.60**
Obese	255	24.7	**3.05**	**2.08, 4.49**
Paternal weight change over 16 y of follow-up[c]				
≤ -3.0 kg	109	20.2	1.30	0.73, 2.30
-2.9 - +2.9 kg	321	15.6	Ref.	
+3.0 - +7.9 kg	554	15.0	1.08	0.73, 1.61
+8.0 - +17.9 kg	647	14.2	1.05	0.71, 1.55
≥ +18.0	134	19.4	1.50	0.87, 2.59
Parents' BMI class change over 16 y of follow-up[a]				
I Both parents remained normal weight	356	8.7	Ref.	
II Mother remained normal weight, father became overweight	319	7.2	0.81	0.45, 1.45
III Father remained normal weight, mother became overweight	156	9.0	1.03	0.52, 2.05
IV One parent remained normal weight, other remained overweight	318	16.4	**2.07**	**1.26, 3.39**
V Both parents became overweight	173	21.4	**2.94**	**1.73, 5.00**
VI One parent remained overweight, other became overweight	189	30.7	**4.66**	**2.80, 7.75**
VII Both parents remained overweight	114	33.3	**5.66**	**3.12, 10.27**

[a]ORs were adjusted for parental age and education level.
[b]BMI categories: normal weight/underweight BMI <25.0 kg/m^2, overweight BMI ≥25.0 and <30.0 kg/m^2, and obese BMI ≥30.0 kg/m^2.
[c]ORs were adjusted for parental age, education level and pre-pregnancy BMI.
BMI, body mass index; CI, confidence interval; OR, odds ratio; Ref., reference group.

Table 4. Adjusted odds ratios and their 95% confidence intervals for overweight/obesity in girls by maternal and paternal predictors

Parental predictor	**Girls overweight/obesity**			
	n	%	OR	95% CI
Maternal pre-pregnancy BMI class[a,b]				
Normal weight/underweight	1989	10.2	Ref.	
Overweight	324	22.8	**2.73**	**1.97, 3.77**
Obese	92	31.5	**3.95**	**2.34, 6.68**
Maternal BMI class 16 y after pregnancy[a,b]				
Normal weight/underweight	1211	7.6	Ref.	
Overweight	682	15.4	**2.32**	**1.71, 3.14**
Obese	273	29.7	**5.04**	**3.56, 7.14**
Maternal weight change over 16 y of follow-up[c]				
≤ -3.0 kg	91	20.9	1.61	0.82, 3.15
-2.9 - +2.9 kg	373	8.8	Ref.	
+3.0 - +7.9 kg	689	9.3	1.10	0.70, 1.74
+8.0 - +17.9 kg	780	14.4	**1.64**	**1.07, 2.51**
≥ +18.0	203	21.2	**2.36**	**1.42, 3.95**
Paternal pre-pregnancy BMI class[a,b]				
Normal weight/underweight	1420	8.8	Ref.	
Overweight	614	20.5	**2.61**	**1.94, 3.50**
Obese	68	30.9	**5.58**	**3.09, 10.07**
Paternal BMI class 16 y after pregnancy[a,b]				
Normal weight/underweight	823	8.1	Ref.	
Overweight	1037	13.1	**1.69**	**1.23, 2.31**
Obese	285	24.6	**3.72**	**2.56, 5.39**
Paternal weight change over 16 y of follow-up[c]				
≤ -3.0 kg	141	18.4	1.14	0.65, 1.99
-2.9 - +2.9 kg	377	11.9	Ref.	
+3.0 - +7.9 kg	537	11.0	0.94	0.62, 1.44
+8.0 - +17.9 kg	644	10.7	0.92	0.61, 1.39
≥ +18.0	169	21.3	**1.84**	**1.11, 3.07**
Parents' BMI class change over 16 y of follow-up[a]				
I Both parents remained normal weight	393	4.1	Ref.	
II Mother remained normal weight, father became overweight	318	5.7	1.50	0.74. 3.04
III Father remained normal weight, mother became overweight	155	11.0	**3.22**	**1.56, 6.65**
IV One parent remained normal weight, other remained overweight	330	15.2	**4.47**	**2.43, 8.21**
V Both parents became overweight	186	9.7	**2.59**	**1.28, 5.33**
VI One parent remained overweight, other became overweight	252	23.4	**7.77**	**4.23, 14.27**
VII Both parents remained overweight	100	34.0	**14.84**	**7.41, 29.73**

[a]ORs were adjusted for parental age and education level.
[b]BMI categories: normal weight/underweight BMI <25.0 kg/m^2, overweight BMI ≥25.0 and <30.0 kg/m^2, and obese BMI ≥30.0 kg/m^2.
[c]ORs were adjusted for parental age, education level and pre-pregnancy BMI.
BMI, body mass index; CI, confidence interval; OR, odds ratio; Ref., reference group.

6.2 GESTATIONAL WEIGHT GAIN AND THE RISK OF OFFSPRING OBESITY (*STUDY II*)

In the fourths of maternal weight gain, the mean increases were 1.8, 4.5, 6.5 and 9.4 kg for boys and 1.8, 4.5, 6.4 and 9.5 kg for girls. The combined prevalence of overweight and obesity was 16.2% in boys and 13.8% in girls while 15.1% of the boys and 16.1% of the girls were abdominally obese (waist circumference ≥ 83.5 cm and ≥ 79.0 cm, respectively).

The highest fourth of maternal GWG (cut-off value 7.0 kg) during the first 20 weeks gestation was significantly associated with overweight/obesity of the 16-year-old offspring both in the unadjusted and adjusted analyses (Table 5). However, in the regression models, the odds ratios associated with maternal pregravid obesity were 2.5-4.0-fold greater as compared to GWG. Maternal pregravid overweight, smoking during pregnancy and the mother's low or intermediate level of education were also independently associated with an increased risk of overweight or obesity and there was a weak positive association with the highest level of maternal haemoglobin during early pregnancy. On the other hand, female gender, maternal pregravid underweight and multiparity were protective factors for offspring overweight in all models. In the unadjusted analysis, maternal glucose metabolism statuses seemed to be associated with offspring overweight/obesity but these associations were attenuated after multivariable adjustment. In the fully adjusted model, the risk of offspring overweight/obesity was increased when the mothers were not tested for GDM despite indications for testing.

With respect to offspring abdominal obesity, the highest fourth of maternal weight gain remained positively associated after multivariable adjustments, as did maternal pregravid overweight and obesity (Table 6). GDM and indications for OGTT in untested mothers were also positively associated with an increased risk of adolescent abdominal obesity whereas maternal underweight and multiparity were inversely associated in both unadjusted and adjusted analyses. The risk of abdominal obesity was not affected by offspring gender and after full multivariable adjustment, maternal education level, haemoglobin level and smoking were no longer associated with the outcome.

Previous studies have shown that the greatest GWG occurs among non-obese women, i.e. an inverse relationship between GWG and pregravid BMI generally exists (Institute of Medicine 2009). To test for an interaction between pregravid BMI and GWG, interaction terms were included in logistic regression analysis. Interaction terms were non-significant with *p*-values 0.124 (overweight/obesity) and 0.413 (abdominal obesity) indicating that there was no interaction between maternal pregravid BMI and GWG in the NFBC1986 study population.

Table 5. Association between maternal factors during pregnancy and overweight/obesity of offspring at 16 years of age. Odds ratios and their 95% confidence intervals are presented.

