Department of Public Health
Faculty of Medicine
Doctoral Programme in Population Health
University of Helsinki

OBESITY AND EATING BEHAVIOR PATTERNS:

ASSOCIATIONS AND MEDIATION CONSIDERING GENETIC SUSCEPTIBILITY

Guiomar Masip

DOCTORAL DISSERTATION

To be presented, with the permission of the Faculty of Medicine of the University of Helsinki, for public examination in Lecture Hall 2, Biomedicum, on the 22nd of November 2021, at 12 o'clock noon.

Helsinki 2021

Cover image: Guiomar Masip
Cover layout: Anita Tienhaara

The Faculty of Medicine uses the Urkund system (plagiarism recognition) to examine all doctoral dissertations.

Dissertationes Scholae Doctoralis Ad Sanitatem Investigandam
Universitatis Helsinkiensis ***No. 62/2021***

ISSN 2342-3161 (print)
ISSN 2342-317X (online)
ISBN 978-951-51-7611-0 (print)
ISBN 978-951-51-7612-7 (online)

Unigrafia
Helsinki 2021

Supervised by

Professor Anna Keski-Rahkonen, MD, PhD
Department of Public Health, Faculty of Medicine
University of Helsinki, Finland

Docent Leonie-Helen Bogl, PhD
Department of Epidemiology, Center for Public Health
Medical University of Vienna, Austria
Institute for Molecular Medicine Finland (FIMM)
University of Helsinki, Finland

Professor Karri Silventoinen, PhD
Population Research Unit, Faculty of Social Sciences
University of Helsinki, Finland
Department of Public Health, Faculty of Medicine
University of Helsinki, Finland

Reviewed by

Docent Anu Ruusunen, PhD
Institute of Public Health and Clinical Nutrition
University of Eastern Finland, Finland

Assistant Professor Daiva E. Nielsen, PhD
School of Human Nutrition
McGill University, Canada

Official opponent

Docent Susanna Lehtinen-Jacks, MD, PhD
School of Health Sciences, Faculty of Social Sciences
University of Tampere, Finland
Senior Lecturer, School of Health, Care and Social Welfare,
Division of Public Health
Mälardalen University, Sweden

ABSTRACT

Background: Obesity prevalence has dramatically increased during the past decades and is currently a major global public health challenge. Both genes and environmental factors influence weight gain, but our understanding of how these factors impact body weight is still incomplete. Unhealthy diet is a key risk factor in the development of obesity and eating behaviors have been described as predictors of weight gain. Genes identified so far are likely to influence weight partly through appetite traits, representing one behavioral pathway of the genetic susceptibility to obesity. However, some genes are expressed in the adipose tissue, suggesting that there might be other pathways that could lead to weight gain and increased appetite in genetically susceptible individuals.

Aims: This dissertation aims to 1) examine whether a diet quality score derived from a food frequency questionnaire is a valid brief instrument to estimate diet quality by comparing it with obesity measures, nutrient intakes and eating styles (eating behaviors and dietary patterns) (Study I); 2) examine whether eating behavior patterns (diet quality, eating behaviors and dietary patterns) are related to obesity measures in a cross-sectional setting of young adults (Study II) and a prospective setting of children (III); and 3) examine the relationship between genetic susceptibility to obesity, eating behaviors and obesity cross-sectionally in adulthood (Study II) and longitudinally in childhood (Study III).

Materials and methods: This thesis was based on data from the FinnTwin16 study (FT16) at wave 5 (n = 4,407), a representative national longitudinal cohort of young adult Finnish twins (Studies I and II), and the IDEFICS/I.Family cohort (n = 21,293), a European multicenter study of children and adolescents (Study III). Both datasets include obesity measures [body mass index (BMI) and waist circumference], eating-related traits questionnaires (eating behaviors, dietary patterns, food frequency questionnaires, and food diaries), and family-level factors. For 1,055 twin individuals and 2,656 children with genome-wide data (Studies II and III, respectively), two polygenic risk scores for BMI were constructed using ~1 million (Study II) and 2.1 million (Study III) single nucleotide polymorphisms irrespective of genome-wide significance. Linear regression models and logistic regression models were calculated to test the associations between the diet quality score and obesity measures and eating styles in Study I (n = 3,592 twin individuals, n = 764 dizygotic twin pairs and n = 430 monozygotic twin pairs). Pearson's correlations were calculated between the diet quality score and nutrient intakes in a subsample of 249 twin individuals and in n = 45 same-sex dizygotic twin pairs and n = 60 monozygotic twin pairs, who provided food diaries in Study I. Principal component analyses were used to derive eating behavior patterns in Studies II and III. To examine the relationship between eating behavior patterns and obesity measures, heritability estimates and Cholesky decomposition were estimated in 1,500 twin pairs (Study II) and cross-lagged path models were calculated in 2,355 children (Study III). Structural equation modeling (Study II) and causal mediation analyses (Study III) were used to identify the potential mediation models between the polygenic risk scores for BMI, eating behavior patterns and obesity measures.

Results: A higher diet quality score was inversely associated with obesity measures, a lower risk of being overweight or abdominally obese and was associated with healthier eating styles (Study I). Further, the diet quality score was associated with key nutrient intakes, such as lower intakes of sucrose and total fat and higher intakes of magnesium; it can thus be used to rank individuals and twins according to diet quality (Study I). Analyses of twin pairs showed that the co-twin with a higher diet quality score tended to have healthier eating styles and nutrient intakes compared to their twin sibling (Study I). Eating behavior patterns were moderately heritable in adults (Study II). The cross-sectional associations between snacking and emotional and external eating behavior patterns with obesity measures were largely explained by genetic factors in young adults (Study II). The prospective associations between parental concern of overeating and obesity measures in children were bi-directional (Study III). The genetic susceptibility to obesity was partly mediated by the snacking eating behavior pattern, and to a lesser extent by the infrequent and unhealthy and the emotional and external eating behavior patterns during adulthood (Study II) and by parental concern of overeating during childhood (Study III). Futhermore, obesity was also tested as a mediator in the association between the polygenic risk score for BMI and parental concern of overeating, and obesity measures partly mediated the prospective association between genetic susceptibility and parental concern of overeating during childhood (Study III).

Conclusions: This thesis provides new evidence that diet quality, eating behaviors and dietary patterns are important determinants of obesity during childhood and young adulthood. It provides a detailed picture of the complex associations between obesity, dietary risk factors and genetic susceptibility, by showing how eating behavior patterns and obesity measures are temporarily associated and share a common genetic liability. Moreover, it confirms that eating behavior patterns partly mediate the genetic susceptibility to obesity in both children and adults. Further, it suggests that there might be pathways other than eating behaviors by which the genetic susceptibility may lead to weight gain and the increased weight might subsequently increase appetite. A better understanding of the pathways that lead to weight gain and their impact and influences on early- and long-term health will be beneficial for future research and health professionals.

CONTENTS

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following publications:

I **Masip G**, Keski-Rahkonen A, Pietiläinen K.H, Kujala U.M, Rottensteiner M, Väisänen K, Kaprio J, Bogl L.H. Development of a Food-Based Diet Quality Score from a Short FFQ and Associations with Obesity Measures, Eating Styles and Nutrient Intakes in Finnish Twins. Nutrients 2019;11(11):2561. doi:10.3390/nu11112561

II **Masip G**, Silventoinen K, Keski-Rahkonen A, Palviainen T, Sipilä P.N, Kaprio J, Bogl L.H. The genetic architecture of the association between eating behaviors and obesity: combining genetic twin modeling and polygenic risk scores. The American Journal of Clinical Nutrition 2020;112(4):956–966. doi:10.1093/ajcn/nqaa181

III **Masip G**, Foraita R, Silventoinen K, Adan R.A.H, Ahrens W, De Henauw S, Hebestreit A, Keski-Rahkonen A, Lissner L, Mehlig K, Molnar D, Moreno L.A, Pigeot I, Russo P, Veidebaum T, Bogl L.H, Kaprio J, on behalf of the IDEFICS/I.Family Consortia. The temporal relationship between parental concern of overeating and childhood obesity considering genetic susceptibility: longitudinal results from the IDEFICS/I.Family Study. Accepted manuscript (International Journal of Behavioral Nutrition and Physical Activity).

In this thesis, Study I refers to publication I, Study II refers to publication II and Study III refers to publication III. The publications are referred to in the text by their Roman numerals.

ABBREVIATIONS

AHEI	Alternate Healthy Eating Index
BMI	Body mass index
BSDS	Baltic Sea Diet Score
CEBQ	Children's Eating Behavior Questionnaire
CFI	Comparative Fit Index
CI	Confidence interval
CLPM	Cross-lagged path model
CMA	Causal Mediation Analyses
DASH	Dietary Approaches to Stop Hypertension
DEBQ	Dutch Eating Behavior Questionnaire
DII	Dietary Inflammatory Index
DQS	Diet Quality Score
DZ	Dizygotic
FFQ	Food Frequency Questionnaire
FT16	FinnTwin16
GWAS	Genome-wide association studies
HbA1c	Glycated hemoglobin
HEI	Healthy Eating Index
HNFI	Healthy Nordic Food Index
IDEFICS	Identification and prevention of Dietary and lifestyle induced health Effects In Children and infantS
ICC	Intraclass correlations
IOTF	International Obesity Task Force
ISCED	International Standard Classification of Education
MET	Metabolic Equivalent Units
MDS	Mediterranean Diet Score
MZ	Monozygotic
RS	Restraint Scale
RMSEA	Root mean square error of approximation
SEM	Structural equation modeling
SNP	Single nucleotide polymorphism
TEFQ	Three Factor Eating Questionnaire
TLI	Tucker-Lewis Index
WC	Waist circumference
WHO	World Health Organization

1. INTRODUCTION

Obesity is a major global public health challenge, and the prevalence has increased dramatically during the past decades. The worldwide prevalence of obesity was 13% in adults and more than 6% of children and adolescents were obese in 2016 (1). Childhood overweight substantially increases the risk of persistent obesity and related metabolic risks in adulthood (2).

Obesity is a complex multifactorial disease that is influenced by genetic and environmental factors (3,4). In addition, it appears that genetic and environmental factors do not act independently but rather interact with each other to influence overweight risk (5,6). Diet is an important determinant of obesity, and the adherence to a healthy dietary pattern can modify the genetic predisposition to obesity (5). Because it is rather complex to measure the whole diet (7) and the adherence to dietary patterns (8), several diet quality scores describing overall nutritional quality and diet variety have been created to estimate diet quality (9). While some studies have reported associations between diet quality and weight gain (10–12), results of the most recent systematic review have shown that associations between diet quality indices and obesity are inconsistent (13). Besides the quality of the diet, eating behaviors and dietary patterns, such as a tendency to emotional eating or skipping meals, are also associated with overweight (14–16).

The advances in genetic studies have extended the number of genetic variants, single nucleotide polymorphisms (SNPs), associated with body mass index (BMI) to 751 (17). However, these SNPs explained only 6% of the BMI variance. Khera et al. suggested the use of a polygenic risk score by incorporating all available information from 2.1 million SNPs irrespective of genome-wide significance, which increased the variance explained of BMI to 23% (18). An important question of interest is the underlying mechanisms through which obesity-associated SNPs might influence body weight.

To date, only a few studies have addressed the relationship between genetic susceptibility to obesity and eating-related traits, such as eating behaviors or diet. Obesity susceptible genes are highly expressed in the central nervous system (19), and some genes are associated with a reduced basal metabolic rate (20). The first genome-wide association study (GWAS)-identified obesity gene, FTO (21), seems to be involved in both metabolic and appetite pathways (22,23). This does not only make it plausible that appetite traits are potential behavioral pathways of the genetic susceptibility to obesity (24), but also suggests that other potential pathways might be involved (25).

Twin studies have shown that genetic factors explain between 40 to 60% of the proportion of the variability in BMI during childhood and about 80% during adulthood (25), and they are furthermore a perfect platform to separate genetic and environmental influences on multiple health behaviors, including food or nutrient intake (26,27). The study of eating behaviors and diet quality is essential for inclusion into twin and family studies to describe family variation and to test the impact of putative environmental influences on body weight (28,29).

In summary, obesity is a highly prevalent disease with far-reaching consequences on society. This thesis examined the complex and temporary associations between eating

behavior patterns, obesity measures and obesity-predisposing genes in child- and adulthood. The combination of the classical twin methods with novel methodologies such as polygenic risk scores in this thesis may help to understand the complex interrelationships between lifestyle, obesity, and genetic susceptibility. By bridging nutritional and genetic research, this thesis has the potential to increase the current knowledge on the genetic susceptibility to obesity by showing that the genes that increase the risk of obesity might partly act through influencing eating behavior patterns (diet quality, eating behaviors and dietary patterns). An increased knowledge of these pathways and their impact and influences on lifelong health will be beneficial for future research.

2. REVIEW OF THE LITERATURE

2.1. OBESITY

2.1.1. DEFINITION

The World Health Organization (WHO) defined obesity as an abnormal or excessive body fat accumulation that may have negative consequences on health (1). Several measures have been proposed to assess body composition, such as body mass index (BMI), waist circumference (WC), waist-to-hip ratio, fat mass index or body fat mass (30), but due to its simplicity and price, the most widely tools for assessing obesity in epidemiological studies and clinical settings are BMI and WC.

The measurement of BMI gives an estimation of the overall adiposity and is calculated as weight in kg divided by squared meters (kg/m^2). The most commonly used reference values for BMI are given by the WHO: <18.5 kg/m^2 for underweight, 18.5–24.9 kg/m^2 for normal weight, 25.0–29.9 kg/m^2 for overweight, 30–39.9 kg/m^2 for obesity and >40 kg/m^2 for severe obesity (31).

In children, the challenge is how to adjust BMI based on their age and sex. Several growth curves have been created to categorize obesity in early ages, the most commonly used are the WHO (32) and the International Obesity Task Force (IOTF) curves (33). In children 5 to 18 years old, WHO cut-off points for obesity and severe obesity are BMI-for-age >2 standard deviations and >3 standard deviations above the median of WHO Child Growth Standards, respectively. In children below 5 years old, the cut-off point for obesity is BMI-for-age >3 standard deviations above the median of WHO Child Growth Standards (32). There are no WHO reference values for categorizing severe obesity in children younger than 5 years old. The IOTF created international age- and sex-specific cut-off values for BMI, based on the corresponding BMI at the age of 18 years old, BMI >30 kg/m^2 for obesity and >35 kg/m^2 for severe obesity (33).

Because BMI does not provide an accurate measurement of the body fat distribution, WC is used to measure abdominal fat distribution (34) and to assess abdominal obesity (35). WC is associated with a higher cardiometabolic risk than BMI (36,37), and it is a driver of metabolic syndrome (38). The WHO has defined abdominal obesity as follows: WC ≥88cm in women and WC ≥102 cm in men (35,36). In children, there is no consensus about the cut-off values for screening for abdominal obesity (39), although WC is a good indicator of central adiposity in this age group (40).

2.1.2. EPIDEMIOLOGY

The obesity epidemic has risen threefold in the last 40 years (1) and caused 3.4 million deaths globally in 2010 (41). Being obese during childhood is associated with a higher risk of being obese in adulthood and an increased risk of comorbidities and premature death in adulthood (42–45).

In 2016, the WHO estimated that 13% of the worldwide adult population were obese and >6% of child and adolescent populations were obese (1). It is estimated that about 18% of the worldwide adult population will be obese by 2025 (46). A pooled population-based study representing 99% of the worldwide population estimated that during the period from 1975 to 2014, the mean BMI increased globally from 21.7 to 24.2 kg/m^2 in men and 22.1 to 24.4 kg/m^2 in women. Reports in children are showing a similar trend: from 1975 to 2016, the percentage of children and adolescents with obesity has dramatically risen from 0.7% to 5.6% in boys and from 0.9% to 7.8% in girls (47).

Nowadays, 53.1% of European adults are overweight or obese (48). In 2016, the overall prevalence of overweight and obesity in European children was 21.3% (49). Obesity is unequally distributed among countries, for example, overweight and obesity in children below 10 years old ranged from >40% in Southern Europe to <10% in Northern Europe (50). In Finland, 26.1% of men and 27.5% of women were obese in 2017 (adults aged ≥30 years) (51); in contrast, 8% of boys and 4% of girls, aged 2 to 16 years old were obese in Finland in 2019 (52).

2.1.3. RISK FACTORS

During the last decades, the environment has become increasingly obesogenic (53). The high availability of energy-dense foods such as sugar-sweetened beverages, fast food and highly processed foods, and low levels of physical activity have contributed to the obesity epidemic (54,55). Among environmental factors, dietary risk factors, such as diet quality and eating behaviors, which are described in more detail in section 2.2, have greatly contributed to the development of obesity. The higher consumption of foods rich in sugar, saturated fat and salt together with larger portion sizes has led to a major risk of weight gain (56–60). Additionally, meal-skipping patterns or overeating behaviors have been linked to obesity (61,62). Physical activity increases the total energy expenditure and decreases body fat deposits (63). Existing research has shown an inverse association between physical activity and obesity (64–66). Previous studies have found that screen time is a better indicator of weight status in children than physical activity (67,68). Other studies have found that physical activity and sedentary behaviors are independently associated with weight (69–71). Nowadays, an increasing number of children and adults are engaging in sedentary patterns in their current life, such as sitting at work or spending a lot of hours in front of a screen. Engaging in sedentary patterns is related to a reduced energy expenditure (72), which could lead to increased weight gain (73).

In westernized countries, the prevalence of obesity is much higher among socioeconomically disadvantaged children and adults (74–79). Individuals from socioeconomically disadvantaged groups tend to have higher energy intakes (80). Moreover, educational level is also associated with higher obesity rates (81,82). A recent study of Danish adults showed that individuals with a high education level had an increased consumption of fruits and vegetables and a decreased consumption of red meat (83). Previous research also revealed differences among sex, showing that women are more likely to be obese compared to men when their socioeconomic status and education level is low (84–86).

Obesity is not only caused by environmental factors, but also by biological factors, in particular genetics. Previous meta-analyses of GWASs have found several genetic variants associated with BMI (17,19). Further, it has been shown that the variability of BMI is explained to a greater degree by genetic factors rather than environmental factors (25). Details on the genetics of obesity are further described in section 2.3. It is well established that there are differences between body fat and regional adipose tissue among men and women (87). Women have higher subcutaneous adipose mass compared to men, who have higher visceral mass (88). These differences can be explained by the mechanisms by which the gonadal hormones and sex chromosomes influence food intake, metabolism and fat accumulation (89). In addition to the already mentioned risk factors, other factors have been suggested to increase the risk of obesity, for example, ethnic differences. In the US, the prevalence of obesity is higher in African Americans as compared to Asians (90).

Various other factors have also been implicated in the development of obesity. These include: lack of sleep (91), smoking (92), psychosocial stress (93), exposure to endocrine disruptors (94) and the gut microbiota (95,96).

2.2. EATING-RELATED TRAITS

Understanding the mechanisms behind food choices is rather complex. Food choice preferences are established early in life and are likely to persist over time (97–99). Food choices are modifiable in response to social and environmental factors (100). Parents have an active role in the development of children's feeding practices and body weight, which may influence children's future food choices and therefore eating behaviors (97,101). A study of monozygotic (MZ) and same-sex dizygotic (DZ) twin pairs of children showed that mothers differed in feeding practices depending on their child's bodyweight status (102).

A number of factors such as cognitive, physiological, socio-cultural, and psychological factors are known to influence food choice (103). According to the food choice process model (104–106) three major components are involved: *life course*, which refers to the personal experiences and events that establish food choice; *influences*, which include ideals, personal factors, resources, social factors, and contexts that shape particular food choices; and *personal system*, which involves the negotiation processes and strategies that form food choices. This model provides evidence of the complex factors involved in the construction of food choices (104–106).

Eating behaviors and dietary patterns are closely related to energy intake and exert their influence based on food choices: what, where, when and how much to eat (107,108). Extensive research has shown that eating behaviors and dietary patterns are associated with diet quality, showing that individuals who engage in harmful eating behaviors and dietary patterns tend to have a poor diet quality (109–114). Particularly, some studies revealed that restraint eating, emotional eating, and external eating are associated with higher intakes of energy-dense foods such as pizza, cakes, chocolate, hamburgers or French fries (113,115–117). In addition, a randomized trial in postmenopausal women showed that behaviors related to binge eating, emotional eating and uncontrolled eating

improved after a weight loss intervention (118). Hence, a simultaneous assessment of eating behaviors, dietary patterns and diet may provide a more comprehensive picture of the whole eating pattern.

2.2.1. DIET QUALITY

The diet quality concept has lately become of great interest and it refers to a healthy and balanced diet rich in nutrients and nutritious foods (119). Dietary quality scores have led to the evaluation of the whole diet into a single unit (120). The assessment of the whole diet is a major challenge in nutritional epidemiology. Health status is influenced by the whole diet rather than a single nutrient (120,121). Studies analyzing the overall diet provide a better insight of foods and nutrient consumption than studies analyzing single foods or nutrients in relation to chronic diseases and health promotion (8,122). Unhealthy diets entail a greater risk of non-communicable diseases and mortality than the combination of unsafe sex, alcohol and drug consumption and smoking simultaneously (123). For this reason, it is essential to find feasible and accurate dietary assessment methods that measure the whole diet in a comprehensive manner.

There are two approaches to analyze the whole dietary intake pattern, *a priori* and *a posteriori* methods. In the *a posteriori* approach, dietary intake patterns are derived from collected data on food groups and/or nutrient intakes (124). In the *a priori* approach, dietary intake patterns are theoretically defined based on dietary recommendations, which are later quantified and included in the dietary assessment method (124). Food frequency questionnaires (FFQs) used to be the primary method of dietary assessment in the *a priori* approach due to their feasibility. FFQs can be self-administered and they represent the usual dietary intake over an extended period of time, usually 12 months (125,126). On the other hand, dietary food records and 24h recalls are the most widely used reference instruments to validate an FFQ. They provide a more detailed description of nutrient and food intakes during a short period of time (125).

Several diet-quality scores have been developed to represent the intake of dietary components which are considered essential in a healthy dietary intake pattern. Diet quality scores reflect the adherence to specific dietary guidelines or patterns and are able to predict the risk of chronic diseases and mortality (119,127). Several dietary quality scores based on long FFQs have been created: the Healthy Eating Index (HEI) (128), the Alternate Healthy Eating Index (AHEI) (129), the Mediterranean Diet Score (MDS) (130), the Dietary Approaches to Stop Hypertension (DASH) (131) or the Dietary Inflammatory Index (DII) (132). In the Nordic countries, some scores such as the Baltic Sea Diet Score (BSDS) (133) or the Healthy Nordic Food Index (HNFI) (134) have also been developed. Most of these diet quality scores have been associated with inflammatory markers, a lower risk of mortality and a decreased risk of non-communicable diseases (132,135–140). Furthermore, many studies have shown that a higher adherence to these diet quality scores are inversely associated with obesity (13,141–143) and weight gain, especially in women and overweight individuals (144). A recent prospective study identified that higher adherence to diet quality measured with the AHEI-2010 and the DASH scores may attenuate the genetic association with weight gain (145). By contrast, some studies have shown inconsistent associations between diet quality and obesity,

especially when the scores were used in target populations different from the original populations by which the scores have been developed (141,146–148).

Questions have been raised about the use of extensive FFQs to assess diet quality. The use of shorter questionnaires increases response rates (149,150). In the clinical setting, brief dietary screening tools, some of them based on short FFQs, have become popular because they can provide a fast, reliable, and efficient measurement of the whole diet (151–153). In contrast to long assessment tools, short FFQs are developed to analyze the quality of the diet (153–155) or specific nutrient intakes (156–158). Previously validated short FFQs are a reasonably valid measurement to rank individuals according to their diet quality and can be easily used in the clinical setting (153,154,159,160).

2.2.2. EATING BEHAVIORS: OVEREATING AND COGNITIVE CONTROL OF EATING

Emotions and stress have been linked to food consumption in complex ways. Previous experimental studies in individuals with obesity have shown that stressful environments may reduce or increase food intakes (161–165). The five-way model of emotion-induced changes in eating proposed by Macht summarizes how emotions influence eating (166) (**Figure 1**). According to the model, high intense emotion levels lead to the suppression of food intake due to incompatible emotions and behaviors, whereas moderate emotion levels increase food intakes, especially palatable foods in emotional and restrained eaters.

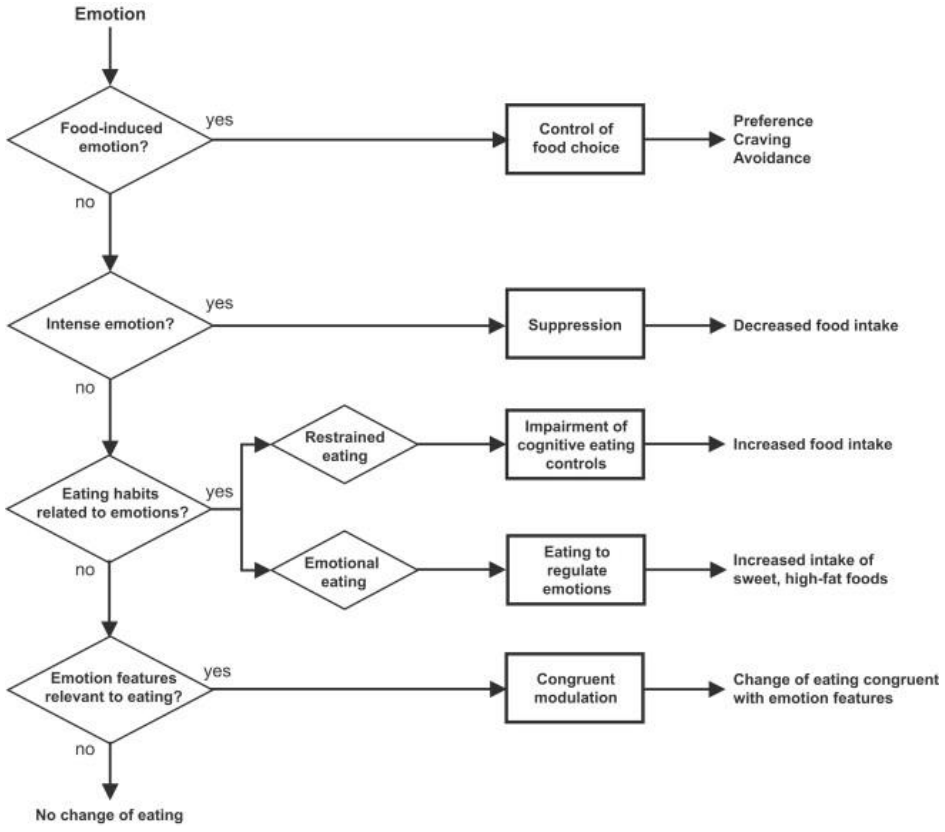


Figure 1 Five-way model of emotion-induced changes in eating (Macht, 2008)

The concepts of emotional eating and restrained eating together with external eating have been widely used to explain overeating and cognitive control of eating. Two behavioral theories have been proposed to explain overeating tendencies, the psychosomatic theory (167,168) and the externality theory (169), which explained the concepts of emotional eating and external eating, respectively. The psychosomatic theory refers to individuals who have a tendency to overeat in response to anxiety and distress (167,168). Experimental research has provided evidence of the consumption of high palatable foods after a negative induced stimulus (e.g, watching a sad movie) in emotional eaters (170). Additionally, emotional eating often co-occurs with external eating (16). The external theory states that individuals with obesity are more prone to external food cues and eat in response to external stimuli, such as sight, smell, or food taste. Furthermore, individuals with obesity are more susceptible to food cues such as hunger or satiety (169,171). An experimental study of adult women from the UK showed that exposure to food cues elicited a larger desire to eat and higher salivation in overweight women compared to normal-weight women (172). Other experimental studies have shown that exposure to food cues (e.g., television food advertisements) was related to a higher food intake, especially of energy-dense foods and beverages in children with overweight and obesity (173–175).

The restrained behavioral theory aims to explain the cognitive control of eating (176,177). This theory is focused on individuals who diet chronically and suppress the signals of hunger and satiety to eat less. These individuals also have episodes of disinhibition (overeating) and binge eating when they are feeling vulnerable. In the classical experiment from Herman and Mack, restrained eaters, measured with a Restraint Scale (RS), were more prone to overeat after the intake of a high-calorie preload (177). This experiment was the precursor of the restrained behavioral theory.

The construct validity of the RS has been seriously criticized because it contains items related to weight fluctuation and concern for dieting, it was based on a multidimensional scale and it only identified those individuals who were unsuccessful dieters (individuals who combine restriction and overeating tendencies). In response to all this criticism, Heatherton et al. argued that the restrained eating concept was based on the assumption that chronic dieters alternate between overeating and undereating (178). The Three Factor Eating Questionnaire (TFEQ) developed by Stunkard and Messick, and the Dutch Eating Behavior Questionnaire (DEBQ) developed by Van Strien, improved the measurement of dietary restraint by incorporating specific subscales that separated overeating tendencies from restrained tendencies and which allowed for the identification of successful and unsuccessful dieters (179,180). Both TFEQ and DEBQ include other constructs as well as the restraint construct. The DEBQ contains scales for emotional eating, external eating, and restrained eating (180), and the TFEQ includes scales for cognitive restraint, disinhibition (emotional and external eating), and hunger (179). The TFEQ was revised by Karlsson et al.; they shortened the questionnaire and changed the scales for uncontrolled eating (related to extreme appetite and loss of control overeating), cognitive restraint and emotional eating (181). The DEBQ has also been adapted for use in children (182,183), but according to Wardle et al.; it was limited to only a few aspects of the whole eating style. Thus, they created the Children's Eating Behavior Questionnaire (CEBQ), which includes questions related to appetitive traits. The CEBQ

provides a broader picture of the whole eating style and includes the following constructs: responsiveness to food; enjoyment of food; satiety responsiveness; slowness in eating; fussiness; emotional overeating; external eating; and desire for drinks (184).

Many previous studies have reported associations between eating behaviors, measured by the mentioned questionnaires, and obesity and weight gain in children and adults (185–190). However, most previous studies did not explicitly examine the temporal direction between eating behaviors and obesity. Prospective studies in infants, below 15 months old, show that appetite traits such as food responsiveness or appetite responsiveness may influence later weight (191–193). Prospective studies that examined the relationship between eating behaviors and obesity traits in older children (4 to 8 year old) indicate that eating behaviors such as emotional overeating are bidirectionally associated with BMI and the effect from BMI to subsequent overeating is stronger than vice versa (194,195). Moreover, in a study of Norwegian children, earlier BMI was strongly associated with later satiety, but food responsiveness was bidirectionally associated with BMI (196). In a study of Dutch adolescents, restrained eating was bidirectionally associated with BMI and the pathway from BMI to subsequent restrained eating was stronger (197). Another study in adolescents and adults showed that higher BMI was associated with a larger increase of cognitive restraint over time (187), and a prospective study of Finnish adults showed that BMI and WC predicted greater changes in restrained eating than the other way around (198). To summarize, these studies suggested that the temporal relationship between eating behaviors and obesity may change across life stages.

2.2.3. DIETARY PATTERNS: SNACKING, REGULAR EATING AND SKIPPING MEALS

Extensive research investigated the role of snacking and meal frequency in the development of weight gain and have yielded mixed results. The hypothesis by Booth suggests that snacking between meals, in particular energy-dense foods and drinks, may contribute to the obesity epidemic (199). Snacking contributes to increased total energy intake, especially when snacks consist of foods rich in sugar, salt, and fat (200–204). Earlier studies have found that a higher eating frequency and a higher snacking frequency were associated with a higher risk of obesity in children and adults (205,206). Overweight and obese individuals tend to consume more snacks than normal-weight individuals (207,208). On the other hand, some studies have found the opposite. In a study of over 3,000 American adults, snacking was associated with a greater energy intake but not with a higher BMI (203). Another study with more than 5,000 adolescents showed that individuals who engaged in the snacking pattern were less likely to be obese compared to those who did not engage in this pattern (209). Further, a smaller prospective study of female adolescents did not find associations between energy-dense foods and BMI over time, with the exception of the consumption of sugar-sweetened beverages, which was associated with BMI (210).

The mechanisms behind the relationship between snacking and the risk of being obese and overweight are still unclear. Previous research has suggested that the quality of the snacks may contribute to the development of weight gain. A recent review highlighted

that snacks rich in nutrients can be beneficial for health, especially in children and elderly population groups (211). The consumption of healthy snacks may contribute to reduced weight gain and may help to control appetite (212). Hence, identifying snacks as harmful or healthy may help to elucidate the relationship between snacking and weight gain. Furthermore, some studies corroborated that snacking consumption was associated with increased meal skipping, especially in adolescents and young adults (61,213,214). A study of Swedish adults showed that a higher meal frequency was related to a better nutrient intake in men and women and a reduced risk of being abdominally obese in men (215). In addition, a meta-analysis of 15 published reports relating meal frequency and weight revealed that increased meal frequency was associated with a reduced fat mass and body fat percentage and higher levels of fat free mass (216). Contrary to these findings, some studies suggested that increasing the number of meals per day may increase hunger and decrease satiety responses (217,218).

Meal skipping has been associated with irregular meal patterns (61). A few experimental studies in adult women have shown that regular eating is associated with greater metabolic effects such as higher postprandial thermogenesis, fasting lipid and lower glucose response (219–221). Interestingly, a recent study suggested that having a regular meal timing may decrease BMI regardless of the number of meals per day (222). Further, this previous study has shown that those who usually have their largest meal at breakfast had a lower BMI compared to those who have their largest meal at lunch or dinner (222). Eating breakfast is an important determinant of a healthy diet (223) and skipping breakfast has been associated with a poor diet quality (112,224). In contrast, other studies have shown that breakfast is unrelated to diet quality (225) and eating breakfast may increase the amount of daily calories, which will lead to major weight gain (226). Despite these contradictory findings, the majority of studies suggest that breakfast consumption is associated with reduced weight gain in children and adults (227–229).

2.3. GENETICS OF OBESITY AND EATING-RELATED TRAITS

Obesity and eating-related traits, such as diet, eating behaviors or dietary patterns, are influenced by genetic and environmental factors (25). Advances in genetic studies have increased our knowledge on common susceptibility genetic loci associated with obesity (17,19). However, the genes identified so far only explain a fraction of the overall BMI variance (6%) (17) compared with quantitative genetic studies (40–90%) (25,230), and the identified genes mostly influence appetite traits (231–233) which are predictors of weight gain.

2.3.1. QUANTITATIVE GENETIC STUDIES

A century ago, Fisher and Wright introduced the concept of heritability (h^2), which refers to the proportion of variation attributable to genetic factors of a particular trait (234,235). The classical twin modelling design relies on twins familial resemblance, MZ and DZ twins share 100% and 50% of their segregating genes, respectively, whereas both types

of twins share 100% of their shared environment and 0% of their unique environment (236).

A large number of twin and family studies have shown that the familial resemblance in BMI is largely due to genetic similarity with higher heritability estimates from twin designs (40–90%) compared to family (24–81%) and adoption designs (20–60%) (25,230). Twin study designs have been widely used to estimate genetic and environmental variation of obesity and eating-related traits without the need of genomic data. Heritability estimates of BMI change across life with estimates of about 60% in infants (1–2 years old), 40% in children (4 years old) and 80% in adults (25). A recent family study has shown that individuals in the 10th percentile of BMI have heritability estimates around 30% whereas individuals in the 90th percentile of BMI have heritability estimates close to 90%, suggesting that heritability estimates of BMI increase with increasing adiposity (237). Heritability estimates for WC have also been reported with an average range from 45 to 82% in twin studies (238–242) and 37 to 62% in family studies (243,244).

Twin and family studies have also tested the heritability estimates of eating-related traits. Appetite traits have been analyzed in infants (<1 year old) showing moderate-to-high heritability estimates (53–84%) (245) and children also showing moderate-to-high heritability estimates (62–75%) (246,247). Findings from adult studies have shown that eating behaviors were partly heritable (26–69%) (248–250). In addition, other studies have shown that basal metabolic rate was partly heritable (40–52%) (251,252) as well as food specific dietary components (>40%) (253).

Twin and family studies are not only useful to test heritability estimates but have also been used to estimate the underlying genetic and environmental factors of two different traits. In a study of young twin children (<1 year old), genetic factors slightly influenced the association between appetite traits and weight gain (254). Further, in a study of young adult twins, genetic factors significantly influenced the associations between BMI and eating behaviors, particularly the association between BMI and emotional eating (248).

2.3.2. MOLECULAR GENETIC STUDIES

Earlier molecular genetic studies of obesity were based on candidate genes and genome-wide linkage approaches (255). The candidate gene approach has been used to analyze the association between obesity traits and genes implicated in the leptin-melanocortin pathway found in animal models or monogenic forms of obesity (256). Genome-wide linkage studies have tested specific chromosomal regions related to common obesity (256). These studies were underpowered, used small samples and findings were difficult to replicate (257,258). With the advance of molecular genetic studies, there has been a shift from linkage and candidate gene approaches toward GWASs. GWASs aim to identify common genetic variants (SNPs) associated with complex traits in the population (259).

GWASs have led to the discovery of common genetic susceptibility loci associated with BMI. In 2007, a GWAS identified the first common genetic variant in the FTO gene which explained 0.34% of the BMI variance (21,260). Thereafter, several GWASs of BMI have been conducted. In 2014, Locke et al. (19) published a large meta-analysis of 340,000

individuals of European ancestry. They identified 97 SNPs associated with BMI, which accounted for <4% of the BMI variance (19). The most recent meta-analysis of GWASs of BMI was performed in 2018 by Yengo et al. (17). In this meta-analysis, ~250,000 individuals of European ancestry were included and they found 941 BMI-associated SNPs, which explained 6% of the BMI variance (17).

Missing heritability

The mismatch between higher heritability estimates and smaller variation explained by genetic variants is known as missing heritability. Much of the speculation about missing heritability from GWAS has focused on the contribution of rare genetic variants, together with SNPs without genome-wide significance (17,261). For example, some genetic variants that are rare elsewhere are ten times as common in Finland (262). Further, it has been suggested that heritability estimates from twin studies might be overestimated when familial resemblance is not properly accounted by non-additive genetic factors and shared environmental factors (263). Polygenic risk scores provide information of all the genetic variants into a single measure that reflects an individual's inherited susceptibility to a disease (18). The use of a polygenic risk score for BMI using all common genetic variants irrespective of genome-wide significance (2.1 million SNPs) increased the explained variance of BMI to 23%. A yet-unpublished study that used rare genetic variants increased the explained variance of BMI to 40% (264), which is close to the variance accounted for from twin and family studies.