		Overweight/obesity based on BMI			
	Total n	Yes n (%)	Model I[a] OR (95% CI)	Model II[b] OR (95 % CI)	Model III[c] OR (95% CI)
Maternal weight gain during the first 20 weeks of gestation[d]					
I quartile	1709	251 (14.7)	1.13 (0.93, 1.36)	0.87 (0.71, 1.08)	0.87 (0.70, 1.08)
II quartile	1838	244 (13.3)	Ref.	Ref.	Ref.
III quartile	1454	191 (13.1)	0.99 (0.81, 1.21)	0.97 (0.77, 1.21)	0.97 (0.78, 1.21)
IV quartile	1054	210 (19.9)	**1.63 (1.33, 1.99)**	**1.48 (1.18, 1.86)**	**1.46 (1.16, 1.83)**
Maternal BMI before pregnancy					
Underweight	459	19 (4.1)	**0.29 (0.18, 0.46)**	**0.27 (0.16, 0.46)**	**0.28 (0.16, 0.47)**
Normal weight	4892	642 (13.1)	Ref.	Ref.	Ref.
Overweight	856	210 (24.5)	**2.15 (1.80, 2.57)**	**2.25 (1.84, 2.76)**	**1.81 (1.40, 2.35)**
Obese	245	94 (38.4)	**4.12 (3.14, 5.40)**	**5.97 (4.31, 8.27)**	**4.57 (3.18, 6.57)**
Gender					
Boy	3198	517 (16.2)	Ref.	Ref.	Ref.
Girl	3322	457 (13.8)	**0.83 (0.72, 0.95)**	**0.78 (0.66, 0.91)**	**0.78 (0.66, 0.91)**
Maternal level of education					
Comprehensive school	1380	243 (17.6)	**1.56 (1.28, 1.91)**	**1.32 (1.06, 1.66)**	**1.30 (1.04, 1.64)**
Vocational school	2596	420 (16.2)	**1.41 (1.18, 1.69)**	**1.28 (1.05, 1.55)**	**1.27 (1.04, 1.54)**
Secondary school graduate	1754	211 (12.0)	Ref.	Ref.	Ref.
Maternal smoking during pregnancy					
No	5222	730 (14.0)	Ref.	Ref.	Ref.
1-10 cigarettes/day	553	102 (18.4)	**1.39 (1.11, 1.75)**	**1.33 (1.02, 1.73)**	**1.36 (1.04, 1.77)**
>10 cigarettes/day	606	124 (20.5)	**1.58 (1.28, 1.96)**	**1.46 (1.13, 1.88)**	**1.47 (1.14, 1.90)**
Maternal glucose metabolism					
Pre-pregnancy DM	17	6 (35.3)	**4.27 (1.57, 11.60)**		2.22 (0.65, 7.63)
Gestational DM	96	23 (24.0)	**2.47 (1.53, 3.98)**		1.74 (0.99, 3.06)
OGTT not performed despite indications	1388	297 (21.4)	**2.13 (1.81, 2.51)**		**1.39 (1.09, 1.77)**
No OGTT or indications	3920	444 (11.3)	Ref.		Ref.
OGTT normal	779	139 (17.8)	**1.70 (1.38, 2.09)**		1.26 (0.98, 1.62)
Not known	249	45 (18.1)	**1.73 (1.23, 2.42)**		1.45 (0.90, 2.32)

[a]Model I: Unadjusted associations.
[b]Model II: Adjusted for all covariates including parity and haemoglobin at 8-10 weeks of gestation and excluding maternal glucose metabolism.
[c]Model III: Adjusted for all covariates including parity and haemoglobin at 8-10 weeks of gestation.
[d]Quartile cut-off values for maternal weight gain: Q1 ≤3.0 kg; Q2 >3.0 kg and ≤5.0 kg; Q3 >5.0 kg and ≤7.0 kg; Q4 >7.0 kg.
BMI, body mass index; CI, confidence interval; DM, diabetes mellitus; OGTT, oral glucose tolerance test; OR, odds ratio; Ref., reference group.

Table 6. Association between maternal factors during pregnancy and abdominal obesity of offspring at 16 years of age. Odds ratios and their 95% confidence intervals are presented.

		Abdominal obesity			
	Total n	Yes n (%)	Model I[a] OR (95% CI)	Model II[b] OR (95 % CI)	Model III[c] OR (95% CI)
Maternal weight gain during the first 20 weeks of gestation[d]					
I quartile	1722	281 (16.3)	1.14 (0.95, 1.37)	0.94 (0.76, 1.15)	0.94 (0.76, 1.15)
II quartile	1842	269 (14.6)	Ref.	Ref.	Ref.
III quartile	1477	198 (13.4)	0.91 (0.74, 1.10)	0.92 (0.74, 1.14)	0.91 (0.73, 1.14)
IV quartile	1073	206 (19.2)	**1.39 (1.14, 1.70)**	**1.37 (1.10, 1.71)**	**1.37 (1.10, 1.72)**
Maternal BMI before pregnancy					
Underweight	461	28 (6.1)	**0.41 (0.28, 0.60)**	**0.44 (0.29, 0.67)**	**0.43 (0.28, 0.67)**
Normal weight	4941	676 (13.7)	Ref.	Ref.	Ref.
Overweight	864	216 (25.0)	**2.10 (1.77, 2.50)**	**2.25 (1.85, 2.75)**	**1.75 (1.35, 2.26)**
Obese	248	99 (39.9)	**4.19 (3.21, 5.47)**	**5.88 (4.27, 8.09)**	**4.43 (3.10, 6.34)**
Gender					
Boy	3245	491 (15.1)	Ref.	Ref.	Ref.
Girl	3339	538 (16.1)	1.01 (0.94, 1.23)	1.01 (0.87, 1.18)	1.02 (0.87, 1.19)
Maternal level of education					
Comprehensive school	1405	250 (17.8)	**1.37 (1.13, 1.66)**	1.23 (0.99, 1.53)	1.24 (0.99, 1.55)
Vocational school	2622	434 (16.6)	**1.26 (1.06, 1.49)**	1.17 (0.97, 1.41)	1.16 (0.96, 1.39)
Secondary school graduate	1761	240 (13.6)	Ref.	Ref.	Ref.
Maternal smoking during pregnancy					
No	5273	786 (14.9)	Ref.	Ref.	Ref.
1-10 cigarettes/day	560	103 (18.4)	**1.29 (1.03, 1.61)**	1.14 (0.88, 1.48)	1.17 (0.90, 1.53)
>10 cigarettes/day	611	118 (19.3)	**1.37 (1.10, 1.69)**	**1.29 (1.00, 1.65)**	1.28 (0.99, 1.65)
Maternal glucose metabolism					
Pre-pregnancy DM	17	4 (23.5)	2.26 (0.73, 6.96)		1.51 (0.39, 5.81)
Gestational DM	96	24 (25.0)	**2.45 (1.53, 3.93)**		**2.15 (1.26, 3.69)**
OGTT not performed despite indications	1382	303 (21.9)	**2.06 (1.76, 2.42)**		**1.42 (1.12, 1.80)**
No OGTT or indications	3915	469 (12.0)	Ref.		Ref.
OGTT normal	772	143 (18.5)	**1.67 (1.36, 2.05)**		1.26 (0.98, 1.61)
Not known	251	52 (20.7)	**1.92 (1.39, 2.64)**		1.49 (0.95, 2.35)

[a]Model I: Unadjusted associations.
[b]Model II: Adjusted for all covariates including parity and haemoglobin at 8-10 weeks of gestation and excluding maternal glucose metabolism.
[c]Model III: Adjusted for all covariates including parity and haemoglobin at 8-10 weeks of gestation.
[d]Quartile cut-off values for maternal weight gain: Q1 ≤3.0 kg; Q2 >3.0 kg and ≤5.0 kg; Q3 >5.0 kg and ≤7.0 kg; Q4 >7.0 kg.
BMI, body mass index; CI, confidence interval; DM, diabetes mellitus; OGTT, oral glucose tolerance test; OR, odds ratio; Ref., reference group.

6.3 ASSOCIATION OF MEAL FREQUENCIES WITH OBESITY AND MetS TRAITS (*STUDY III*)

The prevalence of overweight and obesity based on BMI was higher in boys than girls (16.3% and 13.4%, respectively; $p = 0.001$), whereas abdominal obesity was more common among girls than boys (13.2% and 10.1%, respectively; $p < 0.001$). Hyperglycaemia, low HDL-cholesterol concentration and hypertension were more prevalent in boys (23.9%, 11.7%, 23.6%) than in girls (7.8%, 3.7%, 4.7%) (all p-values < 0.001) .

Table 7 presents the overall distribution of meal frequency patterns among boys and girls. Boys reported eating five meals per day more often than girls (52.9% and 41.9%, respectively). Approximately one third of both boys and girls were semi-regular eaters, i.e. had breakfast but skipped at least one other meal. Girls (23.9%) were more likely than boys (16.0%) to skip breakfast on weekdays ($p < 0.001$ for meal frequency distribution).

Table 7. Distribution of meal patterns in the NFBC1986 study population

Meal pattern	**Boys**		**Girls**	
	n	%	n	%
Regular meal pattern	**1382**	**52.9**	**1210**	**41.9**
Semi-regular patterns				
Breakfast + dinner + snack + evening snack	100	3.8	95	3.3
Breakfast + lunch + snack + evening snack	74	2.8	136	4.7
Breakfast + lunch + dinner + snack	59	2.3	159	5.5
Breakfast + lunch + dinner + evening snack	426	16.3	375	13.0
Breakfast + lunch + dinner	46	1.8	84	2.9
Breakfast + lunch + evening snack	27	1.0	45	1.5
Breakfast + lunch + snack	2	0.1	21	0.7
Breakfast + dinner + evening snack	54	2.1	31	1.1
Breakfast + dinner + snack	14	0.5	19	0.7
Breakfast + snack + evening snack	6	0.2	8	0.3
Breakfast + lunch	0	0	5	0.2
Breakfast + dinner	3	0.1	11	0.4
Breakfast + evening snack	0	0	1	0.03
Breakfast + snack	1	0.04	0	0
Breakfast + no other meals	1	0.04	0	0
Subtotal	**813**	**31.1**	**990**	**34.3**
Breakfast skipping patterns				
Lunch + dinner + evening snack + snack	229	8.8	272	9.4
Lunch + dinner + evening snack	85	3.2	96	3.3
Lunch + dinner + snack	32	1.2	72	2.5
Lunch + evening snack + snack	16	0.6	65	2.2
Lunch + dinner	15	0.6	54	1.9
Lunch + evening snack	13	0.5	26	0.9
Lunch + snack	2	0.08	12	0.4
Dinner + evening snack + snack	10	0.4	51	1.8
Dinner + evening snack	9	0.3	23	0.8
Dinner + snack	5	0.2	8	0.3
Evening snack + snack	1	0.04	3	0.1
Lunch	0	0	3	0.1
Dinner	2	0.08	5	0.2
Evening snack	0	0	0	0
Snack	0	0	0	0
Subtotal	**419**	**16.0**	**690**	**23.9**
Total	**2614**	**100**	**2890**	**100**

The results of unadjusted analyses (Table 8 and 9) show that the regular five-meal-a-day pattern was associated with reduced risks of overweight/obesity and abdominal obesity among boys and girls, and hypertriglyceridaemia and low HDL-cholesterol concentration among boys. The semi-regular meal pattern, i.e. meal-skipping combined with regular breakfast, was associated with lower risks of abdominal obesity and hypertriglyceridaemia in boys and with hypertension in girls.

Table 8. Unadjusted associations of meal patterns with overweight/obesity and metabolic syndrome traits in boys. Odds ratios and their 95% confidence intervals are presented.

	Boys					
	Overweight/obesity		**Abdominal obesity**		**Hyperglycaemia**	
Meal pattern	n/Total n (%)	OR (95% CI)	n/Total n (%)	OR (95% CI)	n/Total n (%)	OR (95% CI)
Five meals per day including breakfast (regular)	151/1374 (11.0)	**0.39 (0.29, 0.51)**	79/1382 (5.7)	**0.27 (0.20, 0.38)**	302/1302 (23.2)	0.84 (0.65, 1.09)
Four meals or less per day including breakfast (semi-regular)	159/809 (19.7)	0.76 (0.57, 1.01)	99/813 (12.2)	**0.63 (0.45, 0.87)**	168/752 (22.3)	0.80 (0.60, 1.06)
Four meals or less per day without breakfast (breakfast skipping)	100/412 (24.3)	Ref.	75/414 (18.1)	Ref.	103/390 (26.4)	Ref.
	Hypertriglyceridaemia		**Low HDL-cholesterol concentration**		**Hypertension**	
Meal pattern	n/Total n (%)	OR (95% CI)	n/Total n (%)	OR (95% CI)	n/Total n (%)	OR (95% CI)
Five meals per day including breakfast (regular)	35/1313 (2.7)	**0.37 (0.22, 0.61)**	134/1313 (10.2)	**0.65 (0.47, 0.90)**	310/1381 (22.4)	0.84 (0.65, 1.08)
Four meals or less per day including breakfast (semi-regular)	29/765 (3.8)	**0.53 (0.31, 0.90)**	96/765 (12.5)	0.82 (0.58, 1.16)	191/812 (23.5)	0.89 (0.68, 1.17)
Four meals or less per day without breakfast (breakfast skipping)	28/402 (7.0)	Ref.	60/402 (14.9)	Ref.	106/413 (25.7)	Ref.

CI, confidence interval; HDL, high-density lipoprotein; OR, odds ratio; Ref., reference group.

Table 9. Unadjusted associations of meal patterns with overweight/obesity and metabolic syndrome traits in girls. Odds ratios and their 95% confidence intervals are presented.

	Girls					
	Overweight/obesity		**Abdominal obesity**		**Hyperglycaemia**	
Meal pattern	n/Total n (%)	OR (95% CI)	n/Total n (%)	OR (95% CI)	n/Total n (%)	OR (95% CI)
Five meals per day including breakfast (regular)	119/1204 (9.9)	**0.57 (0.43, 0.75)**	120/1210 (9.9)	**0.56 (0.43, 0.74)**	94/1057 (8.9)	1.18 (0.82, 1.70)
Four meals or less per day including breakfast (semi-regular)	140/987 (14.2)	0.86 (0.65, 1.12)	142/990 (14.3)	0.85 (0.65, 1.12)	51/894 (5.7)	0.73 (0.49, 1.10)
Four meals or less per day without breakfast (breakfast skipping)	110/679 (16.2)	Ref.	112/682 (16.4)	Ref.	47/616 (7.6)	Ref.
	Hypertriglyceridaemia		**Low HDL-cholesterol concentration**		**Hypertension**	
Meal pattern	n/Total n (%)	OR (95% CI)	n/Total n (%)	OR (95% CI)	n/Total n (%)	OR (95% CI)
Five meals per day including breakfast (regular)	31/1115 (2.8)	0.72 (0.42, 1.24)	39/1115 (3.5)	0.81 (0.49, 1.34)	60/1209 (5.0)	0.88 (0.58, 1.34)
Four meals or less per day including breakfast (semi-regular)	27/921 (2.9)	0.76 (0.44, 1.33)	35/921 (3.8)	0.88 (0.53, 1.47)	34/989 (3.4)	**0.60 (0.37, 0.96)**
Four meals or less per day without breakfast (breakfast skipping)	24/630 (3.8)	Ref.	27/630 (4.3)	Ref.	38/679 (5.6)	Ref.

CI, confidence interval; HDL, high-density lipoprotein; OR, odds ratio; Ref., reference group.

Tables 10 and 11 show the results of two logistic regression models. After taking into account several early life factors (model I), the five-meal-a-day pattern was associated with lower risks of overweight/obesity and abdominal obesity in both genders and hypertriglyceridaemia in boys. In girls, the semi-regular meal pattern was associated with a lower risk of hypertension.

After adjustment for variables from the 16-year follow-up data (model II), the risk of overweight/obesity remained significantly lower among the adolescents who ate five meals a day. Metabolic syndrome components were also adjusted for body mass index. In boys, both regular five-meal-a-day pattern and semi-regular pattern were associated with a decreased risk of abdominal obesity.

Table 10. Associations between meal patterns and overweight/obesity and metabolic syndrome traits adjusted for early-life factors (model I) later childhood factors (model II) in boys. Odds ratios and their 95% confidence intervals are presented.

	Overweight/obesity		**Abdominal obesity**		**Hyperglycaemia**	
	Model I[a]	Model II[b]	Model I[a]	Model II[c]	Model I[a]	Model II[c]
Meal pattern	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Five meals per day including breakfast (regular)	**0.47 (0.34, 0.65)**	**0.41 (0.29, 0.58)**	**0.32 (0.22, 0.48)**	**0.32 (0.16, 0.63)**	0.92 (0.68, 1.24)	0.90 (0.65, 1.25)
Four meals or less per day including breakfast (semi-regular)	0.84 (0.60, 1.17)	0.77 (0.55, 1.09)	0.71 (0.48, 1.03)	**0.45 (0.23, 0.88)**	0.88 (0.63, 1.21)	0.81 (0.57, 1.15)
Four meals or less per day without breakfast (breakfast skipping)	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.

	Hypertriglyceridaemia		**Low HDL-cholesterol concentration**		**Hypertension**	
	Model I[a]	Model II[c]	Model I[a]	Model II[c]	Model I[a]	Model II[c]
Meal pattern	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Five meals per day including breakfast (regular)	**0.48 (0.26, 0.89)**	0.56 (0.28, 1.15)	0.74 (0.50, 1.08)	0.86 (0.57, 1.30)	0.96 (0.71, 1.29)	0.93 (0.67, 1.29)
Four meals or less per day including breakfast (semi-regular)	0.71 (0.38, 1.33)	0.59 (0.29, 1.22)	0.84 (0.56, 1.27)	0.81 (0.53, 1.26)	1.00 (0.73, 1.36)	1.00 (0.71, 1.40)
Four meals or less per day without breakfast (breakfast skipping)	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.