In addition, missing heritability might be explained by gene–environmental interactions, particularly in obesity and BMI which vary over time depending on multiple environmental factors (265,266). In a recent study of ~14,000 American adults, the association between obesity susceptibility genes and BMI change was attenuated with an increasing adherence to healthy dietary patterns (145). Furthermore, Loos and Bouchard established four main categories to classify the genetic susceptibility to obesity depending on the obesogenic environment, these categories were: genetic obesity, strong genetic predisposition, slight genetic predisposition, and genetically resistant (**Figure 2**) (267).

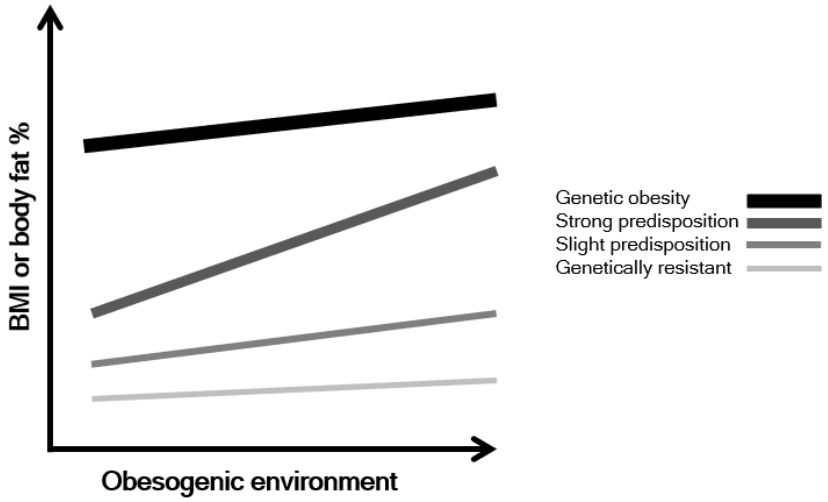


Figure 2 Levels of genetic susceptibility to obesity according to obesogenic conditions (modified from Loos and Bouchard, 2003)

According to these groups, individuals who are genetically obese will be obese independently of the environment, whereas those who are genetically resistant will be lean even after being exposed to an obesogenic environment. Individuals with a predisposition to obesity will become obese in an obesogenic environment but may maintain their normal weight with a healthy lifestyle (267).

Gene–environment interaction and mediation

The mechanisms by which obesity genes express themselves are not clearly understood. The obesity-associated FTO gene has been implicated in metabolic and appetite pathways (22–24). Many studies have provided evidence that some obesity genes are expressed in the brain (19,268,269), particularly in brain areas that are involved in the appetite regulation such as the insula and substantia nigra (270), leading to obesity through the central nervous system (271). Other studies have suggested that obesity genes are expressed in the adipose tissue (272) and are implicated with pathways that control energy intake and energy expenditure (269).

Several interaction and mediation studies have examined the relationship between eating-related traits and the genetics of obesity. Gene–diet interaction studies highlighted that genetic variants may modify changes in adiposity and metabolic responses after being exposed to certain dietary intake patterns (273). Mediation studies have aimed to identify the underlying mechanisms of an observed association (274), which is one of the aims of this thesis; for this reason, special attention is given to mediation studies using polygenic risk scores for BMI (**Table 1**).

Many mediation studies have focused on the role of eating behaviors as mediators of the genetic susceptibility to obesity in children and adults. These studies have shown that the association between a polygenic risk score for BMI, based on <100 SNPs in adults and <35 SNPs in children, with obesity was mediated by eating behaviors (231–233,275,276). In contrast, the findings from a Norwegian study in children showed that appetite traits do not mediate the genetic susceptibility to childhood obesity (277). Two other studies showed that grey matter volume mediated the genetic susceptibility to obesity (278,279). Furthermore, one of these previous studies showed that impulsivity was associated with the polygenic risk score for BMI and was mediated by the grey matter volume, suggesting that there might be other potential mediation pathways by which obesity susceptibility genes may exert their influence (279). One of the earliest mediation studies has shown that rapid growth in early childhood mediated half of the genetic susceptibility to obesity in adults in their 20s, 30s and 40s (280). More recent studies analyzed other mediation pathways such as leptin, education, physical activity, conscientiousness, and depressive symptoms (281,282), providing new evidence of the possible mediation pathways of the genetic susceptibility to obesity. Moreover, in the last two years, a few mediation studies have analyzed the association of the polygenic risk scores for BMI with traits other different than BMI. A study using American and British populations of adults has shown that depressive symptoms were associated with a polygenic risk score for BMI and this association was further mediated by early life stress (283). Results from two studies in adolescents and young adults showed that the polygenic risk score for BMI was associated with eating disorders (284) and weight

Table 1. *Mediation studies using polygenic risk scores for body mass index*

Study	Design and country	Exposure	Outcome	Mediator	Main results
Belsky et al. 2012	38-y prospective study (New Zealand) n = 856 (followed from birth to 38y-old)	PRS_{BMI} 32 SNPs	Obesity outcomes: BMI, triceps and subscapular skinfolds, waist girth and fat mass	Rapid growth phenotypes: birth weight, postnatal growth, adiposity rebound	Adiposity rebound mediated the genetic susceptibility to obesity during the 2nd, 3rd, 4th decades of life and in individuals with chronic obesity; to a weaker extent postnatal growth only mediated the association during adolescence and in individuals with chronic obesity
Llewellyn et al. 2014	Cross-sectional (UK) n = 2,258 children (mean age = 10y-old)	PRS_{BMI} 28 SNPs	BMI and WC SD scores	Satiety responsiveness	Satiety responsiveness mediated the association between the PRS_{BMI} and BMI and WC
Konttinen et al. 2015	Cross-sectional study (Finland) n = 5,863 adults (21-74y-old)	PRS_{BMI} 90 SNPs	BMI and WC	Emotional eating and uncontrolled eating	Emotional and uncontrolled eating mediated the association between the PRS_{BMI} and BMI and WC, respectively
Steinsbekk et al. 2016	4-y prospective study (Norway) n = 652 children (followed at 4, 6 and 8y-old)	PRS_{BMI} 32 SNPs	BMI and body fat	Appetite traits: enjoyment of food, emotional overeating, food responsiveness, satiety responsiveness, and slowness in eating	Appetite traits did not mediate the association between the PRS_{BMI} and weight gain

Table 1 continued

Study	Design and country	Exposure	Outcome	Mediator	Main results
de Lauzon-Guillain et al. 2017	Cross-sectional study of adults (France and UK) n = 5,669 adults (French cohort n = 2,154, mean age = 31y-old; UK cohort n = 3,515 mean age 51y-old)	PRS_{BMI} 27 SNPs (French cohort) and 96 SNPs (UK cohort)	BMI	Cognitive restraint, emotional eating, and uncontrolled eating	Emotional and uncontrolled eating mediated the association between the PRS_{BMI} and BMI, and cognitive restraint mediated the association only in women from the French cohort
Opel et al. 2017	Cross-sectional study of adults (Germany) n = 777 (MNC study n = 330, mean age = 39y-old; BD study n = 347, mean age = 51y-old)	PRS_{BMI} 169,167 SNPs (MNC study) and 172,030 SNPs (BD study)	BMI	Grey matter volume	Grey matter volume mediated the association between PRS_{BMI} and BMI
Jacob et al. 2018	Cross-sectional study of adults (Canada) n = 768 (mean age 44y-old)	PRS_{BMI} 97 SNPs	BMI and WC	Cognitive restraint, disinhibition and susceptibility to hunger	Disinhibition and susceptibility to hunger mediated the association between the PRS_{BMI} and BMI and WC, respectively
Avinun et al. 2019	Cross-sectional study of adults (USA and UK) n = 6,454 (USA cohort n = 524, mean age = 20y-old; UK cohort n = 5,930, mean age = 63y-old)	PRS_{BMI} 386,679 SNPs (USA cohort) and 215,200 SNPs (USA cohort)	Depressive symptoms	Early life stress	Early life stress mediated the association between the PRS_{BMI} and depressive symptoms

Table 1 continued

Study	Design and country	Exposure	Outcome	Mediator	Main results
Barker et al. 2019	Cross-sectional study adolescents (Europe: UK, Germany, France and Ireland) n = 604 (mean age = 19y-old)	PRS_{BMI} and PRS_{ADHD}	BMI and impulsivity	Grey matter	Grey matter volume mediated the association between the PRS_{BMI} and BMI and impulsivity, respectively. Further, grey volume matter also mediated the association between the PRS_{ADHD} and BMI and impulsivity, respectively.
de Lauzon-Guillain et al. 2019	5-y prospective study of children (France) n = 1,142 (followed from birth to 5y-old)	PRS_{BMI} 16 SNPs	z-score BMI	Appetitive traits	Appetite at 2y-old mediated the association between the PRS_{BMI} and BMI from 2 to 5y-old
Fu et al. 2019	Cross-sectional and prospective study of children and adolescents (China) n = 3,211 baseline (6-18y old) and n = 848 10-y follow-up	PRS_{BMI} 6 SNPs (related to leptin)	BMI	Leptin level (sleep duration is used as moderator)	Leptin levels mediated the association between the PRS_{BMI} and baseline and follow-up BMI. Further, sleep duration interacted in this association.
Nagata et al. 2019	Prospective study of young adults (USA) n = 4,397 (wave 1 11-18y-old, wave 2 18-24y-old)	PRS_{BMI} 609,130 SNPs	Weight loss and weight gain behaviors measured at wave 2	BMI measured at wave 1	BMI at wave 1 mediated the association between the PRS_{BMI} and weight loss and weight gain behaviors at wave 2.

Table 1 continued

Study	Design and country	Exposure	Outcome	Mediator	Main results
Abdulkadir et al. 2020	Prospective study of adolescents (UK) n = 8,654 (11-18y-old)	Different PRS_{BMI} for each outcome ranging from 9,075 SNPs to 66,075 SNPs	Eating disorders: Fasting, binge eating, and purging measured at 14, 16 and 18y-old. Thin ideal internalization, body dissatisfaction, restrained eating, emotional eating and external eating measured at 14y-old	z-score BMI measured at 11y-old	z-score BMI mediated the association between the PRS_{BMI} and eating disorders, except for thin ideal internalization
Stephan et al. 2020	Cross-sectional and prospective study of middle-aged and older adults (USA) n = 9,139 (50-107y-old)	PRS_{BMI} 761,985 SNPs and PRS_{WC} 765,699 SNPs	BMI and WC measured at the beginning of the study and 4 years later	Neuroticism, extraversion, openness, agreeableness, conscientiousness, physical activity, depressive symptoms, education and cognition	Education, physical activity, conscientiousness, and depressive symptoms mediated the associations between the PRS_{BMI} and BMI and the PRS_{WC} and WC, respectively. Analyses using BMI and WC measured 4 years later indicated the same mediation patterns.

Abbreviations: attention deficit hyperactivity disorder (ADHD), body mass index (BMI), polygenic risk score (PRS), standard deviation (SD), single nucleotide polymorphism (SNP), waist circumference (WC).

control behaviors (285), and BMI mediated these associations. A recent review suggested that the mechanisms by which obesity-genetic variants express themselves are the key to understanding the biology of obesity (286). More research is needed to analyze the different pathways and elucidate the different mechanisms by which obesity susceptibility genes exert their influence.

2.4. GAPS IN THE PREVIOUS RESEARCH

This literature review described the current knowledge on obesity and eating-related traits (diet quality, eating behaviors and dietary patterns), with a specific focus on their underlying genetic factors. Despite the recent advances in this field, this review acknowledged three major gaps:

1. Diet quality is closely related to eating behaviors and dietary patterns (109–114) and diet quality scores provide a more comprehensive picture of the whole eating pattern. To date, dietary quality scores based on FFQs have been validated with nutrient intake data (125), but they have not yet been compared with eating behaviors, dietary patterns and obesity measures, in particular using the co-twin control design.

2. Genetic factors have been found to influence the association between eating behaviors and BMI in children and adults (248,254), suggesting that they may share the same genetic liability. Previous research did not assess the causal relationship between eating behaviors and obesity, despite the fact that longitudinal studies have shown that eating behaviors and obesity measures are bidirectionally associated (191,192,194–198). Furthermore, these studies have shown that there is always a pathway that is more expressed across different life stages, but research in this area is still scarce.

3. The mechanisms by which obesity susceptibility genes exert their influence are not fully understood. Previous studies have shown that eating behaviors mediated the genetic susceptibility of obesity (231–233,275,276). However, some studies have shown other plausible mediators such as leptin, physical activity, education or depression (281,282) and other studies have analyzed whether obesity measures mediated the association between a polygenic risk score for BMI and eating disorders or eating behaviors (284,285), suggesting that there are different pathways by which obesity susceptibility genes might be expressed.

3. AIMS

This thesis examined the complex interrelationships between eating behavior patterns (diet quality, eating behaviors and dietary patterns), obesity measures and the latest polygenic risk score for BMI and the pathways potentially involved in the development of obesity in the nationwide FinnTwin16 cohort (n ~ 5,600) and the European multicenter study IDEFICS/I.Family (n = 16,000+) cohort. A better understanding of the liability of these pathways will provide targets for future obesity prevention efforts.

The specific aims were:

1. To examine whether a diet quality score derived from a short food frequency questionnaire is a valid instrument to estimate diet quality by comparing it with obesity measures, nutrient intakes and eating behaviors (Study I).

2. To examine whether eating behavior patterns are related to obesity measures in a cross-sectional setting of young adults (Study II) and a prospective setting of children (Study III).

3. To examine the relationship between genetic susceptibility to obesity, eating behavior patterns and obesity cross-sectionally in adulthood (Study II) and longitudinally in children (Study III).

4. METHODS

4.1. STUDY POPULATIONS

To address the aims of this thesis, participants from Studies I and II were identified from the FinnTwin16 (FT16) cohort. In Study I, two subsamples of the FT16 cohort were included: the TwinFat sub-study and the FITFATTWIN sub-study. Participants from Study III were identified from the IDEFICS/I.Family cohort.

4.1.1. THE FINNTWIN16 STUDY

The FT16 study is a population-based cohort aimed to investigate health-related behaviors in twins born between 1975 and 1979 (287). Finnish twins were identified from the Central Population Register of Finland. The FT16 study comprised five study waves when the twins were 16 (wave 1), 17 (wave 2), 18.5 (wave 3), 22–28 (wave 4) and 31–37 (wave 5) years old. Participants from the TwinFat sub-study were invited between 2002–2003, based on their BMI. The TwinFat study aimed to investigate metabolism and obesity and included ~ n = 550 MZ and DZ twins concordant and discordant for BMI (288). The FITFATTWIN sub-study investigated the associations between physical activity and body composition, glucose homeostasis and brain morphology in n = 23 male MZ twin pairs concordant and discordant for physical activity, recruited during 2011–2012 (289).

Studies I and II included data from the latest follow-up (wave 5) based on an internet survey. Of the 6,132 twin individuals that were contacted, 4,407 returned their questionnaire (response rate 72%). Study I was based on the main sample of twins with data on BMI, physical activity (using metabolic equivalent units (MET)), education level, diet quality and eating styles (eating behaviors and dietary patterns) (n = 3,592 twin individuals and 1,194 twin pairs), and a subsample with data from the TwinFat and FITFATTWIN sub-studies which included all twin individuals who returned their food diaries (n = 249 twin individuals and n = 105 twin pairs). In Study II, participants with data on zygosity, BMI, eating styles and diet quality were included (n = 3,977 twin individuals and n = 1,500 twin pairs). In mediation analyses, only twin individuals with genome-wide data were included (n = 949). **Table 2** shows the general characteristics of the main samples and subsamples included in Studies I and II.

Table 2. *Descriptive statistics of the study populations*

	Studies			
	I		II	
	Main Sample	Subsample	Main Sample	Subsample
Study sample (n)	3,592	249	3,977	949
Women/men (n)	2,014/1,578	95/154	2,245/1,732	539/410
Age, mean (SD)	34.1 (1.2)	34.1 (1.1)	34.1 (1.2)	34.0 (1.1)

Table 2 continued

	Studies			
	I		II	
	Main Sample	Subsample	Main Sample	Subsample
BMI, mean (SD)	24.7 (4.2)	25.5 (3.9)	24.8 (4.3)	24.9 (4.6)
WC, mean (SD)[1]	85.7 (13.2)	87.2 (11.6)	86.1 (12.9)	86.4 (13.4)

Abbreviations: body mass index (BMI), waist circumference (WC). Data are presented as means and standard deviations (SD). [1]Sample size is smaller due to missing values.

4.1.2. THE IDEFICS/I.FAMILY STUDY

The IDEFICS/I.Family Study is a Pan-European cohort aimed at investigating eating habits and lifestyle factors of children and adolescents from the following eight countries: Belgium, Cyprus, Estonia, Germany, Hungary, Italy, Spain and Sweden (290). The IDEFICS study (Identification and prevention of Dietary and lifestyle induced health Effects In Children and infantS) started in 2007–2008 when the children were 2–9 years old (wave 1, n = 16,229). The first follow-up was two years later when the children were 4–11 years old (wave 2, n = 13,586). The I.Family study was a longitudinal follow-up of the previous cohort (wave 3, n = 9,639), recruited 6 years later, between 2013–2014 and included 2,521 newly recruited children.

Study III included data from waves 1 to 3. In waves 1 and 2, questionnaires were completed by parents or legal guardians. In wave 3, children ≥12 years old completed the questionnaires by themselves. In Study III, different samples were used according to different inclusion criteria: a) participants with data on eating behaviors and obesity measures in waves 1 and 3 (n = 2,355); b) participants with data on eating behaviors and obesity measures in waves 1, 2 and 3 (n = 1,848); c) participants with genome-wide data, obesity measures at wave 1 and eating behaviors at wave 3 (n = 1,246); and d) participants with genome-wide data, obesity measures at wave 3 and eating behaviors at wave 1 (n = 2,386). **Table 3** shows the general characteristics of the different samples included in Study III.

Table 3. *Descriptive statistics of the study population*

	Samples of Study III						
	a		b			c	d
	Wave 1	Wave 3	Wave 1	Wave 2	Wave 3	Wave 1	Wave 3
Study sample (n)	2,355	2,355	1,848	1,848	1,848	1,246	2,386
Girls/boys (n)	1,124/ 1,231	1,124/ 1,231	884/ 964	884/ 964	884/ 964	618/ 628	1185/ 1201
Age, y, mean (SD)	4.4 (1.0)	10.1 (1.0)	4.4 (1.1)	6.3 (1.1)	10.1 (1.0)	4.5 (1.1)	11.8 (1.8)
z-BMI, mean (SD)	-0.01 (1.0)	0.39 (1.2)	-0.01 (1.1)	0.08 (1.2)	0.36 (1.2)	-0.01 (1.1)	0.44 (1.3)
z-WC, mean (SD)[1]	-0.09 (1.2)	0.69 (1.2)	-0.06 (1.2)	0.29 (1.3)	0.65 (1.2)	-0.10 (1.2)	0.76 (1.3)

Abbreviations: z-score body mass index (z-BMI), z-score waist circumference (z-WC). Data are presented as means and standard deviations (SD). a) participants with data on eating behaviors and obesity measures (waves 1 and 3); b) participants with data on eating behaviors and obesity measures (waves 1, 2 and 3); c) participants with genome-wide data, obesity measures (wave 1) and eating behaviors (wave 3); d) participants with genome-wide data, obesity measures (wave 3) and eating behaviors (wave 1). [1]Sample size is smaller due to missing values.

4.1.3. ETHICAL CONSIDERATIONS

In Studies I and II, written informed consent was obtained from all study participants. Local ethics committees and internal review boards in Finland and the U.S. approved the study protocols of the FT16 study.