[a]Adjusted for birth weight for gestational age, maternal weight gain during the first 20 weeks of gestation, maternal pre-pregnancy body mass index, maternal level of education before pregnancy, maternal smoking during pregnancy, maternal glucose metabolism and parity.
[b]Adjusted for tobacco use, sleep duration, physical activity, sedentary time, Tanner stage of puberty, and maternal and paternal education level.
[c]Adjusted for tobacco use, sleep duration, physical activity, sedentary time, Tanner stage of puberty, maternal and paternal education level, and body mass index.
CI, confidence interval; HDL, high-density lipoprotein; OR, odds ratio; Ref., reference group.

Table 11. Associations between meal patterns and overweight/obesity and metabolic syndrome traits adjusted for early-life factors (model I) later childhood factors (model II) in girls. Odds ratios and their 95% confidence intervals are presented.

	Overweight/obesity		**Abdominal obesity**		**Hyperglycaemia**	
	Model I[a]	Model II[b]	Model I[a]	Model II[c]	Model I[a]	Model II[c]
Meal pattern	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Five meals per day including breakfast (regular)	**0.57 (0.41, 0.79)**	**0.63 (0.45, 0.89)**	**0.54 (0.39, 0.75)**	0.71 (0.42, 1.19)	1.18 (0.78, 1.80)	1.25 (0.78, 2.00)
Four meals or less per day including breakfast (semi-regular)	0.83 (0.61, 1.14)	0.89 (0.64, 1.24)	0.88 (0.64, 1.20)	0.92 (0.55, 1.54)	0.79 (0.50, 1.25)	0.87 (0.52, 1.43)
Four meals or less per day without breakfast (breakfast skipping)	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.

	Hypertriglyceridaemia		**Low HDL-cholesterol concentration**		**Hypertension**	
	Model I[a]	Model II[c]	Model I[a]	Model II[c]	Model I[a]	Model II[c]
Meal pattern	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Five meals per day including breakfast (regular)	0.70 (0.38, 1.28)	0.93 (0.46, 1.85)	0.81 (0.46, 1.41)	1.13 (0.61, 2.12)	0.84 (0.53, 1.33)	0.98 (0.59, 1.63)
Four meals or less per day including breakfast (semi-regular)	0.59 (0.31, 1.13)	1.04 (0.52, 2.07)	0.88 (0.50, 1.55)	1.09 (0.58, 2.06)	**0.55 (0.33, 0.93)**	0.65 (0.37, 1.13)
Four meals or less per day without breakfast (breakfast skipping)	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.

[a]Adjusted for birth weight for gestational age, maternal weight gain during the first 20 weeks of gestation, maternal pre-pregnancy body mass index, maternal level of education before pregnancy, maternal smoking during pregnancy, maternal glucose metabolism and parity.
[b]Adjusted for tobacco use, sleep duration, physical activity, sedentary time, Tanner stage of puberty, and maternal and paternal education level.
[c]Adjusted for tobacco use, sleep duration, physical activity, sedentary time, Tanner stage of puberty, maternal and paternal education level, and body mass index.
CI, confidence interval; HDL, high-density lipoprotein; OR, odds ratio; Ref., reference group.

6.4 INTERACTION EFFECTS OF MEAL FREQUENCIES AND GENETIC PREDISPOSITION ON BMI (*STUDY IV*)

Sample characteristics

The genotypic distributions of all eight polymorphisms included in the GRS were in Hardy-Weinberg equilibrium ($p > 0.05$). In addition, all SNPs had call rates > 95% and minor allele frequencies ≥ 0.16.

Among the whole population, the mean BMI was 21.2 (SD 3.4) kg/m². For regular eaters, the mean BMI was 0.9 kg/m² lower than the corresponding value for meal skippers. Each additional BMI-increasing allele in the GRS was associated with a 0.21 kg/m² increase in BMI, corresponding to a 0.61 kg increase in body weight for a person of 170 cm height (Figure 4). For the individuals with a high genetic risk based on the GRS, the mean BMI was 0.7 units greater than that for those belonging to the low-risk group. The carriers of two risk alleles in *FTO* rs1421085 had an increased BMI (21.7 [95% CI 21.5, 22.0] kg/m²) compared with individuals with zero or one risk allele (20.9 [95% CI 20.8, 21.1] kg/m² and 21.2 [95% CI 21.0, 21.3] kg/m², respectively). Similarly, the carriers of both of the risk-conferring alleles of rs17782313 at the *MC4R* locus had a greater BMI (22.2 [95% CI 21.6, 22.9] kg/m²) compared with the other two genotypes (TT: 21.1 [95% CI 21.0, 21.2] kg/m² and CT: 21.3 [95% CI 21.1, 21.5] kg/m²). Per-allele effects were 0.36 [95% CI 0.22, 0.50] kg/m² for the *FTO* variant and 0.32 [95% CI 0.14, 0.50] kg/m² for the *MC4R* variant. There was no association between the two meal patterns and GRS, *FTO* rs1421085 or *MC4R* rs17782313 (all *p*-values > *0.05*).

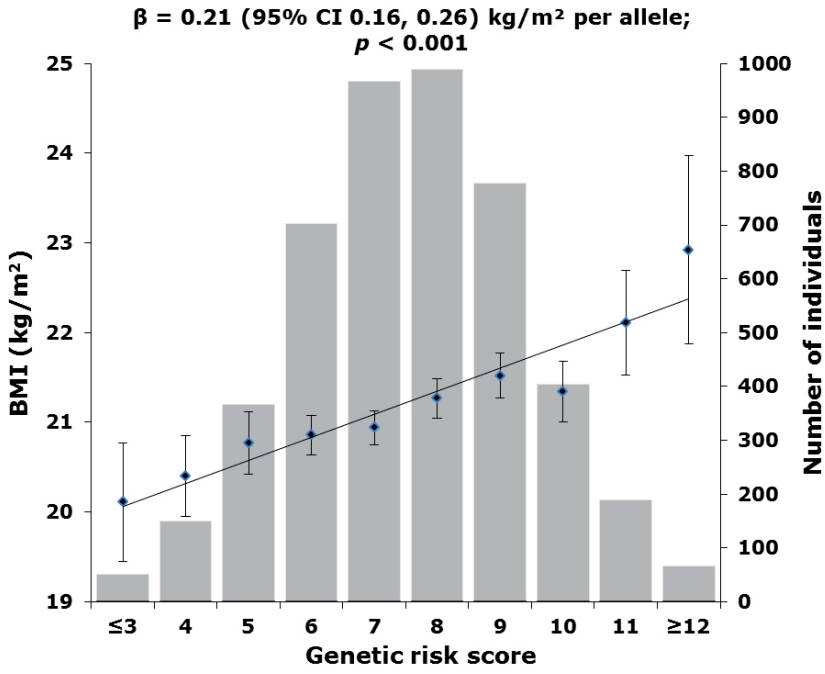

Figure 4. Distribution and cumulative effect of the genetic risk score (adjusted for gender and stage of puberty) on body mass index in the NFBC1986 (n = 4664)

Interaction analyses

Examination of the effect of GRS on BMI separately for the two meal patterns showed effect modification by meal frequency: in meal skippers, the per-allele effect was elevated to 0.27 kg/m^2 (0.78 kg), whereas in regular eaters it was attenuated to 0.15 kg/m^2 (0.43 kg) ($p_{interaction}$ = 0.020). Furthermore, by using the GRS as a dichotomous variable and comparing high- and low-risk groups (Figure 5A), a significant modifying effect of meal frequency on the association between genetic risk and BMI was observed ($p_{interaction}$ = 0.003). Interactions of meal frequencies with *FTO* rs1421085 and *MC4R* rs17782313 genotypes were analysed with an additive model of inheritance. The per-allele effect of the *FTO* variant was 0.24 kg/m^2 (0.78 kg) for regular eaters and 0.46 (1.33 kg) for meal skippers but the interaction was non-significant ($p_{interaction}$ = 0.288). Nevertheless, gender-stratified analysis showed that the interaction between the *FTO* variant and meal frequencies on BMI was significant in boys (Figure 5B), but not in girls (Figure 5C). The per-allele effect of the *MC4R* variant was 0.18 kg/m^2 (0.52 kg) for regular eaters and 0.47 kg/m^2 (1.36 kg) for meal skippers ($p_{interaction}$ = 0.016, Figure 5D).

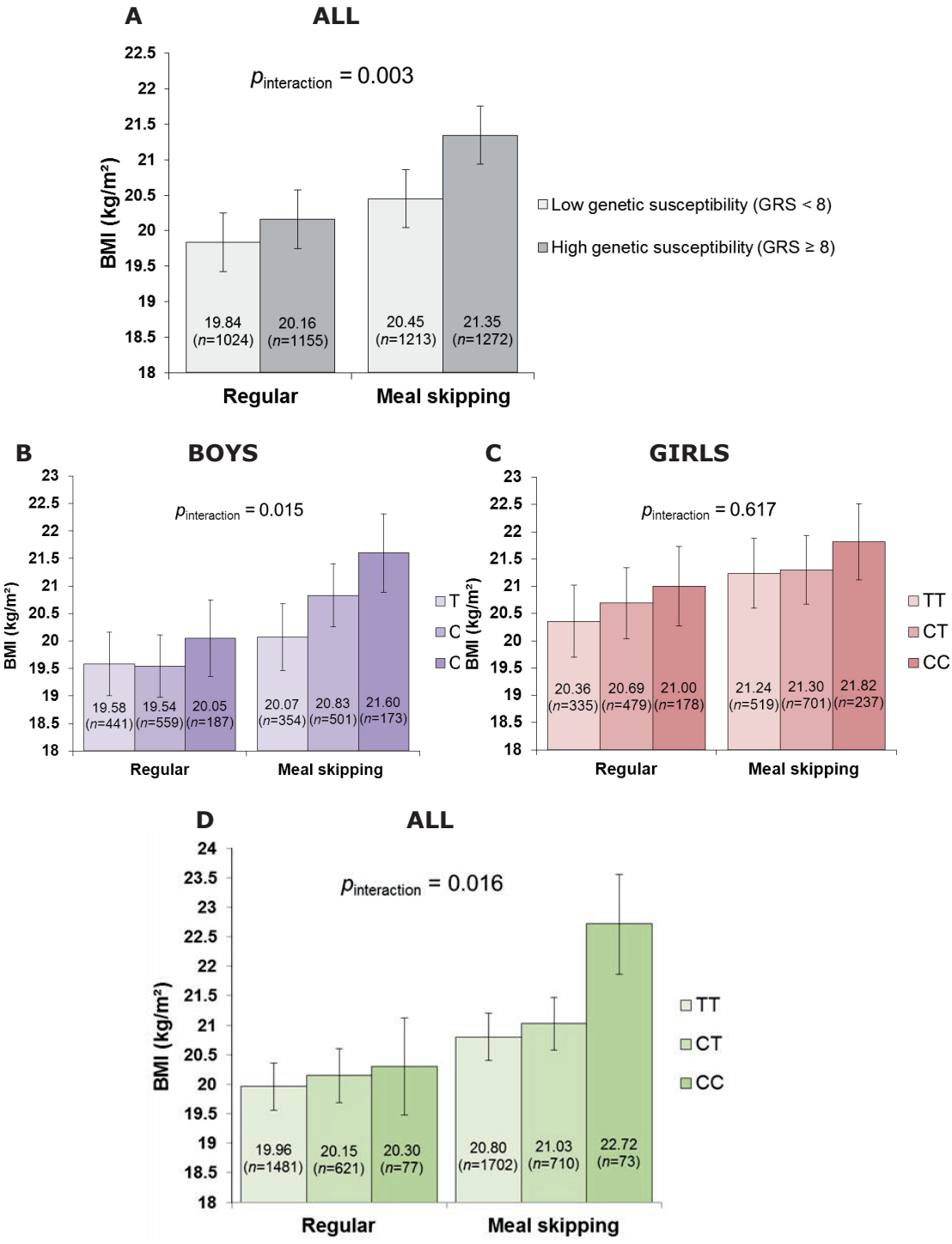

Figure 5. Interaction between meal frequency patterns and (A) genetic risk score (GRS), *FTO* rs1421085 genotypes for boys (B) and girls (C), and (D) *MC4R* rs17782313 genotypes on body mass index (mean BMI values with 95% confidence interval error bars).

7 Discussion

7.1 STUDY POPULATION AND DATA QUALITY

A major strength of this study series is the large general population-based sample and prospective data collection with exceptionally high follow-up participation rates. The participants were born in the same geographic region during the same time period and were similarly followed-up. Longitudinal data collected from pre-pregnancy to adolescence was utilised in *Studies I-III* while in *Study IV*, only cross-sectional data were analysed.

In general, people willing to participate in a cohort study might be more interested in health than the average individual and may thus differ from the general population in health behaviours, including dietary practices (Freudenheim 1999). The high retention rate in the 16-year follow-up (participation rates 74-80%) reduced potential selection bias (Greenland 1977). On the grounds of multidisciplinary data collection in the NFBC1986, it is also appropriate to exclude self-selection bias arising from a particular study question. It is possible however, that the study participation rate for overweight adolescents was lower than for normal weight adolescents, which might dilute the observed associations. The question of potential selection bias is an important issue and previously, Kapi and co-workers (2007) undertook the analysis of differences between initial and follow-up study populations of the NFBC1986 and found the latter to be a representative sample of the original cohort.

In the NFBC1986, anthropometrics of adolescents were measured by trained nurses using a standardised procedure and ongoing quality control. Although less easily obtained and more time-consuming, direct measurements are preferred over self-reports for their accuracy (Sherry et al. 2007). For instance, in Greek schoolchildren, the prevalence of obesity more than doubled when using measured instead of self-reported heights and weights (Tokmakidis et al. 2007). While weight and height have demonstrated high reliability and precision in population studies, waist circumference measurements are known to be more prone to subjectivity and between-observer differences (Klipstein-Grobusch et al. 1997; Sicotte et al. 2010).

Parental data, on the other hand, were gathered from self-report questionnaires and could be influenced by measurement error and social desirability bias. Parental pre-pregnancy BMI used in *Studies I-III* was based on recalled height and weight and similarly, data on parental weight and height at 16-year follow-up (*Study I*) were self-reported and given as round figures with no decimal place. As a result of self-reported data, the prevalence of overweight may be underestimated since in general, weight is under-reported and height is over-reported (Connor Gorber et al. 2007; Shields et al. 2008). This would also bias observed associations (risk estimates) towards the null (Jepsen et al. 2004). With respect to the potential recall bias in pre-pregnancy data, it was minimised by a relatively short recall period: the questionnaires to collect information on pregravid weight were given to all mothers at their first antenatal visit (i.e. at 12 weeks' gestation at latest) and they returned them by the 24th week of gestation.

The study population was remarkably homogeneous in terms of ethnicity and thus, population stratification, i.e. genetically heterogeneous subgroups, due to ethnicity was

unlikely to be a problem in the data (Freedman et al. 2004). Due to the fact that virtually all participants were white adolescents of Northern European ancestry, the results may not be generalised to other age or ethnic groups. For other populations with similar ancestral background, however, genome-wide analyses have demonstrated the comparability and generalisability of the findings from the NFBC1986 (Speliotes et al. 2010; International Consortium for Blood Pressure Genome-Wide Association Studies 2011).

Among the 9479 children who were born in the cohort, there were 226 twin individuals and 6 triplet individuals. Although some studies have indicated a possible effect of shared intrauterine conditions on later body size (Muhlhausler et al. 2011), the difference in the mean BMI between singletons and twins in the NFBC1986 was non-significant. Thus, in *Studies I* and *IV* where BMI was the sole dependent variable, the offspring born from multiple gestations were included in the analyses.

An important limitation in this series of studies is the difficulty of establishing causality on the basis of observational data. Cross-sectional designs are inherently susceptible to reverse causality bias since the temporal order of events cannot be determined. Meal skipping has been found to be a popular dieting method among adolescents, especially in girls (Neumark-Sztainer 2000), and thereby the relationship between irregular meal frequencies and increased BMI observed in *Studies III-IV* may be partly due to reverse causation. However, according to a study on weight control practices among adolescents in seven countries, skipping meals as a weight control method was equally common among non-overweight and overweight Finnish teens (Ojala et al. 2007). Furthermore, for most adolescents, unhealthy weight control behaviours are counterproductive and lead to weight gain over time (Neumark-Sztainer 2012).