In Study III, research ethics committees in each country approved the study. All parents and children ≥12 years old provided written consent for all examinations and/or the collection of samples, subsequent analyses, and storage of personal data and collected samples. The children gave oral consent to the different parts of the examinations.

4.2. MEASUREMENTS

A summary of the measurements in Studies I–III are presented in Table 4.

Table 4. *Measures used in Studies I, II and III*

	Studies		
	I	II	III
Anthropometric assessment			
Body mass index	x	x	x
Waist circumference	x	x	x
Dietary assessment			
Food frequency questionnaire	x	x	x
Food diaries	x		
Eating behaviors and dietary patterns questionnaire	x	x	x
Genetic assessment			
Polygenic risk score for BMI		x	x
Validated zygosity questionnaire	x	x	
Other assessments			
Physical activity	x		x
Education level	x		x
Income level			x
Well-being score			x
Screen time			x
Glycated hemoglobin			x

4.2.1. OBESITY MEASURES

BMI was calculated by using self-reported (Studies I and II) or measured (Study III) height and weight. WC was self-measured (Studies I and II) or measured by research staff (Study III), midway between the lower ribs and the iliac crest in the upright position. Participants who self-measured their WC received instructions and a tape measure by mail. In Study I, participants were categorized as follows: underweight (BMI <18.5 kg/m^2), normal weight (BMI = 18.5–24.9 kg/m^2), overweight (BMI = 25.0–29.9 kg/m^2) and obese (BMI >30 kg/m^2) (31); normal (WC <88 cm for women and <102 cm for men) and abdominal obese (WC >88 cm for women and >102 cm for men) (35,36).

In Study III, BMI z-scores were calculated according to the IOTF growth standards (33) and WC z-scores were calculated according to the IDEFICS reference values (291).

4.2.2. DIETARY ASSESSMENT

Food Frequency Questionnaires

In Studies I and II, diet quality was assessed with a short 14-item food frequency questionnaire (FFQ), from which a diet quality score (DQS) inspired from a short FFQ from Leppälä et al. (155), was calculated according to the Nordic (292) and Finnish (293) nutrition recommendations. The developed DQS included questions about the usual intake of 14 food and beverage items from 13 categories: dark bread, mixed flour bread, white bread, fruits and berries, vegetables, fish, whole grains, fast food, fat-free or reduced-fat milk, sour milk or yogurt, sugar-sweetened soft drinks or juices, energy drinks, butter and margarine and vegetable oil (Appendix 1). Participants were asked to select the answer that best described their overall food and beverage consumption over the previous 12 months with 5 different alternatives: "not at all", "few times per month", "few times per week", "once a day" and "many times per day". For bread consumption, participants were asked about the number of slices they usually consume per day. For each category, 1 point was given if the recommendation was met. The overall DQS ranged from 0 to 12 points and a higher score indicated a better diet quality. In selected analyses from Study I, twin individuals were classified to have lower (0–6 points) or higher (7–12 points) diet quality, and twin pairs were considered discordant for diet quality when the within-pair difference in the DQS was ≥3 points.

In Study III, the consumption of fruits and vegetables was obtained from a validated FFQ, which comprises 43 food items. Parents or caregivers were asked to estimate how often the children usually consumed each of the food items (294).

Food Diaries

In Study I, participants from sub-studies TwinFat and FITFATTWIN completed a 3-day or 4-day food diary, respectively. Participants were instructed to record all foods and beverages that they usually consumed during one weekend day and two or three weekdays, using household measures. The completed food diaries were checked by a researcher or dietitian and corrections and additions were made if needed. Nutrient intakes were computed based on the National Food Composition Database Fineli® (National Institute for Health and Welfare, Nutrition Unit, Helsinki, Finland) using Diet 32 and AivoDiet 2.0.1.2 software (Aivo Finland Oy). Nutrient intakes were calculated as the mean intakes of the 3 or 4 days as percentage of energy or grams per 1000 kcal.

4.2.3. EATING BEHAVIORS AND DIETARY PATTERNS

In Studies I and II, eating styles were collected by a questionnaire (14). Participants were asked to select one of four options that best describes their overall eating style with 2 items addressing meal frequency and 2 items addressing regular eating. In addition, participants completed a short 12-item questionnaire addressing health-conscious eating (3 items), night eating (1 item), external eating (1 item), emotional eating (2 items) and

snacking (5 items) eating styles, with 4 possible response alternatives ranging from "usually" to "seldom". The night eating style item was excluded in Study II, due to a lack of variability in participants responses.

In Study III, parents were asked to complete an 11-item (wave 1 and 2) and 10-item (wave 3) questionnaire modified from Baughcum et al. (295) that covered 5 different constructs as follows: difficulty in child feeding, concern about children overeating and becoming overweight, pushing the child to eat more, the situation and structure during feeding, and age-inappropriate feeding; using five alternatives ranging from "never" to "always". Further, they reported on 2 more items, "How concerned are you about your child eating too much when you are not around him/her?" with 4 response alternatives from "unconcerned" to "concerned" and "How often does your child eat while doing something else (e.g., watching TV, playing, sitting at a computer, looking at a book)?" with 4 response categories from "never" to "on several occasions per day".

Derivation of eating behavior patterns

Eating behavior patterns from Studies II and III were derived by principal component analyses. In both studies, 4 components were retained based on their eigenvalues (>1.0 for Study II and >0.80 for Study III). Factor loadings were calculated after a varimax rotation to facilitate their interpretability. Factor loadings ≥0.30 were considered to contribute to the eating behavior pattern.

In Study II, eating behavior patterns were derived from 16-items, 15 questions on eating styles and the DQS from the FT16 study and are described in **Table 5** (items response coding were also described in the table). The extracted 4 components explained ~56% of the variance and were labeled as "snacking", "infrequent and unhealthy eating", "avoidant eating" and "emotional and external eating". "Snacking" loaded positively on alternating restriction and overeating style; eating sufficiently during meals and does not need to snack; replacing meals with snacks; and munching constantly in the evenings. The second pattern "infrequent and unhealthy eating" loaded positively on the DQS, eating breakfast, meal frequency and regularity of eating. The third pattern "avoidant eating" loaded positively on eating healthily, avoiding greasy meals and avoiding calories. The last pattern "emotional and external eating" loaded positively on watching TV while eating, eating tempted by advertisements, rewarding oneself with good food and consoling oneself by eating or drinking.

In Study III, eating behavior patterns were derived from 13-items (waves 1 and 2) and 12-items (wave 3) from the questions on eating behaviors in the IDEFICS/I.Family study (**Table 6**). The extracted 4 components explained ≥67% of variance in all study waves. The components were named as "overeating", "low appetite", "structure during feeding practices", and "pushing the child to eat more". From these 4 components, only overeating, the component with the larger variance (~30% in all study waves), was used in Study III analyses. Overeating loaded positively on the following items: stopping your child from eating too much, thinking about putting your child on a diet, worried that your child is eating too much and child eating too much when no one is around him/her.

Table 5. *Eating behavior patterns and factor loadings in varimax-rotated principal components from Study II*

		Snacking	Infrequent and unhealthy eating	Avoidant eating	Emotional and external eating
Eigenvalue		4.00	2.43	1.38	1.09
% variance explained		16.6	13.6	12.8	12.7
Variables	**Response coding**				
Diet quality score	From healthy to unhealthy	0.00	**0.33**	0.24	0.04
How often do you eat breakfast?	From usually to seldom	0.07	**0.50**	-0.03	-0.04
How often in a day do you usually eat?	From usually to seldom	-0.18	**0.58**	-0.06	0.01
Regularity of your eating habits	From regular to irregular	0.28	**0.36**	-0.02	-0.09
Alternating restriction and overeating style	From seldom to usually	**0.33**	0.02	-0.20	0.07
During meals I eat sufficiently - I don't need to snack	From usually to seldom	**0.52**	-0.19	0.05	-0.07
I replace my meals with snacks	From seldom to usually	**0.45**	0.05	-0.07	-0.11
I eat most in the evenings	From seldom to usually	0.28	0.19	-0.01	0.14
I usually munch constantly in the evenings	From seldom to usually	**0.38**	-0.06	0.06	0.14
I tend to eat healthily	From usually to seldom	0.19	0.14	**0.36**	-0.05
I avoid greasy meals	From usually to seldom	0.02	0.01	**0.60**	0.04
I avoid calories	From usually to seldom	-0.04	-0.08	**0.63**	-0.02

Table 5 continued

Variables	Response coding	Snacking	Infrequent and unhealthy eating	Avoidant eating	Emotional and external eating
While I am eating, I watch TV	From seldom to usually	-0.02	0.22	-0.05	**0.40**
I am tempted to eat based on the advertisements	From seldom to usually	-0.08	0.04	0.04	**0.55**
I reward myself with good food	From seldom to usually	-0.02	-0.08	-0.01	**0.56**
I console myself by eating or drinking	From seldom to usually	0.17	0.13	-0.01	**0.40**

Eating behaviors with factor loadings (≥0.30) are in bold. Sample size n = 3,977

Table 6. *Eating behavior patterns and factor loadings in varimax-rotated principal components from Study III*

	Wave 1 (n = 13,219)				Wave 2 (n = 11,061)				Wave 3 (n = 4,805)			
	Parental concern of overeating	Parental concern of low appetite	Structure during feeding practices	Pushing the child to eat more	Parental concern of overeating	Parental concern of low appetite	Structure during feeding practices	Pushing the child to eat more	Parental concern of overeating	Parental concern of low appetite	Structure during feeding practices	Pushing the child to eat more
Eigenvalue	3.56	2.70	1.38	1.01	3.63	2.69	1.41	0.98	3.69	2.41	1.17	0.88
% variance explained	0.27	0.21	0.11	0.08	0.28	0.21	0.11	0.08	0.31	0.20	0.10	0.07
Variables												
How often does your child eat while doing something else?	-0.04	-0.06	**0.66**	0.05	-0.03	-0.05	**0.70**	0.01	0.00	-0.08	0.03	**0.79**
Child watches TV at meals	0.01	0.01	**0.66**	-0.03	0.01	0.01	**0.67**	-0.07				
Is it a struggle to get your child to eat?	0.00	**0.55**	-0.01	0.00	-0.01	**0.52**	-0.02	-0.04	0.00	**0.55**	-0.01	-0.02
Do you feed your child yourself if he/she does not eat enough?	-0.02	0.20	0.09	**0.41**	0.03	0.23	0.12	**0.38**	-0.01	0.12	**0.46**	0.22
Do you have to stop your child from eating too much?	**0.51**	-0.05	-0.03	-0.02	**0.49**	-0.06	-0.02	-0.05	**0.47**	-0.06	0.00	-0.07
Do you think about putting your child on a diet?	**0.52**	0.04	-0.03	-0.09	**0.50**	0.01	-0.03	-0.09	**0.50**	0.02	-0.08	-0.01
Do you make your child eat all the food on his/her plate?	-0.03	-0.06	0.07	**0.62**	0.01	0.09	0.06	**0.54**	-0.06	-0.01	**0.60**	0.12
Do you worry that your child is eating too much?	**0.54**	-0.01	-0.01	-0.01	**0.52**	-0.03	-0.02	-0.04	**0.52**	-0.02	-0.01	-0.03

Table 6 continued

	Wave 1 (n = 13,219)				Wave 2 (n = 11,061)				Wave 3 (n = 4,805)			
	Parental concern of overeating	Parental concern of low appetite	Structure during feeding practices	Pushing the child to eat more	Parental concern of overeating	Parental concern of low appetite	Structure during feeding practices	Pushing the child to eat more	Parental concern of overeating	Parental concern of low appetite	Structure during feeding practices	Pushing the child to eat more
Variables												
Do you worry that your child is not eating enough?	0.00	**0.51**	0.01	0.06	-0.01	**0.50**	-0.01	0.01	-0.02	**0.52**	0.02	-0.01
Do you use foods that your child likes as a way to get your child to eat "healthy" foods?	0.11	0.13	0.08	**0.40**	0.17	0.23	0.10	**0.33**	0.18	0.21	0.28	0.22
Does your child have a poor appetite?	-0.01	**0.59**	-0.06	-0.08	-0.04	**0.55**	-0.09	-0.12	0.00	**0.59**	-0.06	-0.10
Do you sit down together with your child when he/she eats meals?	-0.06	-0.13	**-0.32**	**0.47**	-0.08	-0.21	-0.14	**0.64**	0.03	-0.12	**0.58**	**-0.48**
Does your child eat too much when you are not around him/her?	**0.39**	-0.01	0.06	0.19	**0.44**	0.01	0.03	0.14	**0.46**	0.03	0.05	0.09

Eating behaviors with factor loadings (≥0.30) are in bold.

4.2.4. ZYGOSITY

In Studies I and II, zygosity status was determined using a validated questionnaire, based on questions on physical similarity and confusion by others, a method that has shown high reliability in the FT16 cohort (296).

4.2.5. GENOTYPING AND WEIGHTED POLYGENIC RISK SCORES

In Studies II and III, DNA was extracted from either saliva or blood samples using standard methods. The samples of 1,055 adults were genotyped at the Wellcome Trust Sanger Institute (Cambridge, UK), University of Chicago Genomics Facility (Chicago, IL, USA) and Institute for Molecular Medicine Finland (Helsinki, Finland) and the Affymetrix FinnGen Axiom array at Thermo Fisher Scientific (Santa Clara, CA, USA) in three batches (Study II). The samples of 3,515 children were genotyped using the UK Biobank Axiom array (Thermo-Fisher Scientific, Santa Clara, CA, USA) in two batches (2015 and 2017). Sample and genotype quality control measures were applied, genome-wide imputation was done with Minimac3 v2.0.1 (study II) and Minimac3 v5 (study III) (https://genome.sph.umich.edu/wiki/Minimac3) resulting in 1,055 adults and 39,117,105 (batch 1 and 2) and 39,127,678 (batch 3) genotypes (Study II) and 3,098 children and 3,424,677 genotypes with an estimated posterior genotype probability >0.8 and a minor allele frequency ≥ 0.05. Genetic relatedness matrices were calculated using PLINK *(https://www.cog-genomics.org/plink/1.9/general_usage#cite)* in study II and EMMAX (https://genome.sph.umich.edu/wiki/EMMAX) in order to estimate the degree of relatedness within the study sample. In Study II, the polygenic risk score for BMI was calculated based on the European HapMap3 variants which represents the whole genome, and the Finnish FINNRISK Study sample (n = 27,284) (297,298) was used as an external reference panel. The total number of genetic variants used for the polygenic risk score calculations in Study II was 996,919. In Study III, the polygenic risk score for BMI was calculated as proposed and validated by Khera et al. (18) and the same reference population sample from Locke et al. (n ~ 300,000) (19). The total number of genetic variants used for the polygenic risk score calculations were 2,100,302 for Study III. Both polygenic risk scores were based on genome-wide summary statistics for BMI from European ancestry populations.

4.2.6. OTHER MEASUREMENTS

Multiple confounders such as physical activity, socioeconomic status and screen time were addressed by questionnaire. Moreover, biological samples were used to analyze some biomarkers such as glycated hemoglobin (HbA1c).

Physical Activity

In Study I, leisure time physical activity was assessed as the sum score of MET hours per day (299). In Study III, playing outdoors was used as a proxy of physical activity, and it was calculated by asking the parents how many hours per day during weekdays and weekends their child was playing outdoors (78).

Socioeconomic variables

Participants' education level was assessed based in the Finnish educational system (300) in Study I. In Study III, parental education level was assessed using the International Standard Classification of Education (ISCED) (301). Parents from the IDEFICS/I.Family study also reported their monthly household net income (78). Further, in Study III, children's well-being score was determined by using the KINDL ® questionnaire (302).

Screen time

In Study III, screen time was calculated based on the total screen time spent on audiovisual media (78).

Glycated hemoglobin

In Study III, HbA1c was analyzed by high-performance liquid chromatography (303).

4.3. STATISTICAL ANALYSES

Statistical analyses were carried out by using Stata (https://www.stata.com) and R statistical software (https://www.r-project.org). When analyzing twins as individuals (Studies I and II) and siblings in the cross-lagged path model analyses (Study III), the effect of family clustering was considered by using survey methods with standard errors yielded by cluster variance estimators (304). In Study III, chained random forest imputation was used to replace missing data of confounders. A p-value <0.05 was considered as the level of significance.

4.3.1. GENERAL STATISTICAL METHODS

In Study I, non-normally distributed variables were log-transformed. The associations between the DQS and obesity measures and eating styles were calculated using linear regression models for individual-level and within-pair analyses. Regression models using obesity measures were adjusted for age, sex, education level and physical activity. Regression models using eating styles were adjusted for the same set of confounders and additionally BMI and presented as multiple regression models. The associations between the DQS and overweight, obesity and abdominal obesity were calculated using logistic

regression analyses in individual-level and within-pair analyses. Logistic regression analyses were adjusted for age, sex, education level and physical activity. Differences in nutrient intakes between lower and higher diet quality were evaluated by the adjusted Wald test in individual analyses and paired t-test or Wilcoxon rank test, depending on the distribution of variables, in within-pair analyses. Pearson's correlations were calculated to assess whether nutrient intakes are related to diet quality between individuals and within–twin pairs. All correlations were adjusted for age, sex, BMI, education level and physical activity.

4.3.2. QUANTITATIVE GENETIC ANALYSES

In Study II, eating behavior patterns, BMI and WC were analyzed using quantitative genetic twin modeling. Classical twin modeling relies on the assumption that MZ twins share virtually the same gene sequence, whereas DZ twins share, on average, 50% of their segregating genes. On the basis of this assumption, genetic and environmental variation can be decomposed into the following components: additive genetic factors (A), the sum of the additive effect of alleles at a locus over all loci; non-additive genetic factors (D), the sum of intra-locus allelic interactions over all loci; common environment (C), all shared environmental factors within co-twins; and unique environment (E), all non-shared environmental factors within co-twins including measurement error as well. The additive and non-additive genetic correlations are 1 for MZ co-twins and 0.5 and 0.25, respectively, for DZ co-twins. The expected correlations for common and unique environments are 1 and 0, respectively, for both MZ and DZ co-twins. Because study II included twins reared together, it was not possible to estimate C and D in the same model. Thus, ACE and ADE models were fitted to test whether the presence of C or D could explain the variation in eating behavior patterns and obesity measures. There was no evidence of C and D, leading to a more parsimonious AE model. Prior to genetic model fitting, intraclass correlations (ICCs) were calculated for MZ and DZ twin pairs to analyze the presence of genetic effects. ICCs were higher among MZ twin pairs, indicating the presence of genetic influences.

To analyze genetic and environmental correlations, Cholesky decomposition models were based on AE models. Prior to decomposition, Pearson partial correlations were calculated between eating behavior patterns and obesity measures. According to the bivariate Cholesky models, the correlation between traits was decomposed into additive genetic (r_a) and unique environmental (r_e) correlations. All the models were adjusted for age and sex.

4.3.3. CROSS-LAGGED PATH MODEL

In Study III, cross-lagged path models (CLPM), part of the structural equation modeling (SEM) framework, were used to estimate the structural relationships of obesity measures and parental concern of overeating between two (children at 4 and 6 years old, respectively) and three (children at 4, 6 and 10 years, respectively) time points. Prior to CLPM, to account for the effect of confounders, obesity measures (z-score BMI and z-score WC) and parental concern of overeating were regressed on age, sex, country,

parental education, parental income, well-being, screen time, playing outside, fruit and vegetable consumption and glycated hemoglobin at each study wave. The obtained residuals were standardized and used in the path model. CLPM included linear correlations and linear regressions to cross-sectionally and longitudinally analyze the associations between obesity measures and parental concern of overeating. CLPM models in Study III had a reasonable fit to the data, a Root Mean Square Error of Approximation (RMSEA) close to 0.06, a Comparative Fit Index (CFI) $\geq$ 0.90 and a Tucker-Lewis Index (TLI) $\geq$ 0.90 (305,306).