A further limitation of *Studies III* and *IV* is that the meal frequencies were assessed by a self-administered questionnaire with a limited choice of responses. As a result, data were lacking on the composition of the daily meals and the actual number of daily snacks. In addition, there were no previous measures of meal frequency for longitudinal analyses. Regarding further the validity of the dietary assessment, the questionnaire was specially constructed for the 16-year follow-up data collection; however, the fact that the inverse relationship between meal frequency and body weight was already reasonably well established and the results corroborated the existing clinical evidence can be considered as good qualitative support for the validity of the meal frequency assessment (Willett and Lenart 1998).

The IOTF age- and gender-specific BMI cutoffs used in *Studies I-III* are based on data collected in six countries and their appropriateness for defining overweight and obesity has been questioned due to the biological differences existing between populations (Wang 2004). Specifically, the underrepresentation of non-Western populations and the great variations in obesity prevalence in the reference datasets has raised concerns. On the other hand, the IOTF reference is based on large datasets, is linked to adult cutoffs for overweight and obesity which indicate health, is simple to use for children and adolescents alike and is particularly useful for comparing findings across populations as well as for monitoring the global obesity epidemic (Wang 2004). In 2001, Flegal and co-workers compared the prevalence of overweight in US children calculated with three sets of reference BMI values: the growth charts of the Centers for Disease Control and Prevention, the IOTF criteria proposed by Cole and colleagues, and values developed by Must and colleagues. They

found that the methods gave similar but not identical results and concluded that each method had its own advantages and limitations with no method being necessarily superior to the others. For example, the method of Cole and co-workers gave lower prevalence estimates than the other two methods at younger ages and higher prevalence estimates at older ages (Flegal et al. 2001).

7.2 PARENT-OFFSPRING BMI ASSOCIATIONS

In *Study I*, both maternal and paternal BMI before pregnancy predicted offspring BMI at the age of 16 years among intact families. The children whose parents were overweight/obese during the whole 16-year follow-up period were at a strikingly high risk of being overweight/obese. The results emphasise the beneficial effect of avoidance of parental weight gain on the body size of their offspring on the verge of adulthood and highlight the importance of targeting the whole family in preventing excessive weight gain in the offspring. The relevance of the results is the possibility of early detection of individuals at high risk for obesity based on maternal and paternal pre-pregnancy BMI. The strengths of this study were the use of longitudinal data ranging from pre-pregnancy to adolescence and the inclusion of both mothers and fathers in the analyses, allowing for comparisons of effect sizes between parents.

In the NFBC1986, the associations of maternal pre-pregnancy BMI with offspring BMI were not consistently stronger than the associations of paternal pre-pregnancy BMI with offspring BMI. In fact, the odds for overweight related to paternal pre-pregnancy overweight and obesity were stronger for daughters than for sons. These findings are in line with the studies where the associations of maternal and paternal adiposity with offspring adiposity have been reported to be of a similar magnitude (Lake et al. 1997; Davey Smith et al. 2007; Kivimäki et al. 2007; Patel et al. 2011; Fleten et al. 2012; Veena et al. 2013) and where stronger father-offspring associations have been observed (Freeman et al. 2012). Consequently, the findings do not provide support for the intrauterine programming and fetal overnutrition hypotheses (Whitaker and Dietz 1998; Oken and Gillman 2003). Instead, they indicate that shared familial environment and genetic factors explain the maternal-offspring associations. In addition, a recent systematic review (including *Study I*) on the associations between parental pre-pregnancy BMI and offspring BMI concluded that the evidence supporting the fetal overnutrition hypothesis is limited (Patro et al. 2013).

Compared with contemporaneous estimates based on self-reported nationwide data (Kautiainen et al. 2002), the combined prevalence of overweight and obesity in the NFBC1986 study population was lower in boys (15.1% vs. 18.0%) and higher in girls (12.8% vs 8.7%). Nevertheless, the prevalence estimates of overweight and obesity have markedly risen from those reported in 1977 (8.5% in boys and 4.2% in girls at 16 years of age), irrespective of data collection and sampling methods (Kautiainen et al. 2002). Over the 16-year follow-up period in the NFBC1986, the proportion of parents with BMI ≥ 25.0 kg/m^2 increased from 32.3% to 62.3% in fathers and from 16.8% to 43.2% in mothers agreeing well with the observations of the Finnish adult population between 1982 and 1997 reported by Lahti-Koski and colleagues (Lahti-Koski et al. 2000).

Due to the various family structures and for the generalisability of the results, those adolescents not living in intact families were excluded from the analyses. Thus, the situation of youths in one-parent families or stepfamilies was not addressed in this study but this may require further examination. Although the adolescents who self-reportedly were not living with both biological parents were excluded, cases of nonpaternity could not be ruled out. Unrecognised or undeclared nonpaternity in family sample studies could result in an underestimate of the father-offspring association. However, on the basis of relatively high observed father-offspring associations in the NFBC1986 and estimated nonpaternity rates of 2-3% in recent reviews (Voracek et al. 2008), the degree of paternal discrepancy in the analysed data can be presumed to be very low.

7.3 MATERNAL GESTATIONAL HEALTH IN RELATION TO OFFSPRING OBESITY

In *Study II*, maternal weight gain > 7.0 kg (the cutoff value for the highest fourth) during the first half of pregnancy was associated with a nearly 1.5-fold increased risk for BMI-based overweight/obesity and abdominal obesity in adolescent offspring. However, maternal pregravid obesity (BMI ≥ 30 kg/m^2) conferred more than a 4-fold greater risk for both outcomes compared with normal weight mothers. Furthermore, maternal pre-pregnancy overweight (BMI 25.0-29.9 kg/m^2), smoking during pregnancy and a low level of education were associated with an increased risk of adolescent overweight/obesity whereas the offspring of multiparous mothers with four or more previous pregnancies were at a decreased risk of overweight/obesity. Maternal gestational diabetes predicted abdominal obesity but not BMI-based overweight/obesity. The risk for both overall obesity and abdominal obesity was increased in the adolescents whose mothers had risk factors for GDM but were not tested with the OGTT during pregnancy.

These results are in agreement with previous findings which suggest that early gestation is a sensitive period for fetal development and later body size. In fact, Andersen and colleagues reported that GWG in the first and second, but not in the third trimester were positively associated with the offspring BMI at the age of 7 years (Andersen et al. 2011). Margerison-Zilko et al. (2011) also examined trimester-specific associations and found that only the first trimester GWG predicted the BMI of 5-year-old offspring. The long-lasting effects of excessive weight gain in early pregnancy on offspring development could be due to the adverse changes in maternal body composition and metabolism. According to Muscati and colleagues, excessive weight gain during the first 20 weeks of pregnancy predisposed women to high postpartum weight retention, irrespective of the BMI value (Muscati et al. 1996). With respect to the composition and components of GWG, weight gain in the first half of pregnancy is primarily explained by the deposition and expansion of maternal tissues, including fat mass accumulation, whereas weight gains in the second half of pregnancy are mainly due to fetal and placental growth and the accumulation of amniotic fluid (Institute of Medicine 2009).

The other observed associations involving maternal obesity, smoking and level of education, may be explained by several pathways that reflect the multi-factorial nature of obesity. The offspring of obese mothers may be genetically predisposed toward obesity and

are likely to adopt their mother's dietary and other lifestyle habits, resulting in weight gain. Offspring of smoking mothers have been found to have a lower birth weight (Rantakallio 1978; Kramer 1987; Power and Jefferis 2002) and may be "programmed" to the unfavourable hormonal changes occurring during gestation which associate with fat distribution and insulin metabolism later in life (Varvarigou 2010). However, also a birth weight-independent association between maternal smoking and excess weight in childhood has been reported (Gravel et al. 2013). Another potential underlying mechanism could be structural alterations in the brain: prenatal exposure to maternal cigarette smoking was linked to a lower volume of the amygdala which in turn correlated inversely with dietary fat intake (Haghighi et al. 2013). On the other hand, there is evidence indicating that living conditions and lifestyle habits in smoking families, rather than intrauterine exposure to tobacco smoke in itself, might account for the association (Florath et al. 2013). Children of smokers tend to be less physically active and have a poorer-quality diet than children of non-smoking parents (Crawley and While 1996; Burke et al. 1998; Rogers et al. 2003). Compared with mothers with higher education levels, less-educated mothers are more likely to make unhealthy lifestyle choices that favour the development of obesity in their offspring (van der Horst 2007).

Previously, Pirkola et al. (2010) demonstrated that in the NFBC1986 study population, GDM was not independently associated with offspring overweight and abdominal obesity: the risks of offspring overweight and abdominal obesity associated with prenatal exposure to overweight and GDM simultaneously were high but in the offspring of normal-weight women, no statistically significant risks for overweight and abdominal obesity were found to be associated with prenatal exposure to GDM *per se*. Pirkola et al. (2010) and Vääräsmäki et al. (2009) also examined the issue of oral glucose tolerance testing in the NFBC1986 and noted that the OGTT was not conducted according to prevailing guidelines in all women at risk for GDM with overweight being the most often overlooked indication for performing the test. As a result, a substantial number of women were not tested for GDM despite indications. They also speculated that some women with no risk factors for GDM but with the disease may have gone undetected, and the screen-positive group could have included mothers with relatively mild metabolic disturbances. These possible misclassifications of glucose metabolism may have resulted in a dilution of the measure of association between GDM and offspring obesity.

It can be discussed whether offspring birth size should have been included in the analysis. While birth weight is associated with later body size, it is also evidently causally related to GWG. Since birth weight could be seen as a mediator on the causal pathway between GWG and offspring body size, it was omitted from the regression analysis. Recently, Hinkle and co-workers presented evidence that GWG may also have a direct long-term effect on child adiposity, independent of its effect through mechanisms reflected by birth weight (Hinkle et al. 2012).

Although maternal pregravid BMI outweighed the importance of GWG for both overall overweight and abdominal obesity in offspring, efforts to determine whether women with a high rate of gestational weight gain and their children could benefit from intensified dietary and lifestyle counselling should be continued. A modest weight gain in early pregnancy is beneficial, and pregnancy is a period when women are likely to be motivated to make lifestyle changes. Indeed, Doyle and colleagues have argued for the

'antenatal investment hypothesis', i.e. that the antenatal period is the phase when investment in early interventions achieves the highest return. According to their view, promoting parental health is an important investment strategy in efforts to promote child health since it holds the potential to prevent the effect of intergenerational risk factors, including socioeconomic inequalities, on offspring health (Doyle et al. 2009). Thus far, the effect of antenatal dietary and lifestyle interventions on maternal and infant health remains unclear (Campbell et al 2011; Gardner et al. 2011).

In addition to the increased risk of obesity and other long-term disadvantages for the offspring health (Rodriguez et al. 2008; Fraser et al. 2010; Hochner et al. 2012), maternal overweight and obesity in pregnancy predisposes to multiple adverse pregnancy outcomes, including gestational diabetes mellitus and hypertension, pre-eclampsia, thromboembolism, induced labour, caesarean delivery, pre-term birth, stillbirth, postpartum haemorrhage, largeness for gestational age, macrosomia, congenital abnormalities and difficulties in breastfeeding (Robinson et al. 2005; Bhattacharya et al. 2007; Athukorala et al. 2010; McDonald et al. 2010; Flenady et al. 2011; Wojcicki 2011). However, it does seem common that women do not recognise themselves as being overweight or obese and this also may contribute to an underestimation of associated risks (Callaway et al. 2009). Raising awareness of negative weight-related maternal and offspring outcomes is likely to be a vitally important component in efforts to reduce these health hazards. In a recent study, Berge and colleagues found the health promoting behaviours and attitudes of 'significant others', e.g. boyfriend/girlfriend or partner, to be positively associated with health behaviours in young adult women and men, and that this could reduce the likelihood of young women becoming overweight and obese. Thus, involving the partner in a health behaviour change could be an important strategy in reducing the risk of adverse pregnancy outcomes related to maternal overweight and obesity (Berge et al. 2012).

7.4 MEAL FREQUENCY AS A PREDICTOR OF OBESITY AND MetS

In *Study III*, the associations of three meal patterns on weekdays (five meals a day including breakfast, four or fewer meals a day including breakfast and four or fewer meals a day not including breakfast) with obesity and metabolic syndrome components were investigated. After adjusting for several prenatal and early-life risk factors related to health outcomes, the regular five-meal-a-day pattern including breakfast remained significantly associated with a decreased risk of overweight/obesity in both genders and abdominal obesity in boys as compared to the breakfast skipping pattern. The semi-regular pattern (i.e. four meals or less per day including breakfast) was associated with lower odds of hypertension in girls and less risk of abdominal obesity in boys, although these associations were not very robust.

Since the association of breakfast consumption as well as higher meal frequency with healthy body weight had been demonstrated in previous studies, the interest was in examining whether the importance of breakfast could be surpassed by that of regular daily meal frequency and whether meal frequencies would also have effect on other metabolic parameters. The results support the hypothesis that the impact of frequent daily meals

outweighs the importance of breakfast and are in line with the previous findings presented by Toschke et al. (2009) and Antonogeorgos et al. (2012) who studied associations between meal frequencies and childhood obesity with special focus on breakfast consumption.

In Western nations, the rise in the prevalence of obesity has coincided with that of irregular meal patterns (Moreno et al. 2010; Patro and Szajewska 2010) and skipping meals is currently a relatively common behaviour among adolescents (Story et al. 2002). Breakfast is the meal most often skipped and girls are found to be more likely than boys to practice meal-skipping behaviour, as was the case with the NFBC1986 adolescents. The perceived meal-skipping of peers and family members, especially mothers, has been found to promote similar behaviours among adolescents (Pearson et al. 2012). In addition to being a risk factor for obesity, meal skipping has been associated with other negative effects on adolescent health and wellbeing. Meal skipping might predispose to poorer nutrient intake, mental distress, compromised learning and lower academic performance (Rampersaud et al. 2005; Szajewska and Ruszczynski 2010; Veltsista et al. 2010). Since obesity-related behaviours including eating habits seem to track from childhood into adulthood (Mikkilä et al. 2004; Craigie et al. 2011), a case can be made for nutrition interventions planned to reduce meal skipping among youth.

Based on the literature, the possible mechanisms explaining the association between meal frequency and obesity could lie in the regulation of food intake, thermic effect of food or endocrine responses. In their brief review, Leidy and Campbell (2011) concluded that experimental studies have pointed to significant increases in perceived appetite and reductions in perceived satiety when eliminating one or two meals from the daily diet. On the other hand, the effect of increased eating frequency (> 3 eating occasions a day) on appetite control and food intake seems to be minimal to none: although increased eating frequency led to lower peaks in perceived appetite, satiety, glucose, insulin, ghrelin, and peptide YY responses compared with reduced eating frequency, over the course of the day, no differences in any of these outcomes (i.e. using area under the curve assessments) were observed. However, it is noteworthy that in some experimental studies, eating frequencies have been beyond what could realistically be followed in daily living (Leidy and Campbell 2011). In a cross-over trial in nine lean women, Farshchi and co-workers found that irregular meal frequency led to a reduced postprandial energy expenditure which could predispose to weight gain in the long term (Farshchi et al. 2004a). In other experimental studies in adults, Farshchi et al. (2004b) and Carlson et al. (2007) described the unfavourable effects of reduced meal frequency on postprandial insulin responses and plasma glucose concentrations. Koletzko and Toschke (2010) have even suggested that in the association between meal frequency and childhood obesity, energy intake might be unimportant and consider the effects on endocrine regulation as a more plausible explanation.

Thus, the evidence of explanatory biological mechanisms promoting positive energy balance and weight gain among meal skippers is still limited and conflicting, including the role of energy intake. In several previous studies, breakfast skipping has been associated with lower total daily intakes of energy compared with breakfast consumption (Nicklas et al. 1993; Nicklas et al. 2000; Berkey et al. 2003; Sjöberg et al. 2003; Rampersaud et al. 2005) suggesting that breakfast skippers do not compensate for the caloric deficit at other meals. It has been proposed that the inverse association between eating frequency and obesity is

due to underreporting of eating occasions concurrent with underestimation of energy intake, and by taking into account implausible energy reporting, the association becomes positive (McCrory et al. 2011).

Since food records were not collected in the NFBC1986, there was no measure of dietary energy intake available to permit statistical adjustment. On the other hand, the accuracy of estimates of energy intake based on food records is known to be compromised by misreporting and the findings may also be biased by reverse causality. In a literature review of 28 articles (Forrestal 2011), approximately half of children and adolescents were classified as misreporters, including both over- and underreporting. According to Lioret and colleagues, the rate of underreporting in 11-17 year-old French adolescents based on 7-day diet records was 26%. Underreporting was associated with several characteristics related to weight status, diet and lifestyle, such as being overweight, skipping meals and a wish to weigh less (Lioret et al. 2011). Further, Sichert-Hellert and colleagues observed that 12% of males and 20% of females aged 14-18 years underreported their food intakes. They also found differences between underreporters and plausible reporters related to diet or dietary recording behaviour and concluded that the simple exclusion of underreporters was not sufficient to ensure validity in dietary studies (Sichert-Hellert et al. 1998).