4.3.4. MEDIATION ANALYSES

In Studies II and III, mediation analyses were conducted to identify the potential mediation models between the polygenic risk score for BMI, obesity measures and eating behavior patterns using two different approaches: SEM (Study II) and causal mediation analyses (CMA) based on the counterfactual approach from VanderWeele (307) (Study III).

In Study II, mediation models examined whether eating behavior patterns mediated the cross-sectional association between the polygenic risk score for BMI and obesity measures (**Mediation Model 1, Figure 3**). Prior to SEM analyses, to control for age, sex and population stratification, the main variables, polygenic risk score for BMI, obesity measures and eating behavior patterns, were regressed on age, sex and eight genetic principal components. The resultant residuals were standardized and used in the SEM models. The results were reported as total effect, direct effect and indirect effect.

In study III, mediation models examined whether parental concern of overeating at wave 1 mediated the association between the polygenic risk score for BMI and obesity measures at wave 3 (**Mediation Model 2, Figure 3**) and whether obesity measures at wave 1 mediated the association between the polygenic risk score for BMI and parental concern of overeating at wave 3 (**Mediation Model 3, Figure 3**). The med4way Stata package was used to decompose the total effect into four components: controlled direct effect, pure indirect effect, reference interaction and mediated interaction (308). In CMA, we adjusted all models by baseline age, sex, country, parental education, parental income, well-being, screen time, playing outside, fruit and vegetable consumption, glycated hemoglobin and 12 genetic principal components. Further, CMA sensitivity analyses were conducted to examine the presence of unmeasured variables that may confound the relationship between the mediator and the outcome (Appendix 2).

In both mediation approaches, SEM and CMA, sample bias correction estimates and 95% CIs were calculated using the bootstrapping approach of 1,000 or 2,000 draws.

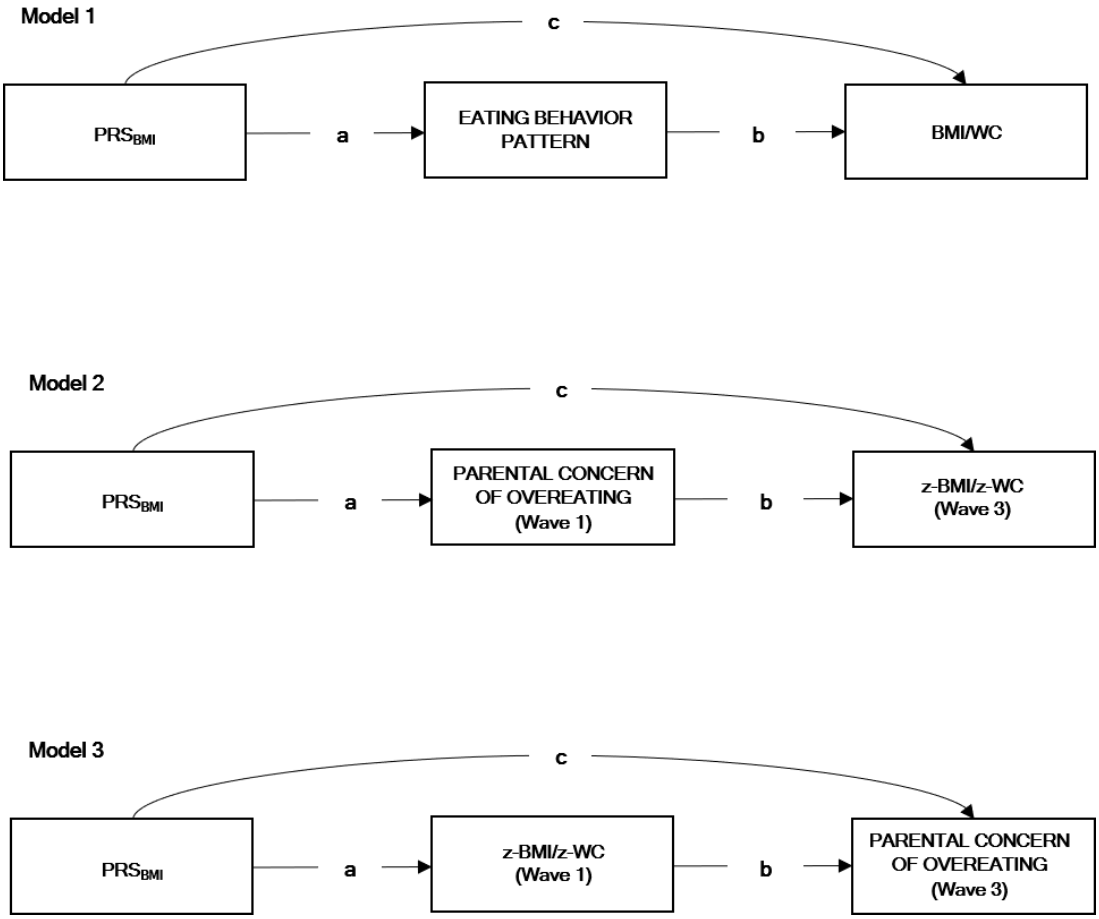


Figure 3 Mediation models. The indirect effect (or mediation effect) is represented by **ab**, and **c** represents the direct effect; total effect = **ab + c**. Model 1 is cross-sectional in adults; Models 2 and 3 are longitudinal in children. Abbreviations: body mass index (BMI), polygenic risk score for BMI (PRS_{BMI}), z-score body mass index (z-BMI), z-score for waist circumference (z-WC), waist circumference (WC).

5. RESULTS

5.1. ASSOCIATIONS BETWEEN THE DIET QUALITY SCORE, OBESITY AND EATING STYLES

The relationships between the newly developed diet quality score (DQS) with obesity measures, nutrient intakes and eating styles (eating behaviors and dietary patterns) were investigated in Study I.

Individuals with a better diet quality were less likely to be overweight and abdominally obese. Further, a higher adherence to the DQS was inversely associated with BMI and WC. To control for genetic and socioeconomic factors, the same analyses were performed in twin pairs, but the DQS was not significantly associated with obesity measures within twin pairs.

Twin individuals with a higher diet quality had higher intakes of several nutrients including fiber, folate, vitamin C and magnesium as compared to individuals with a lower diet quality. On the other hand, individuals with a higher diet quality had lower intakes of total fat, saturated fat, sucrose, and cholesterol as compared to individuals with a lower diet quality.

Diet quality was correlated with protein, total fat, saturated fat, sucrose, fiber, and magnesium in twin individuals (**Figure 4**). In within-pair analyses, saturated fat, sucrose, fiber, and magnesium were correlated with diet quality.

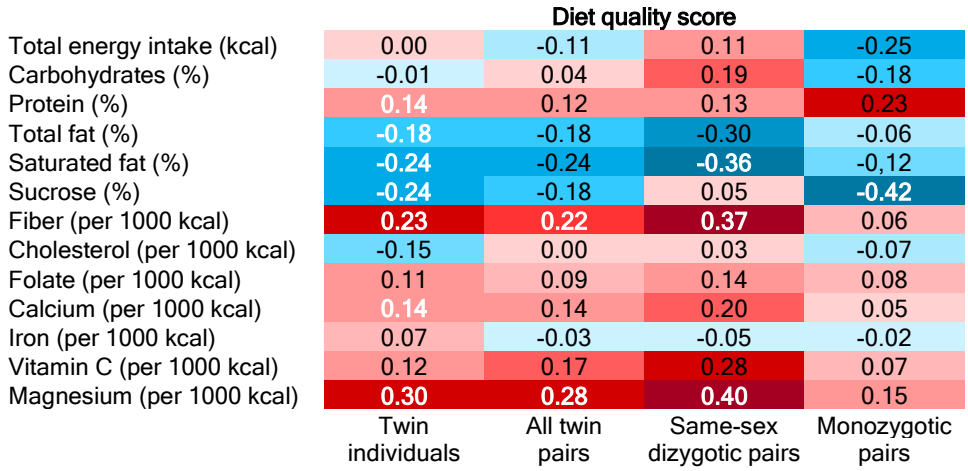


Figure 4 Pearson partial correlations between the food-based diet quality score (DQS) and nutrient intakes. Correlations were adjusted for: sex, age, BMI, physical activity (expressed as MET hours per day) and education level. Significant correlations are shown in bold and white ($p<0.05$); n = 249 twin individuals, n = 105 all twin pairs, n = 45 same-sex dizygotic pairs, n = 60 monozygotic twin pairs.

The DQS reflected a greater adherence to healthier eating styles in twin individuals and twin pairs. Greater category changes have been observed for frequency of meals per day, regular eating, eating healthily and avoiding greasy meals than for the other eating styles variables in both twin individuals and twin pairs (**Table 7**).

Table 7. *Associations between the food-based diet quality score (DQS) and eating styles*

Eating Style	All individuals n = 3,592	All twin pairs n = 1,194	All dizygotic twin pairs n = 764	Monozygotic twin pairs n = 430
Meal Frequency				
How often do you eat breakfast?	-0.56 (-0.62, -0.50)	-0.46 (-0.56, -0.36)	-0.46 (-0.59, -0.34)	-0.53 (-0.70, -0.41)
How often do you usually eat?	0.87 (0.76, 0.98)	0.76 (0.57, 0.94)	0.81 (0.57, 1.05)	0.80 (0.45, 1.15)
Regular eating				
Regularity of your eating habits	-0.85 (-0.94, -0.76)	-0.72 (-0.86, -0.58)	-0.80 (-0.98, -0.62)	-0.91 (-1.15, -0.66)
Alternating restrictive an overeating style	-0.15 (-0.24, -0.07)	-0.16 (-0.30, -0.02)	-0.20 (-0.37, -0.02)	-0.16 (-0.41, 0.09)
Health-conscious eating style				
I tend to eat healthily	-0.99 (-1.08, -0.90)	-0.82 (-0.97, -0.68)	-0.92 (-1.09, -0.74)	-0.59 (-0.83, -0.34)
I avoid greasy meals	-0.71 (-0.78, -0.64)	-0.58 (-0.70, -0.47)	-0.73 (-0.88, -0.59)	-0.29 (-0.48, -0.11)
I avoid calories	-0.48 (-0.56, -0.41)	-0.43 (-0.55, -0.30)	-0.52 (-0.67, -0.36)	-0.22 (-0.42, 0.02)
Night eating style				
At night I wake up to eat	0.24 (0.01, 0.46)	-0.07 (-0.44, 0.30)	-0.02 (-0.51, 0.47)	-0.13 (-0.68, 0.43)
External eating style				
I am tempted to eat based on the advertisements	0.39 (0.27, 0.51)	0.20 (0.01, 0.39)	0.21 (-0.05, 0.46)	0.20 (-0.08, 0.48)
Emotional eating style				
I reward myself with good food	0.04 (-0.05, 0.13)	0.10 (-0.04, 0.24)	0.07 (-0.11, 0.25)	0.17 (-0.05, 0.40)
I console myself by eating or drinking	0.15 (0.05, 0.25)	0.16 (0.00, 0.32)	0.11 (-0.10, 0.32)	0.25 (0.01, 0.50)
Snacking eating style				
During meals I eat sufficiently - I don't need to snack	-0.30 (-0.37, -0.22)	-0.25 (-0.38, -0.12)	-0.34 (-0.50, -0.18)	-0.01 (-0.23, 0.20)
I replace my meals with snacks	0.51 (0.41, 0.61)	0.41 (0.25, 0.57)	0.45 (0.24, 0.66)	0.32 (0.07, 0.58)
I eat most in the evenings	0.44 (0.38, 0.51)	0.41 (0.30, 0.53)	0.48 (0.33, 0.63)	0.28 (0.09, 0.46)
I usually munch constantly in the evenings	0.34 (0.25, 0.37)	0.40 (0.27, 0.54)	0.40 (0.22, 0.57)	0.42 (0.20, 0.64)
While I am eating, I watch TV	0.30 (0.23, 0.37)	0.25 (0.12, 0.37)	0.27 (0.11, 0.43)	0.23 (0.02, 0.43)

Data are β-coefficients and their 95% confidence intervals. All models were adjusted by sex, age, BMI, physical activity (expressed as MET-hours per day) and education level.

5.2. HERITABILITY OF EATING BEHAVIOR PATTERNS AND OBESITY

Heritability estimates are shown in **Figure 5** (Study II). Eating behavior patterns were moderately heritable (ranging from 33% to 50%). Heritability estimates for obesity measures were higher compared to heritability estimates for eating behavior patterns (>75% for BMI and ≥60% for WC).

5.3. ASSOCIATIONS BETWEEN EATING BEHAVIOR PATTERNS AND OBESITY

The relationship between eating behavior patterns and obesity was investigated cross-sectionally in Study II and longitudinally in Study III.

'Snacking' and 'emotional and external eating' behavior patterns were correlated with BMI ($r = 0.35$ and $r = 0.26$, $p<0.001$, respectively) and WC ($r = 0.32$ and $r = 0.23$, $p<0.001$, respectively) in study II. These correlations were decomposed into additive genetic correlations and non-shared environmental correlations.

The additive genetic component accounted for a major part of the association between the 'snacking' behavior pattern and BMI (75%, 95% CI: 61, 88%) and WC (71%, 95% CI: 58, 93%). Similar results were observed for the 'emotional and external eating' behavior pattern and BMI (75%, 95% CI: 55, 87%) and WC (64%, 95% CI: 44, 85%).

Parental concern of overeating and z-score WC were bi-directionally associated in Models A and B (**Figure 6**) (Study III). The association between z-score BMI and parental concern of overeating was bi-directional when analyzing two time points (Model A) and from wave 1 to 2 when analyzing three time points (Model B). Additionally, the associations between z-score BMI and z-score WC to later parental concern of overeating were stronger than the other way around.

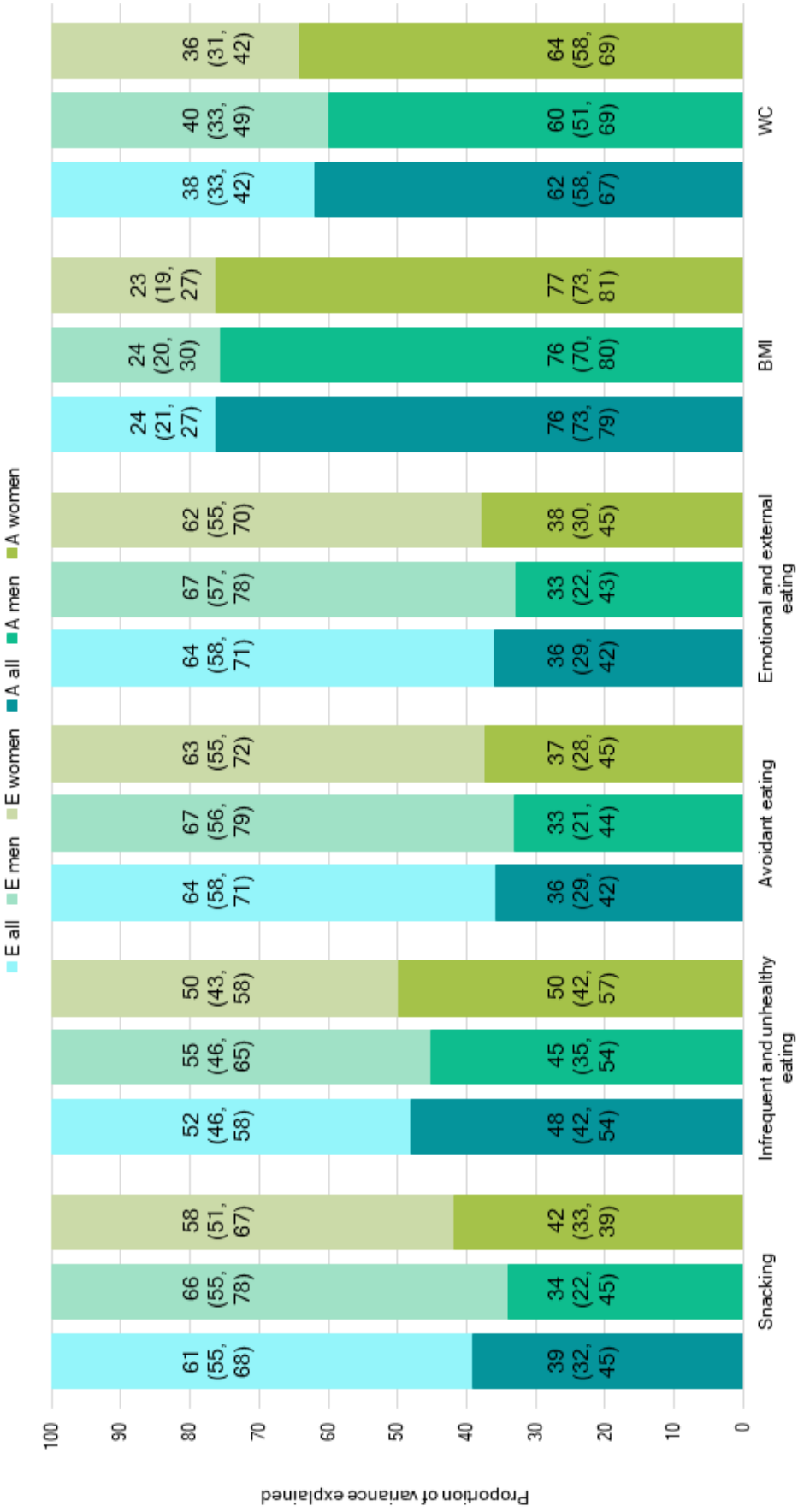


Figure 5 Proportion of the eating behavior patterns and obesity measures explained by additive genes (A) and environmental factors (E) in young adults. The numbers within the bars are 95% confidence intervals; n = 3,000 twin pairs, n = 1,325 men twin pairs, n = 1,675 women twin pairs. Abbreviations: body mass index (BMI), waist circumference (WC)

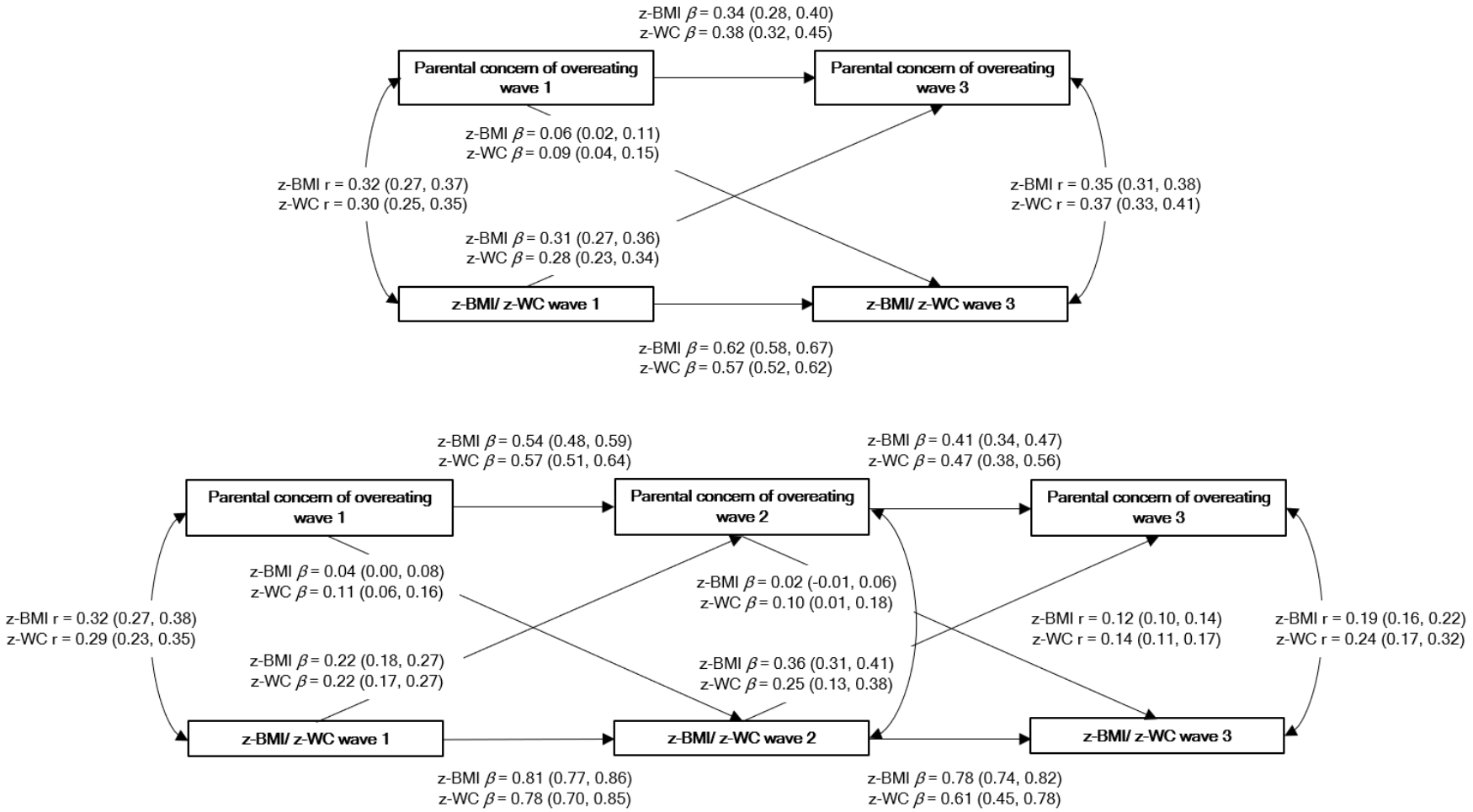


Figure 6 Cross-lagged path models for parental concern of overeating and obesity measures in children. All models were adjusted for: age, sex, country, parental education, well-being, playing outside, fruit and vegetable consumption and glycated hemoglobin. Model A: z-BMI n = 2,355; z-WC n = 2,022; Model B: z-BMI n = 1,848; z-WC n = 1,576. Abbreviations: z-score body mass index (z-BMI), z-score waist circumference (z-WC).