While the role of energy intake is under debate, it has also been postulated that the positive energy balance and excess weight among breakfast skippers is partly explained by lower levels of engagement in physical activity (Aarnio et al. 2002; Cohen et al. 2003; Keski-Rahkonen et al. 2003; Rampersaud et al. 2005). In the present study, energy balance was taken into account in the analysis by adjusting for sedentary behaviour and leisure-time physical activity.

Meal frequencies were not found to be robustly associated with the features of metabolic syndrome except for the association between the five-meal pattern and the abdominal obesity in boys. The prevalence of MetS in NFBC1986 adolescents was 3.3% in boys and 1.0% in girls. In contrast, in a study of Finnish 45-54 year-old adults conducted around the time of the NFBC data collection, the prevalence of MetS according to the IDF definition was 47.1% in men and 36.9% in women (Hu et al. 2008). Possibly due to the low prevalence of individual MetS traits, some of the associations between meal patterns and metabolic variables were attenuated and not statistically significant after the adjustments despite the large sample size. In addition, the body mass index was a plausible confounder of the relationship between meal patterns and MetS traits. Alternatively, MetS components could have been treated as continuous variables in the analyses. In fact, it has been argued that the dichotomous approach is statistically less sensitive and more prone to errors, especially when the prevalence rate is low (Ragland 1992). Previously, it was demonstrated that in the NFBC1986, the IDF paediatric definition of MetS yielded a higher prevalence estimate (2.4%) than the adult definition (1.7%); however, further large-scale longitudinal research is required to assess the best method for defining MetS among adolescents (Pirkola et al. 2008). Also for adults, there is still a need to develop uniform, universally acceptable criteria that enables comparing study results and accurately identifies individuals at risk for cardiovascular diseases and type 2 diabetes (Kassi et al. 2011).

7.5 OBESITY-SUSCEPTIBILITY VARIANTS AND GENE-DIET INTERACTIONS

While the association between meal frequencies and obesity has been relatively extensively studied, *Study IV* is the first of the studies on gene-environment interactions to consider the combined effect of meal frequencies and common genetic variants on body mass index. In *Study IV*, the regular five-meal pattern was found to attenuate the genetic predisposition to increased BMI in adolescence in terms of both single gene variants, i.e. *FTO* rs1421085 and *MC4R* rs17782313, and a multiple-locus indicator, i.e. a genetic risk score based on the number of BMI-increasing alleles across eight obesity-susceptibility loci. However, for the *FTO* rs1421085 variant, significant interaction effects were observed only in boys.

In NFBC1986 data, meal frequencies were similarly distributed across the genotypes and thereby were independent. Nonetheless, food preferences and habitual dietary intakes seem to have both environmental and genetic components (Keller et al. 2002; Hasselbalch et al. 2008) and there is some evidence to suggest that there are genetic influences also on meal frequencies. De Castro (1993) estimated that genetic differences accounted for 44% of the variance in meal frequency which corresponded to the observation that genetic variation explained 20-50% of the variation in dietary traits in twins (Hasselbalch 2010). In an ethnically diverse sample of overweight and obese adults with type 2 diabetes, the risk allele at *FTO* rs1421085 predicted more eating episodes per day (McCaffery et al. 2012); per-allele effect was 0.109 ± 0.038 (β ± SE) eating occasions. The generalisability of this finding is limited by the characteristics of the study population (a multiethnic sample excluding non-obese individuals).

The effect sizes of the obesity-susceptibility SNPs in *Study IV* were comparable to previous reports on polymorphisms. The largest per-allele effects were seen for the *FTO* and *MC4R* variants; for the other SNPs, the associations with BMI were modest. Regarding the predictive value of obesity-related SNPs in estimating the risk of child and adolescent obesity, Morandi and co-workers showed using NFBC1986 data that traditional risk factors such as parental BMI, birth weight, maternal occupation and GWG formed a valid tool to discriminate newborns at risk for obesity, whereas the predictive accuracy of common genetic variants was low (Morandi et al. 2012).

All in all, this study adds to the still sparse knowledge on gene-diet interactions (Papoutsakis and Dedoussis 2007). To date, only three genes detected by GWAS - *FTO*, *MC4R*, and Niemann-Pick C1 (*NPC1*) - have been shown to interact with nutritional components and promote obesity at an early age; these genes interact with a high-fat diet to promote early-onset or childhood obesity (Garver 2011). In the present study, the five-meal pattern - breakfast, lunch, dinner and two snacks - reduced BMI in genetically predisposed adolescents down to the level of those with a lower genetic risk for obesity whereas among irregular eaters, a significant difference was detected in BMI due to a different genetic background.

8 Conclusions

Undoubtedly, the most effective means of curbing the globally growing problem of obesity is to focus efforts on prevention instead of treatment. Fortunately, the risk factors for overweight and obesity are modifiable and there are numerous paths leading to obesity prevention in children and adolescents; one of those could be promoting regular meal frequency. In the present work, the adolescents who ate five meals on weekdays were found to be at a decreased risk for being overweight and obese. Furthermore, an attenuating effect was demonstrated for the five-meal pattern to influence obesity-predisposing genetic factors.

In addition to being a risk factor for obesity, meal skipping has been associated with several other negative effects on adolescent wellbeing. Since meal skipping is a relatively common behaviour in adolescents and childhood eating habits seem to track into adulthood, interventions aimed at promoting regular meal frequency among adolescents could have a significant impact on public health. The example of peers and family members, especially mothers, has been found to predispose to similar behaviour among adolescents and could be important in establishing healthy dietary habits.

Further research is needed to clarify the biological mechanisms that explain the observed inverse association between meal frequency and obesity. Despite a number of experimental studies conducted to address the issue, the mechanism accounting for the effect of meal patterns on BMI remains elusive. However, there are certain methodological issues which still need to be overcome. First, meal skipping might be used as a method for weight control which complicates assessment of the temporal relationship between increased BMI and irregular meal frequencies. Moreover, dietary underreporting has been postulated to explain the association between higher BMI and lower number of daily meals. Considering the energy balance theory, health benefits from the consumption of multiple meals should ultimately depend on the amount of energy consumed instead of the regularity of eating occasions.

Detection of excessive weight gain early in its progression is a key to lowering the incidence rates of overweight and obesity and in this effort, the role of parents and caregivers is critical. Alarmingly, there is a large body of high quality and consistent evidence demonstrating that only a minority of parents of obese children and adolescents recognise their sons and daughters as being obese (Parry et al. 2008). Here, the risk for adolescent obesity was associated with increased maternal and paternal pre-pregnancy BMI and high maternal gestational weight gain. Thus, the benefits of antenatal dietary and lifestyle counselling directed at parents should be further explored in well-designed, randomised clinical trials.

Future studies on gene-lifestyle interactions on weight development are also warranted. Although environmental factors seem to outweigh common genetic variants in their predictive value in estimating the risk of child and adolescent obesity, there are individuals with multiple genetic (low-risk) variants or rare (high-risk) mutations that predispose them to excessive weight gain already in youth. Therefore, in view of the current obesogenic environment and the possibly still rising obesity rates, it is very

important to clarify how environmental factors and lifestyle can modify the impact of genetic factors on the risk of obesity.

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Anne Jääskeläinen

Epidemiologic Studies on Overweight and Obesity in Adolescents

The Role of Early-Life Risk Factors, Eating Patterns and Common Genetic Variants

This thesis investigated the factors related to adolescent overweight and obesity using data from the prospective, population-based Northern Finland Birth Cohort 1986. The study highlights the importance of parental pre-pregnancy obesity and maternal gestational weight gain as early-life risk factors. A regular five-meal pattern has a protective effect whereas meal skipping exerts a detrimental effect. The study also adds to knowledge of gene-lifestyle interactions; a regular meal pattern can attenuate the impact of common genetic variants on the adolescent body mass index.

UNIVERSITY OF EASTERN FINLAND

Publications of the University of Eastern Finland
Dissertations in Health Sciences

ISBN 978-952-61-1222-0