5.4. MEDIATORS OF THE GENETIC SUSCEPTIBILITY TO OBESITY

The relationship between the polygenic risk score for BMI, eating behavior patterns and obesity measures was investigated in Studies II and III. In both studies, the genetic susceptibility to obesity was partly mediated by eating behavior patterns cross-sectionally (Mediation Model 1) and longitudinally (Mediation Model 2) (**Table 8**).

Table 8. *Eating behavior patterns as mediators of the association between the polygenic risk score for BMI and obesity measures*

	Sample size, n	BMI / z-BMI *β (95% CIs)*	WC / z-WC *β (95% CIs)*[3]
Mediation Model 1 through snacking[1]	949		
Total effect of PRS_{BMI}		0.29 (0.20, 0.38)	0.24 (0.15, 0.32)
Direct effect of PRS_{BMI}		0.23 (0.16, 0.31)	0.19 (0.12, 0.26)
Indirect effect (*via snacking*) of PRS_{BMI} on obesity measures		0.06 (0.02, 0.09)	0.05 (0.02, 0.08)
% mediation		21%	21%
Mediation Model 1 through infrequent and unhealthy eating[1]	949		
Total effect of PRS_{BMI}		0.29 (0.20, 0.38)	0.24 (0.15, 0.32)
Direct effect of PRS_{BMI}		0.28 (0.20, 0.36)	0.23 (0.15, 0.31)
Indirect effect (*via infrequent and unhealthy eating*) of PRS_{BMI} on obesity measures		0.01 (0.00, 0.02)	0.01 (0.00, 0.02)
% mediation		3%	4%
Mediation Model 1 through emotional and external eating[1]	949		
Total effect of PRS_{BMI}		0.29 (0.20, 0.38)	0.24 (0.15, 0.32)
Direct effect of PRS_{BMI}		0.26 (0.19, 0.34)	0.22 (0.16, 0.29)
Indirect effect (*via emotional and external eating*) of PRS_{BMI} on obesity measures		0.03 (0.00, 0.05)	0.02 (0.00, 0.04)
% mediation		10%	-
Mediation Model 2 through parental concern of overeating[2]	2,386		
Total effect of PRS_{BMI}		0.46 (0.40, 0.52)	0.41 (0.35, 0.47)
Direct effect of PRS_{BMI}		0.37 (0.32, 0.43)	0.33 (0.27, 0.39)
Indirect effect (*via parental concern of overating wave 1*) of PRS_{BMI} on obesity measures (wave 3)		0.10 (0.03, 0.17)	0.09 (0.07, 0.12)
% mediation		19%	20%

Data are *β*-coefficients and their 95% confidence intervals. [1]Cross-sectional models from Study II (FT16 study), were adjusted for age, sex, and genetic principal components. [2]Longitudinal model from Study III (IDEFICS/I.Family study) was adjusted for baseline age, sex, country, parental education, parental income, well-being, screen time, playing outside, fruit and vegetable consumption, glycated hemoglobin, and genetic principal components. [3]Sample sizes smaller due to missing values in WC or z-WC. Abbreviations: body mass index (BMI), waist circumference (WC), polygenic risk score for BMI (PRS_{BMI}), z-score body mass index (z-BMI), z-score waist circumference (z-WC).

In the FT16 cohort of young adults, the mediation model through snacking was significant in women (21% for BMI and 22% for WC). In men, snacking only mediated the association between the polygenic risk score for BMI and WC (20%). The infrequent

and unhealthy eating behavior pattern mediated the genetic susceptibility to obesity in men (6% for BMI and 10% for WC). The emotional and external eating behavior pattern only mediated the association between the polygenic risk score for BMI and BMI in the overall sample (10%) and in women (17%).

In the IDEFICS/I.Family cohort of children (Study III, Mediation Model 2), prospective mediation models were significant in both boys and girls. Mediation percentages were slightly higher in boys (20% and 23% for z-score BMI and z-score WC, respectively) than in girls (17% and 18%, for z-score BMI and z-score WC, respectively).

Table 9. *Obesity measures as mediators of the association between the polygenic risk score for BMI and parental concern of overeating*

	Sample size, n	Parental concern of overeating
Mediation Model 3 through z-score BMI[1]	1,246	
Total effect of PRS_{BMI}		0.40 (0.27, 0.52)
Direct effect of PRS_{BMI}		0.23 (0.12, 0.35)
Indirect effect (*via z-score BMI wave 1*) of PRS_{BMI} on parental concern of overeating (wave 3)		0.16 (0.10, 0.21)
% mediation		44%
Mediation Model 3 through z-score WC[1]	1,134	
Total effect of PRS_{BMI}		0.40 (0.27, 0.52)
Direct effect of PRS_{BMI}		0.25 (0.12, 0.37)
Indirect effect (*via z-score WC wave 1*) of PRS_{BMI} on parental concern of overeating (wave 3)		0.17 (0.11, 0.23)
% mediation		51%

Data are β-coefficients and their 95% confidence intervals. [1]Longitudinal models from Study III (IDEFICS/I.Family study) were adjusted for baseline age, sex, country, parental education, parental income, well-being, screen time, playing outside, fruit and vegetable consumption, glycated hemoglobin, and genetic principal components. Abbreviations: polygenic risk score for body mass index (PRS_{BMI}), z-score body mass index (z-BMI), z-score waist circumference (z-WC).

Baseline obesity measures (wave 1) mediated the prospective association between the polygenic risk score for BMI and parental concern of overeating in children (Study III) (**Table 9**).

Significant interaction effects were observed between baseline z-score WC on the prospective association between the polygenic risk score for BMI and parental concern of overeating (9%, $p = 0.01$). Prospective mediation models through baseline z-score BMI were significant in boys and girls (43% for both). The mediation model through baseline z-score WC was only significant in boys (39%).

6. DISCUSSION

The research presented in this thesis examined whether eating behavior patterns (diet quality, eating behaviors and dietary patterns) were associated with obesity measures. The second aim was to investigate the role of these factors in the genetic susceptibility to obesity in children and young adults.

The main findings of the present studies were as follows:

1. The diet quality score (DQS) developed and validated in Study I proved to be a useful and brief dietary screening tool to estimate diet quality. The DQS reflected a greater adherence to healthier eating styles (eating behaviors and dietary patterns) and nutrient intakes and was inversely associated with obesity measures. Furthermore, analyses in twin pairs discordant for diet quality showed significant differences in eating styles and nutrient intakes (Study I).

2. Individual differences in eating behavior patterns and obesity measures were partly explained by genetic factors in young adults (Study II). Cross-sectional associations between the snacking and the emotional and external eating behavior patterns and BMI and WC were largely due to common genetic factors in young adults (Study II); and BMI and WC largely influenced later parental concern of overeating rather than the reverse pathway in children (Study III).

3. Eating behavior patterns partly mediated the genetic susceptibility to obesity in a cross-sectional setting of young adults and a prospective setting of children (Studies II and III). Another finding was that the prospective association between the polygenic risk score for BMI and parental concern of overeating was partly mediated by BMI and WC in children (Study III).

6.1. VALIDITY OF THE DIET QUALITY SCORE

The validity of the DQS derived from a 14-item food frequency questionnaire (FFQ) based on Nordic and Finnish nutritional guidelines was assessed by comparing it with nutrient intakes, obesity measures and eating styles. The DQS was associated with key nutrients such as protein, total fat, saturated fat, sucrose, fiber and magnesium intakes. All of these nutrients are considered essential in the maintenance of a healthy diet (309).

Other short FFQs show similar associations between nutrient intakes and diet quality (154,310–314). The associations between the DQS and nutrient intakes followed the same direction of two previously constructed diet quality scores developed for Finnish adults (155,160). However, the short FFQ developed by Hemiö et al. was associated with a larger number of nutrients (160). Furthermore, correlations between nutrient intakes

and the short FFQ from Hemiö et al. were higher (160) compared to the correlations between nutrient intakes and the DQS developed in Study I. A possible explanation might be that in the study from Hemiö et al. more food groups were included (160). Previous findings have shown that longer FFQs tend to be associated with a larger number of nutrients (128–131,133,134). Questionnaires that include more food items also show higher correlations with diet quality compared to those with less food items (315). Nevertheless, the developed DQS is a quick and useful tool to broadly classify individuals according to their diet quality. In Study I, individuals with high diet quality scores showed better nutrient intakes compared to those with low diet quality scores, similar to previous validation studies (153,154,310–314).

The associations between the DQS with BMI and WC and the risk of overweight or abdominal obesity are novel. To date, only dietary quality scores based on longer FFQs have shown their ability to predict chronic diseases including obesity (13,141–144). Previous short dietary screening tools have not been assessed for associations with obesity, except a brief dietary screening tool derived from the AHEI score (153). In that study, the authors found that those individuals with a low diet quality had higher BMI and WC compared to those with a high diet quality (153), similar to the reported findings. The constructed DQS was associated with a risk of being overweight and abdominally obese but not with a risk of being obese.

In previous research, eating styles were associated with weight gain when the quality of the diet was low, for example individuals with emotional and restrained eating tend to eat more palatable foods (166). Moreover, in Study I, individuals with high diet quality engaged in healthier eating styles such as a higher meal frequency, eating breakfast every day, lower emotional eating and external eating and less snacking. Most of these are in line with earlier research findings (110–112,211), but a few studies have shown that eating breakfast regularly was not associated with a better dietary quality profile (225,226). Hence, more research is needed to carefully investigate the association between eating breakfast and diet quality.

6.2. HERITABILITY ESTIMATES

Study II estimated heritabilities of eating behavior patterns and obesity measures in young adults. Some studies have shown that restrained eating, emotional eating and external eating were heritable (248,249,316). Study II supported these earlier findings by showing that heritability estimates of eating behavior patterns were moderately heritable. As a novelty, the constructs of this study not only included these above-mentioned eating behaviors, they also included diet quality and dietary patterns such as snacking or eating breakfast. The heritability estimates found in this sample of young Finnish adults were slightly lower compared to previous heritability estimates measured with the TFEQ in European populations (248,249) or the RS in an American population (250). In contrast, the obtained heritability estimates were higher compared to the estimates of eating behaviors measured with the DEBQ in a Korean sample of adults (316). A recent study in Spanish female twins showed that eating behaviors were mostly explained by non-shared environmental factors (317). Differences between heritability estimates might be

explained by the use of populations of different ancestry (250,316) and the rather smaller sample size of the Spanish study (317).

A few studies have examined the heritability estimates of snack consumption showing moderate heritability estimates (318–320), similar to the estimates of the snacking behavior pattern. A previous study using the same study population (FT16) showed that eating breakfast was heritable at age 16 years old ($h^2 = 0.41$ for girls and $h^2 = 0.66$ for boys) (321). Almost twenty years later, heritability estimates of the infrequent and unhealthy eating behavior pattern (which loaded high on eating breakfast) remained similar in magnitude in women but decreased in men. A recent study has shown that not only was eating breakfast heritable, but the heritability of food timing was also partly explained by genetic factors, showing $h^2 = 0.56$ for breakfast timing and $h^2 = 0.38$ for lunch timing (322). Further, in Study II, the infrequent and unhealthy eating behavior pattern also loaded high on diet quality. A study of Dutch adults showed that dietary intake patterns were partly explained by genetic factors, $h^2 = 0.32$ for the healthy dietary intake pattern and $h^2 = 0.27$ for the unhealthy dietary intake pattern (318).

Variation in BMI was largely explained by genetic factors, which was in line with heritability estimates from previous twin studies in young adults (25). In Study II, heritability estimates for WC were lower compared to BMI estimates. A study of Danish adult twins found similar heritability estimates for WC (242). However, two twin studies in American populations with different ancestry showed higher heritability estimates for WC, similar to the heritability estimates for BMI, ranging from 0.72 to 0.82 (238,240).

6.3. THE RELATIONSHIP BETWEEN EATING BEHAVIOR PATTERNS AND OBESITY

Studies II and III examined the associations between eating behavior patterns and obesity. In Study II, the associations between snacking and emotional and external eating behavior patterns with obesity measures were largely explained by genetic factors. These findings are largely consistent with a previous study of adult twins where genetic correlations accounted for a larger part of the association between eating behaviors and BMI (>80%) (248). A study of twin children has shown that the genetic correlations between eating behaviors and weight were moderate (ranging from 0.22 to 0.37) (254). Other twin studies have shown that the associations between BMI and the intake of soda and fast food were largely explained by genetic factors (323,324). Contrary to these studies, other research found that eating behaviors and BMI were largely explained by non-shared environmental factors (317) and the association between the consumption of healthy or unhealthy dietary intake patterns and BMI was not driven by genetic factors (318).

Findings from Study II suggest that eating behavior patterns and obesity measures may share, at least in part, a similar genetic etiology. However, none of these previous twin studies have analyzed the causal relationship between eating-related traits and obesity. Longitudinal studies have also not analyzed the causal relationship between eating-related traits and obesity, but they have shown temporary associations between eating behaviors and obesity.

Eating behaviors are associated with later weight gain and later eating disorders such as the binge eating disorder (325,326). Furthermore, a recent study has shown that childhood BMI was associated with later eating disorders (327). These studies suggested that both BMI and eating behaviors may predict later eating disorders. Hence, it would be essential to find out how eating behaviors and obesity are associated over time.

In Study III, parental concern of overeating and obesity measures were bi-directionally associated during childhood, and the pathways from previous BMI and WC to later parental concern of overeating were stronger. These findings are consistent with other studies in children, adolescents and adults that also found bi-directional associations between eating behaviors and obesity measures and showed that the effect of obesity measures to subsequent eating behaviors was stronger (187,194–197). On the other hand, studies during early infancy (≤ 24 months old) also found bi-directional associations between appetite traits and weight, but the stronger pathways were observed from appetite traits to later weight (191–193). Even if associations seem to be bi-directional throughout life, there is always a pathway which is more expressed. These previous studies suggest that appetite traits have a stronger influence on subsequent weight during early childhood than the other way around. In contrast, as children grow older, this pathway may be reversed. Obesity measures seem to exert more influence on not only appetite traits, but also other eating behaviors, remaining so until adulthood.

6.4. MECHANISMS OF EXPRESSION OF OBESITY SUSCEPTIBILITY GENES

In Studies II and III, eating behavior patterns mediated the genetic susceptibility to obesity in children and young adults. The results were largely consistent with other studies that assessed the same pathway and used polygenic risk scores for BMI with genome-wide significant variants (<100 SNPs) (231–233,275,276). Nevertheless, these previous studies used different eating behavior constructs than those used in Studies II and III. For example, eating behavior patterns were obtained from different TFEQ questionnaires in studies among adults (231–233). Eating behavior patterns from study II were measured with the DQS questionnaire constructed in Study I and the eating styles questionnaire from Keski-Rahkonen et al. (14). In Study II, snacking not only loaded high on the snacking dietary patterns, but also loaded high in 'the restriction and overeating style', similar to the uncontrolled eating behavior reported in previous adult studies (231–233) and to the parental concern of overeating pattern in Study III, which was measured with the questionnaire from Baughcum et al. (295).

The mediation of the genetic susceptibility to obesity through snacking in adults and overeating in children showed mostly the same mediation percentages. Even though, in the adult's study the polygenic risk score for BMI included less genetic variants compared with the polygenic risk score for BMI in the child study, ~1million SNPs vs 2.1 million SNPs, respectively. The polygenic risk score for BMI for adults explained ~8% of the BMI variance in Study II, whereas the polygenic risk score for BMI explained 11% of the BMI variance in children (328). These differences can be explained because some genetic variants had stronger effects during adulthood and others during childhood (329).

Recently, two separate polygenic risk scores for BMI were constructed for children and adults (329). These polygenic risk scores were validated showing that children's polygenic risk score explained more BMI variance in adolescents (7%) than in adults (2.4%) (330). However, the adult polygenic risk score explained mostly the same variance in adults (3.9%) and adolescents (3.6%) (330). Study III used a polygenic risk score for BMI based on Khera et al. (18), which was based on adult BMI. However, it also shows reliable associations in children older than 3.5 years old (18). According to a recent publication, adult BMI genetic variants were more strongly associated with child BMI during their adiposity rebound (5–6 years old) than in their adiposity peak (≤ 9 months old) (331). During the adiposity peak, genetic variants slightly influence BMI (331). These previous studies suggested that polygenic risk scores developed for adults can be used in child and adolescent populations, but a specific polygenic risk score based on children's BMI may increase the percentage of variance explained. Hence, it would help to explain in greater detail the mechanisms of expression of obesity susceptibility genes during childhood.

Previous studies in children have focused on appetite traits (275–277) instead of other eating behaviors. The previous section 6.3 explained that appetite traits seem to be more expressed during infancy and in children younger than 3 or 4 years old than in older children or adults. Findings from a prospective French study in children from 1 to 5 years old showed that the mediation percentages from appetite traits in the association between a polygenic risk score for BMI and BMI decreased overtime from 47% in children at 2 years old to 28% when those children were 5 years old (276). Calculated mediation percentages of the genetic susceptibility to obesity via appetite traits in older children (~10 years old) showed that during late childhood mediation percentages decrease to <10% (275). Furthermore, a prospective Norwegian study of children between 4 to 8 years old did not find mediation via appetite traits (277). In Study III, obesity measures mediated the prospective association between the polygenic risk score for BMI and parental concern of overeating to a greater extent than eating behaviors mediated the genetic susceptibility to obesity. A recent research showed that BMI mainly mediated the association between obesity susceptibility genes and eating disorders in adolescents (284). It can thus be suggested that the interrelationships between eating behaviors, obesity measures and obesity susceptibility genes might be age-dependent. Further, depending on these interrelationships, obesity susceptibility genes may exert their influence via different pathways, which do not necessarily involve eating behaviors, as shown in other studies (278,279,281–283).

6.5. METHODOLOGICAL CONSIDERATIONS

A major strength of this thesis was the use of two large population-based cohorts of European children (IDEFICS/I.Family) and Finnish young adults (FT16) with high participation rates. Despite this, all participants did not participate in all study waves and dropout and non-participation may introduce some bias. Dropout from cohort studies has been associated with participants' low education levels and multiple health outcomes (332). In the IDEFICS/I.Family cohort (Study III), dropout was associated with children's overweight and disadvantageous sociodemographic condition (333). In Study

I, analyses restricted to the FT16 sub-studies (TwinFat and FITFATTWIN) are likely to be underpowered due to low sample size, and genetic confounding might be not addressed in within-pair analyses.

Selection bias might occur due to missing information in some measurements in all studies. In Study III, to address selection bias, data from missing covariates was imputed (334). The cross-sectional nature of Studies I and II did not allow for drawing conclusions on causality or the direction of the pathways. This limitation was partly addressed in Study III examining the direction of the pathways between parental concern of overeating and obesity measures. Furthermore, the prospective design of Study III reduced the risk of reverse causation (334).

In all epidemiological studies, the use of self-reported data is a potential source of error. In Studies I and II, obesity measures and eating-related questionnaires were self-reported. Women and overweight individuals tend to underreport their body weight, nutrient intakes and eating behaviors, especially those related to overeating, whereas they may overreport behaviors related to healthy eating (335–339). In Study III, underreporting might have also occurred since parents of overweight children tend to underestimate their body weight (340). Obesity measures were measured by health professionals, but eating behavior and dietary pattern questionnaires were completed by parents and they may have underreported the behaviors that they consider unhealthy.

Limitations of the DQS constructed in Study I must be acknowledged. The DQS cannot assess individual portion sizes and does not include many food categories, therefore it cannot capture the whole dietary intake. Nevertheless, the DQS is an easy-to-use tool to rank individuals and twins according to their diet quality. In addition, the use of the DQS, together with the eating styles in Study II to derive eating behavior patterns, provided a more detailed picture of the whole eating pattern. Other genetic studies in adults, twin studies or mediation studies were focused on analyzing the role of cognitive behaviors (231–233) or the consumption of certain foods (323,324).

The inclusion of two polygenic risk scores for BMI with ~1million SNPs (Study II) and 2.1 million SNPs (Study III) provided a detailed assessment of the genetic susceptibility to obesity.

All analyses were adjusted for a broad set of covariates, but residual confounding might still exist. To address this limitation, in Study III mediation was assessed by using causal mediation analyses (CMA) instead of structural equation modelling. CMA allowed for testing unmeasured confounding and provided more transparency in the results (307). Hence, the use of CMA in Study III might provide more reliable results. Despite this, Study II aimed to investigate the genetic architecture of eating behavior patterns and obesity. The inclusion of genetic twin modeling together with mediation analyses in Study II provided reliable findings on the shared genetic liability between eating behavior patterns and obesity.

Studies I and II were restricted to Finnish young adults of European ancestry, therefore the generalizability of these findings should be tested in other demographically and ethnically diverse sample sizes. The DQS was constructed based on Finnish and Nordic recommendations and can be used in other Nordic countries or populations with similar dietary recommendations. In Study III, the analyses were extended to children from eight European countries, but in genotyping analyses children from Cyprus were

excluded. Hence, results might not be generalizable to non-European populations of children.

7. CONCLUSIONS AND FUTURE DIRECTIONS

This thesis explored the complex associations between eating behavior patterns, obesity and obesity susceptibility genes among children and adults. The results of this thesis suggested that the newly constructed diet quality score (DQS) is a reliable tool to rapidly assess diet quality and to categorize individuals and twins according to low or high diet quality. The DQS further reflected the intake of key nutrients, eating styles and obesity measures. These results strengthen the idea that a DQS derived from a short food frequency questionnaire might be a useful tool to predict obesity. This thesis has provided a deeper insight of the underlying genetics of eating behavior patterns and obesity. Obesity measures and eating behavior patterns are both explained by environmental and genetic factors during adulthood, with stronger genetic effects on obesity measures. This thesis also provided a comprehensive understanding of the associations between eating behavior patterns and obesity, demonstrating that these associations were bi-directional in children and mostly explained by genetic factors in young adults. The findings of this thesis revealed that obesity susceptibility genes may act through obesity and overeating, indistinctly. These results support previous findings suggesting that genetic variants associated with BMI might also be associated with eating behavior patterns.

In summary, this thesis provided an increased understanding of the role of genetic factors and modifiable environmental factors in obesity and eating behavior patterns. In future studies, it is essential to determine the direction of these associations at different life stages, in order to disentangle the mechanisms by which obesity genetic variants are expressed in these pathways. An increased knowledge of these pathways will provide targeted strategies for vulnerable population groups and can help to reduce stigma toward individuals with obesity. Early prevention studies might benefit by planning interventions on behavioral and nutritional change, especially in those individuals with genetic predisposition to obesity.

ACKNOWLEDGEMENTS

This thesis was carried out at the Department of Public Health between 2016 and 2021 as part of the Doctoral Program in Population Health (DOCPOP), Doctoral School of Health, Faculty of Medicine, University of Helsinki. I wish to acknowledge present and former heads of the Department for the nourishing facilities. In addition, this project has been financially supported by the Finnish Cultural Foundation, the Juho Vainio Foundation and DOCPOP, all of which I acknowledge with gratitude. In addition, I want to thank all the Finnish twins and all the European children and parents who have made this research possible.

I am deeply grateful to my supervisors Professor Anna Keski-Rahkonen, Docent Leonie Bogl and Professor Karri Silventoinen. I admire you all and I am really honored to have benefitted from your constructive supervision, expertise and different points of view throughout these years. Anna and Leonie, I am really indebted to you for giving me the opportunity to start this journey. Anna, thanks for encouraging me to pursue this amazing career, for believing that I was born to become a scientist, for our talks (especially the funny ones), and for your humanity. Leonie, during all these years you have been my example of the scientist and person who I would like to become. Thanks a lot for always sharing with me your knowledge, your expertise and your talent. Thank you for giving me the best ideas to improve the quality of my research and make me shine. Karri, the last member to join this all-star supervising team. I was and I still am really happy that you agreed to be my supervisor. Thank you so much for supporting this journey, for your valuable and different insight, for being so optimistic, for your kindness and for making things easier.

I would also like to thank Professor Jaakko Kaprio, it has been a pleasure to work with you. Thank you for your valuable advice and for always being interested in what I was doing and what I need. I would like to also acknowledge the contributions of all the co-authors of the three articles of this thesis, especially Pyry Sipilä, Teemu Palviainen and Ronja Foraita for assisting me with my statistical issues, and Professor Luis Moreno who gave me the opportunity to visit his group and also to come back to my country when I most needed it.

I wish to thank Docent Susanna Lehtinen-Jacks for accepting the invitation to act as the official opponent of this thesis. I was also lucky to have Assistant Professor Daiva E. Nielsen and Docent Anu Ruusunen as pre-examiners of this thesis, thanks for your help in improving this thesis. I extend my thanks to my thesis committee members Docent Noora Kanerva and Doctor Katri Sääksjärvi, thanks for your helpful comments during our meetings and to remind me that it was my thesis, and that I could do anything that I wanted.

I want to thank my "5th floor" colleagues: Gulnara, Katja, Yasmina, Sara M, Joni, Pyry, Jatta for all the coffee and lunch breaks and for always being ready to help. I wish to especially thank my "academic sister" Jatta Salmela, thank you for your friendship and for being the best colleague I could ever have. Many thanks to my wonderful colleagues

from Kaprio group: Jade, Sara K, Anu, Lalitha, Hannes, Aino and Gabin. Especially thanks to Docent Miina Ollikainen for agreeing to be my faculty representative and Alyce Whipp for carefully reviewing my manuscripts and for your funny way of teaching during doctoral courses.

I want to thank everyone outside academia who made my life easier during all this journey, I cannot name you all, but I guess you know who you are. Moltes gràcies als meus amics de tota la vida: Hugo, Guillem i Josep, gràcies per estar allà sempre que ho he necessitat i per celebrar els meus èxits com si fossin vostres. Mi Laia ¿cuántos años van ya? gracias por estar siempre conmigo y por ser mi mayor fan, yo también soy tu mayor fan. Muchas gracias, kiitos paljon, a mi família finlandesa: Sami, Saku y Susanna, sin vuestro apoyo esta tesis no hubiera sido posible. Nacho y Xavi, si es que os voy a echar de menos, gracias por todos estos años de amistad, sé que sempre estareu amb mi. Finalment moltes gràcies a la meva familia, Guerau, pare i mare, gràcies per entendre les meves decisions encara que impliquin veure'ns menys dies a l'any.

Helsinki, October 2021
Guiomar Masip

REFERENCES

1. World Health Organization. Obesity and overweight. 2020. Available from: https://www.who.int/en/news-room/fact-sheets/detail/obesity-and-overweight
2. Janssen I, Katzmarzyk PT, Srinivasan SR, Chen W, Malina RM, Bouchard C, et al. Utility of childhood BMI in the prediction of adulthood disease: Comparison of national and international references. Obes Res. 2005;13(6):1106–15.
3. Nettleton JA, Follis JL, Ngwa JS, Smith CE, Ahmad S, Tanaka T, et al. Gene × dietary pattern interactions in obesity: analysis of up to 68 317 adults of European ancestry. Hum Mol Genet. 2015;24(16):4728–38.
4. Silventoinen K, Jelenkovic A, Sund R, Hur Y, Yokoyama Y, Honda C, et al. Genetic and environmental effects on body mass index from infancy to the onset of adulthood: an individual-based pooled analysis of 45 twin cohorts participating in the COllaborative project of Development of Anthropometrical measures in Twins (CODATwins). Am J Clin Nutr. 2016;104:371–9.
5. Qi L. Gene-Diet Interactions in Complex Disease: Current Findings and Relevance for Public Health. Curr Nutr Rep. 2012;1(4):222–7.
6. Silventoinen K, Hasselbalch AL, Lallukka T, Bogl L, Pietiläinen KH, Heitmann BL, et al. Modification effects of physical activity and protein intake on heritability of body size and composition. Am J Clin Nutr. 2009;90(4):1096–103.
7. Jacobs Jr DR, Steffen LM. Nutrients, foods, and dietary patterns as exposures in research: a framework for food synergy 1–3. Am J Clin Nutr. 2003;78:508–13.
8. Hu FB. Dietary pattern analysis: A new direction in nutritional epidemiology. Curr Opin Lipidol. 2002;13(1):3–9.
9. Aljadani H, Patterson A, Sibbritt D, Collins C. Diet quality and 6-year risk of overweight and obesity among mid-age Australian women who were initially in the healthy weight range. Heal Promot J Aust. 2016;27:29–35.
10. Livingstone KM, Mcnaughton SA. Diet quality is associated with obesity and hypertension in Australian adults: a cross sectional study. BMC Public Health. 2016;16:1037.
11. Wong JE, Parnell WR, Howe AS, Lubransky AC, Black KE, Skidmore PML. Diet quality is associated with measures of body fat in adolescents from Otago , New Zealand. Pu. 2014;18(8):1453–60.
12. Sundararajan K, Campbell MK, Choi Y, Sarma S. The Relationship Between Diet Quality and Adult Obesity: Evidence from Canada. J Am Coll Nutr. 2014;33(1):1–17.
13. Asghari G, Mirmiran P, Yuzbashian E, Azizi F. A systematic review of diet quality indices in relation to obesity. Br J Nutr. 2017;117(8):1055–65.
14. Keski-Rahkonen A, Bulik C, Pietiläinen K, Rose R, Kaprio J, Rissanen A. Eating styles, overweight and obesity in young adult twins. Eur J Clin Nutr. 2007;61:822–9.
15. Leon-Munoz LM, Garcia-Esquinas E, Soler-Vila H, Guallar-Castillón P, Banegas JR, Rodríguez-Artalejo F. Unhealthy Eating Behaviors and Weight Gain: A Prospective Study in Young and Middle-Age Adults. Obesity. 2016;24(5):1178–84.
16. Van Strien T. Causes of Emotional Eating and Matched Treatment of Obesity. Curr Diab Rep. 2018;18:35.
17. Yengo L, Sidorenko J, Kemper KE, Zheng Z, Wood AR, Weedon MN, et al. Meta-analysis of genome-wide association studies for height and body mass index in ~ 700 000 individuals of European ancestry. Hum Mol Genet. 2018;27(20):3641–9.
18. Khera A V, Chaffin M, Wade KH, Zahid S, Brancale J, Xia R, et al. Polygenic Prediction

of Weight and Obesity Trajectories from Birth to Adulthood. Cell. 2019;177(3):587–96.

19. Locke AE, Kahali B, Berndt SI, Justice AE, Pers TH, Day FR, et al. Genetic studies of body mass index yield new insights for obesity biology. Nature. 2015;518:197–206.
20. Pearce LR, Atanassova N, Banton MC, Bottomley B, Van Der Klaauw AA, Revelli JP, et al. XKSR2 mutations are associated with obesity, insulin resistance, and impaired cellular fuel oxidation. Cell. 2013;155(4):765.
21. Loos RJF, Yeo GSH. The bigger picture of FTO - The first GWAS-identified obesity gene. Nat Rev Endocrinol. 2014;10(1):51–61.
22. Claussnitzer M, Dankel SN, Kim K-H, Quon G, Meuleman W, Haugen C, et al. FTO Obesity Variant Circuitry and Adipocyte Browning in Humans. N Engl J Med. 2015;373(10):895–907.
23. Hubáček JA, Pikhart H, Peasey A, Kubínová R, Bobák M. FTO variant, energy intake, physical activity and basal metabolic rate in caucasians. the HAPIEE study. Physiol Res. 2011;60(1):175–83.
24. Gerken T, Girard CA, Tung YCL, Webby CJ, Saudek V, Hewitson KS, et al. The obesity-associated FTO gene encodes a 2-oxoglutarate-dependent nucleic acid demethylase. Science. 2007;318(5855):1469–72.
25. Silventoinen K, Konttinen H. Obesity and eating behavior from the perspective of twin and genetic research. Neurosci Biobehav Rev. 2020;109:150–65.
26. Pallister T, Spector TD, Menni C. Twin studies advance the understanding of gene-environment interplay in human nutrigenomics. Nutr Res Rev. 2014;27:242–51.
27. Barron R, Bermingham K, Brennan L, Gibney ER, Gibney MJ, Ryan MF, et al. Twin metabolomics: The key to unlocking complex phenotypes in nutrition research. Nutr Res. 2016;36(4):291–304.
28. Allison D. The use of discordant sibling pairs for finding genetic loci linked to obesity: practical considerations. Int J Obes Relat Metab Disord. 1996;20(6):553–60.
29. Plomin R, Asbury K, Dunn J. Why Are Children in the Same Family So Different? Nonshared Environment a Decade Later. Can J Psychiatry. 2001;46.
30. Wells JCK, Fewtrell MS. Measuring body composition. Arch Dis Child. 2006;91(7):612–7.
31. World Health Organization. Obesity: preventing and managing the global epidemic. WHO Technical Report series. 2000.
32. De Onis M, Onyango AW, Borghi E, Siyam A, Nishida C, Siekmann J. Development of a WHO growth reference for school-aged children and adolescents. Bull World Health Organ. 2007;85(9):660–7.
33. Cole TJ, Lobstein T. Extended international (IOTF) body mass index cut-offs for thinness, overweight and obesity. Pediatr Obes. 2012;7(4):284–94.
34. Van Dijk SB, Takken T, Prinsen EC, Wittink H. Different anthropometric adiposity measures and their association with cardiovascular disease risk factors: A meta-analysis. Netherlands Hear J. 2012;20(5):208–18.
35. Lean MEJ, Han TS, Morrison CE. Waist circumference as a measure for indicating need for weight management. BMJ. 1995;311(6998):158.
36. Wang Y, Rimm EB, Stampfer MJ, Willett WC, Hu FB. Comparison of abdominal adiposity and overall obesity in predicting risk of type 2 diabetes among men. Am J Clin Nutr. 2005;81(3):555–63.
37. Smith U. Abdominal obesity: A marker of ectopic fat accumulation. J Clin Invest. 2015;125(5):1790–2.
38. Klöting N, Blüher M. Adipocyte dysfunction, inflammation and metabolic syndrome. Rev Endocr Metab Disord. 2014;15(4):277–87.
39. De Moraes ACF, Fadoni RP, Ricardi LM, Souza TC, Rosaneli CF, Nakashima ATA, et al.

Prevalence of abdominal obesity in adolescents: A systematic review. Obes Rev. 2011;12(2):69–77.

40. Taylor RW, Jones IE, Williams SM, Goulding A. Evaluation of waist circumference, waist-to-hip ratio, and the conicity index as screening tools for high trunk fat mass, as measured by dual-energy X-ray absorptiometry, in children aged 3-19 y[1-3]. Am J Clin Nutr. 2000;72(2):490–5.

41. Lim SS, Vos T, Flaxman AD, Danaei G, Shibuya K, Adair-Rohani H, et al. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990-2010: A systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380(9859):2224–60.

42. Franks PW, Hanson RL, Knowler WC, Sievers ML, Bennett PH, Looker H. Childhood Obesity, Other Cardiovascular Risk Factors, and Premature Death. N Engl J Med. 2010;(362):485–93.

43. Juonala M, Magnussen CG, Berenson GS, Venn A, Burns TL, Daniels SR, et al. Childhood Adiposity, Adult Adiposity, and Cardiovascular Risk Factors. N Engl J Med. 2011;365:1876–85.

44. Simmonds M, Llewellyn A, Owen CG, Woolacott N. Predicting adult obesity from childhood obesity: A systematic review and meta-analysis. Obes Rev. 2016;17(2):95–107.

45. Llewellyn A, Simmonds M, Owen CG, Woolacott N. Childhood obesity as a predictor of morbidity in adulthood: A systematic review and meta-analysis. Obes Rev. 2016;17(1):56–67.

46. NCD RFC. Trends in adult body-mass index in 200 countries from 1975 to 2014: A pooled analysis of 1698 population-based measurement studies with 19.2 million participants. Lancet. 2016;387(10026):1377–96.

47. NCD RFC. Worldwide trends in body-mass index, underweight, overweight, and obesity from 1975 to 2016: a pooled analysis of 2416 population-based measurement studies in 128·9 million children, adolescents, and adults. Lancet. 2017;390(10113):2627–42.

48. Marques A, Peralta M, Naia A, Loureiro N, De Matos MG. Prevalence of adult overweight and obesity in 20 European countries, 2014. Eur J Public Health. 2018;28(2):295–300.

49. Garrido-Miguel M, Cavero-Redondo I, Álvarez-Bueno C, Rodríguez-Artalejo F, Moreno LA, Ruiz JR, et al. Prevalence and Trends of Overweight and Obesity in European Children from 1999 to 2016: A Systematic Review and Meta-analysis. JAMA Pediatr. 2019;173(10).

50. Ahrens W, Pigeot I, Pohlabeln H, De Henauw S, Lissner L, Molnár D, et al. Prevalence of overweight and obesity in European children below the age of 10. Int J Obes. 2014;38:S99–107.

51. Koponen P, Borodulin K, Lundqvist A, Sääksjärvi K, Koskinen S. Terveys, toimintakyky ja hyvinvointi Suomessa - FinTerveys 2017 -tutkimus. Terveyden ja hyvinvoinnin laitos (THL), Raportti 4/2018. Terveyden ja hyvinvoinnin laitos. 2018. 38–41 p.

52. Jääskeläinen S, Mäki P, Mölläri K, Mäntymaa P. Lasten ja nuorten ylipaino ja lihavuus 2018 Joka neljäs poika ja lähes joka viides tyttö on ylipainoinen tai lihava. 2020;1–22.

53. Lake A, Townshend T. Obesogenic environments: Exploring the built and food environments. J R Soc Promot Health. 2006;126(6):262–7.

54. Swinburn BA, Sacks G, Hall KD, McPherson K, Finegood DT, Moodie ML, et al. The global obesity pandemic: Shaped by global drivers and local environments. Lancet. 2011;378(9793):804–14.

55. Townshend T, Lake A. Obesogenic environments: Current evidence of the built and food environments. Perspect Public Health. 2017;137(1):38–44.

56. Allison SJ. Metabolism: High salt intake as a driver of obesity. Nat Rev Nephrol. 2018;14(5):285.

57. Field AE, Willett WC, Lissner L, Colditz GA. Dietary fat and weight gain among women in the nurses' health study. Obesity. 2007;15(4):967–76.
58. Hu F, Malik V. Sugar-sweetened beverages and risk of obesity and type 2 diabetes: Epidemiologic evidence. Physiol Behav. 2010;(1):47–54.
59. Vartanian LR, Schwartz MB, Brownell KD. Effects of soft drink consumption on nutrition and health: A systematic review and meta-analysis. Am J Public Health. 2007;97(4):667–75.
60. Ledikwe J, Ello-Martin J, Rolls B. Symposium: Modifying the Food Environment: Energy Density, Food Costs, and Portion Size Food Choices and Diet Costs: an Economic Analysis 1, 2. J Nutr. 2005;900–4.
61. Pendergast FJ, Livingstone KM, Worsley A, McNaughton SA. Correlates of meal skipping in young adults: A systematic review. Int J Behav Nutr Phys Act. 2016;13(1).
62. Görlach MG, Kohlmann S, Shedden-Mora M, Rief W, Westermann S. Expressive Suppression of Emotions and Overeating in Individuals with Overweight and Obesity. Eur Eat Disord Rev. 2016;24(5):377–82.
63. Hu FB. Obesity Epidemiology. Oxford University Press I, editor. Oxford; 2008. 53–83 p.
64. Lee IM, Djoussé L, Sesso HD, Wang L, Buring JE. Physical activity and weight gain prevention. JAMA - J Am Med Assoc. 2010;303(12):1173–9.
65. Cameron N, Godino J, Nichols JF, Wing D, Hill L, Patrick K. Associations between physical activity and BMI, body fatness, and visceral adiposity in overweight or obese Latino and non-Latino adults. Int J Obes. 2017;41(6):873–7.
66. Fan JX, Brown BB, Hanson H, Kowaleski-Jones L, Smith KR, Zick C. Moderate to Vigorous Physical Activity and Weight Outcomes: Does Every Minute Count? Am J Heal Promot. 2013;28(1):41–9.
67. Maher C, Olds TS, Eisenmann JC, Dollman J. Screen time is more strongly associated than physical activity with overweight and obesity in 9- to 16-year-old Australians. Acta Paediatr Int J Paediatr. 2012;101(11):1170–4.
68. O'Brien W, Issartel J, Belton S. Relationship between Physical Activity, Screen Time and Weight Status among Young Adolescents. Sports. 2018;6(3):57.
69. Cho KO, Lee S, Kim YS. Physical Activity and Sedentary Behavior Are Independently Associated with Weight in Korean Adolescents. J Lifestyle Med. 2014;4(1):47–54.
70. Wanner M, Martin BW, Autenrieth CS, Schaffner E, Meier F, Brombach C, et al. Associations between domains of physical activity, sitting time, and different measures of overweight and obesity. Prev Med Reports. 2016;3:177–84.
71. da Silva BGC, Silva ICM d., Ekelund U, Brage S, Ong KK, De Lucia Rolfe E, et al. Associations of physical activity and sedentary time with body composition in Brazilian young adults. Sci Rep. 2019;9(1):1–10.
72. Newton RL, Han H, Zderic T, Hamilton M. The Energy Expenditure of Sedentary Behavior: A Whole Room Calorimeter Study. PLoS One. 2013;8(5).
73. Carneiro IP, Elliott SA, Siervo M, Padwal R, Bertoli S, Battezzati A, et al. Is obesity associated with altered energy expenditure? Adv Nutr. 2016;7(3):476–87.
74. Poulton R, Caspi A, Milne BJ, Thomson WM, Taylor A, Sears MR, et al. Association between children's experience of socioeconomic disadvantage and adult health: A life-course study. Lancet. 2002;360(9346):1640–5.
75. Heraclides A, Brunner E. Social mobility and social accumulation across the life course in relation to adult overweight and obesity: The Whitehall II study. J Epidemiol Community Health. 2010;64(8):714–9.
76. Hart C, Mcconnachie A, Upton M, Watt G. Risk factors in the Midspan family study by social class in childhood and adulthood. Int J Epidemiol. 2008;37(3):604–14.
77. Knai C, Lobstein T, Darmon N, Rutter H, McKee M. Socioeconomic patterning of

childhood overweight status in Europe. Int J Environ Res Public Health. 2012;9(4):1472–89.

78. Bammann K, Lissner L, Pigeot I, Ahrens W, editors. Instruments for Health Surveys in Children and Adolescents. Springer International Publishing; 2019. XVI, 301.

79. Shrewsbury V, Wardle J. Socioeconomic status and adiposity in childhood: A systematic review of cross-sectional studies 1990-2005. Obesity. 2008;16(2):275–84.

80. Giskes K, Avendaño M, Brug J, Kunst AE. A systematic review of studies on socioeconomic inequalities in dietary intakes associated with weight gain and overweight/obesity conducted among European adults. Obes Rev. 2010;11(6):413–29.

81. Hagman E, Danielsson P, Brandt L, Svensson V, Ekbom A, Marcus C. Childhood Obesity, Obesity Treatment Outcome, and Achieved Education: A Prospective Cohort Study. J Adolesc Heal. 2017;61(4):508–13.

82. Gill N, Gjelsvik A, Mercurio LY, Amanullah S. Childhood Obesity Is Associated with Poor Academic Skills and Coping Mechanisms. J Pediatr. 2021;228:278–84.

83. Laursen UB, Johansen MB, Joensen AM, Lau CJ, Overvad K, Larsen ML. Educational level and living arrangements are associated with dietary intake of red meat and fruit/vegetables: A Danish cross-sectional study. Scand J Public Health. 2019;47(5):557–64.

84. Flegal KM, Kruszon-Moran D, Carroll MD, Fryar CD, Ogden CL. Trends in obesity among adults in the United States, 2005 to 2014. JAMA. 2016;315(21):2284–91.

85. Zahnd WE, Rogers V, Smith T, Ryherd SJ, Botchway A, Steward DE. Gender-specific relationships between socioeconomic disadvantage and obesity in elementary school students. Prev Med (Baltim). 2015;81(2015):138–41.

86. Reyes Matos U, Mesenburg MA, Victora CG. Socioeconomic inequalities in the prevalence of underweight, overweight, and obesity among women aged 20–49 in low- and middle-income countries. Int J Obes. 2020;44(3):609–16.

87. Mauvais-Jarvis F. Sex differences in metabolic homeostasis, diabetes, and obesity. Biol Sex Differ. 2015;6(1):1–9.

88. Liu J, Fox CS, Hickson DMA, May WD, Hairston KG, Carr JJ, et al. Impact of abdominal visceral and subcutaneous adipose tissue on cardiometabolic risk factors: The Jackson Heart Study. J Clin Endocrinol Metab. 2010;95(12):5419–26.

89. Reue K. Sex differences in obesity: X chromosome dosage as a risk factor for increased food intake, adiposity and co-morbidities. Physiol Behav. 2017;176:174–82.

90. Wang L, Southerland J, Wang K, Bailey BA, Alamian A, Stevens MA, et al. Ethnic Differences in Risk Factors for Obesity among Adults in California, the United States. J Obes. 2017;2017.

91. Itani O, Jike M, Watanabe N, Kaneita Y. Short sleep duration and health outcomes: a systematic review, meta-analysis, and meta-regression. Sleep Med. 2017;32:246–56.

92. Koster A, Leitzmann MF, Schatzkin A, Adams KF, van Eijk JT., Hollenbeck AR, et al. The combined relations of adiposity and smoking on mortality. Am J Clin Nutr. 2008;88(5):1206–12.

93. Cuevas AG, Chen R, Thurber KA, Slopen N, Williams DR. Psychosocial Stress and Overweight and Obesity: Findings from the Chicago Community Adult Health Study. Ann Behav Med. 2019;53(11):964–74.

94. Petrakis D, Vassilopoulou L, Mamoulakis C, Psycharakis C, Anifantaki A, Sifakis S, et al. Endocrine disruptors leading to obesity and related diseases. Int J Environ Res Public Health. 2017;14(10):1–18.

95. Rounge TB, Page CM, Lepistö M, Ellonen P, Andreassen BK, Weiderpass E. Genome-wide DNA methylation in saliva and body size of adolescent girls. Epigenomics. 2016;8(11):1495–505.

96. Pîrsean C, Neguț C, Stefan-van Staden RI, Dinu-Pirvu CE, Armean P, Udeanu DI. The salivary levels of leptin and interleukin-6 as potential inflammatory markers in children obesity. PLoS One. 2019;14(1):1–13.

97. Ventura AK, Birch LL. Does parenting affect children's eating and weight status? Int J Behav Nutr Phys Act. 2008;5:15.

98. Nicklaus S, Boggio V, Chabanet C, Issanchou S. A prospective study of food variety seeking in childhood, adolescence and early adult life. Appetite. 2005;44(3):289–97.

99. Northstone K, Emmett PM. Are dietary patterns stable throughout early and mid-childhood? A birth cohort study. Br J Nutr. 2008;100(5):1069–76.

100. Ventura AK, Worobey J. Early influences on the development of food preferences. Curr Biol. 2013;23(9):R401–8.

101. Daniels LA, Mallan KM, Battistutta D, Nicholson JM, Meedeniya JE, Bayer JK, et al. Child eating behavior outcomes of an early feeding intervention to reduce risk indicators for child obesity: The NOURISH RCT. Obesity. 2014;22(5):104–11.

102. Tripicchio GL, Keller KL, Johnson C, Pietrobelli A, Heo M, Faith MS. Differential maternal feeding practices, eating self-regulation, and adiposity in young twins. Pediatrics. 2014;134(5):e1399–404.

103. Chen P-J, Antonelli M. Conceptual Models of Food Choice: Influential Factors Related to Foods. Foods. 2020;9(1898):1–21.

104. Falk L, Bisogni CA, Sobal J. Food choice processes of older adults: A qualitative investigation. J Nutr Educ Behav. 1996;28(5):257–65.

105. Furst T, Connors M, Bisogni CA, Sobal J, Falk LW. Food choice: A conceptual model of the process. Appetite. 1996;26(3):247–66.

106. Connors M, Bisogni CA, Sobal J, Devine CM. Managing values in personal food systems. Appetite. 2001;36(3):189–200.

107. Blundell JE, Cooling J. Routes to obesity: Phenotypes, food choices and activity. Br J Nutr. 2000;83(Suppl. 1):S33–8.

108. Blundell JE, Stubbs RJ, Golding C, Croden F, Alam R, Whybrow S, et al. Resistance and susceptibility to weight gain: Individual variability in response to a high-fat diet. Physiol Behav. 2005;86(5):614–22.

109. Jacob R, Drapeau V, Lamarche B, Doucet É, Pomerleau S, Provencher V. Associations among eating behaviour traits, diet quality and food labelling: A mediation model. Public Health Nutr. 2019;23(4):631–41.

110. Kim J, Choue R, Lim H. Differences of Socio-psychology, Eating Behavior, Diet Quality and Quality of Life in South Korean Women according to Their Weight Status. Clin Nutr Res. 2016;5(3):161.

111. Leech RM, Livingstone KM, Worsley A, Timperio A, McNaughton SA. Meal Frequency but Not Snack Frequency Is Associated with Micronutrient Intakes and Overall Diet Quality in Australian Men and Women. J Nutr. 2016;146(10):2027–34.

112. Hall L, Tejada-Tayabas LM, Monárrez-Espino J. Breakfast Skipping, Anxiety, Exercise, and Soda Consumption are Associated with Diet Quality in Mexican College Students. Ecol Food Nutr. 2017;56(3):218–37.

113. Paans NPG, Gibson-Smith D, Bot M, van Strien T, Brouwer IA, Visser M, et al. Depression and eating styles are independently associated with dietary intake. Appetite. 2019;134(December 2018):103–10.

114. Larson NI, Miller JM, Watts AW, Story MT, Neumark-Sztainer DR. Adolescent snacking behaviors are associated with dietary intake and weight status. J Nutr. 2016;146(7):1348–55.

115. De Lauzon B, Romon M, Deschamps V, Lafay L, Borys JM, Karlsson J, et al. The Three-Factor Eating Questionnaire-R18 is able to distinguish among different eating patterns in

a general population. J Nutr. 2004;134(9):2372–80.

116. Elfhag K, Tholin S, Rasmussen F. Consumption of fruit, vegetables, sweets and soft drinks are associated with psychological dimensions of eating behaviour in parents and their 12-year-old children. Public Health Nutr. 2008;11(9):914–23.

117. Konttinen H, Männistö S, Sarlio-Lähteenkorva S, Silventoinen K, Haukkala A. Emotional eating, depressive symptoms and self-reported food consumption. A population-based study. Appetite. 2010;54(3):473–9.

118. Mason C, De Dieu Tapsoba J, Duggan C, Wang CY, Alfano CM, McTiernan A. Eating behaviors and weight loss outcomes in a 12-month randomized trial of diet and/or exercise intervention in postmenopausal women. Int J Behav Nutr Phys Act. 2019;16(1):1–11.

119. Alkerwi A. Diet quality concept. Nutrition. 2014;30(6):613–8.

120. Wirt A, Collins CE. Diet quality - What is it and does it matter? Public Health Nutr. 2009;12(12):2473–92.

121. Cuenca-García M, Artero EG, Sui X, Lee D chul, Hebert JR, Blair SN. Dietary indices, cardiovascular risk factors and mortality in middle-aged adults: Findings from the Aerobics Center Longitudinal Study. Ann Epidemiol. 2014;24(4):297-303.e2.

122. Ocké MC. Evaluation of methodologies for assessing the overall diet: Dietary quality scores and dietary pattern analysis. Proc Nutr Soc. 2013;72(2):191–9.

123. Willett W, Rockström J, Loken B, Springmann M, Lang T, Vermeulen S, et al. Food in the Anthropocene: the EAT–Lancet Commission on healthy diets from sustainable food systems. Lancet. 2019;393(10170):447–92.

124. Waijers PMCM, Feskens EJM, Ocké MC. A critical review of predefined diet quality scores. Br J Nutr. 2007;97(2):219–31.

125. Willett W. Nutritional Epidemiology. 3rd ed. New York: Oxford University Press; 2013. 529 p.

126. Naska A, Lagiou A, Lagiou P. Dietary assessment methods in epidemiological research: current state of the art and future prospects. F1000Research. 2017;6(0):926.

127. Burggraf C, Teuber R, Brosig S, Meier T. Review of a priori dietary quality indices in relation to their construction criteria. Nutr Rev. 2018;76(10):747–64.

128. Kennedy ET, Ohls J, Carlson S, Fleming K. The Healthy Eating Index: Design and applications. J Am Diet Assoc. 1995;95:1103–8.

129. McCullough ML, Feskanich D, Stampfer MJ, Giovannucci EL, Rimm EB, Hu FB, et al. Diet quality and major chronic disease risk in men and women: Moving toward improved dietary guidance. Am J Clin Nutr. 2002;76(6):1261–71.

130. Trichopoulou A, Costacou T, Barnia C, Trichopoulos D. Adherence to a Mediterranean Diet and Survival in a Greek Population. N Engl J Med. 2003;348(26).

131. Fung TT, Chiuve SE, McCullough ML, Rexrode KM, Logroscino G, Hu FB. Adherence to a DASH-style diet and risk of coronary heart disease and stroke in women. Arch Intern Med. 2008;168(7):713–20.

132. Alkerwi A, Vernier C, Crichton GE, Sauvageot N, Shivappa N, Hébert JR. Cross-comparison of diet quality indices for predicting chronic disease risk: Findings from the Observation of Cardiovascular Risk Factors in Luxembourg (ORISCAV-LUX) study. Br J Nutr. 2015;113(2):259–69.

133. Kanerva N, Kaartinen NE, Schwab U, Lahti-Koski M, Männistö S. The baltic sea diet score: A tool for assessing healthy eating in nordic countries. Public Health Nutr. 2014;17(8):1697–705.

134. Olsen A, Egeberg R, Halkjær J, Christensen J, Overvad K, Tjønneland A, et al. Healthy aspects of the nordic diet are related to lower total mortality1,2. J Nutr. 2011;141(4):639–44.

135. Schwingshackl L, Hoffmann G. Diet Quality as Assessed by the Healthy Eating Index, the Alternate Healthy Eating Index, the Dietary Approaches to Stop Hypertension Score, and Health Outcomes: A Systematic Review and Meta-Analysis of Cohort Studies. J Acad Nutr Diet. 2015;115(5):780-800.e5.

136. Schwingshackl L, Bogensberger B, Hoffmann G. Diet Quality as Assessed by the Healthy Eating Index, Alternate Healthy Eating Index, Dietary Approaches to Stop Hypertension Score, and Health Outcomes: An Updated Systematic Review and Meta-Analysis of Cohort Studies. J Acad Nutr Diet. 2018;118(1):74-100.e11.

137. Panizza CE, Shvetsov YB, Harmon BE, Wilkens LR, Le Marchand L, Haiman C, et al. Testing the predictive validity of the healthy eating index-2015 in the multiethnic cohort: Is the score associated with a reduced risk of all-cause and cause-specific mortality? Nutrients. 2018;10(4).

138. Lemming EW, Byberg L, Wolk A, Michaëlsson K. A comparison between two healthy diet scores, the modified Mediterranean diet score and the Healthy Nordic Food Index, in relation to all-cause and cause-specific mortality. Br J Nutr. 2018;119(7):836–46.

139. Kanerva N, Kaartinen NE, Rissanen H, Knekt P, Eriksson JG, Sääksjärvi K, et al. Associations of the Baltic Sea diet with cardiometabolic risk factors-a meta-analysis of three Finnish studies. Br J Nutr. 2014;112(4):616–26.

140. Kanerva N, Loo BM, Eriksson JG, Leiviskä J, Kaartinen NE, Jula A, et al. Associations of the Baltic Sea diet with obesity-related markers of inflammation. Ann Med. 2014;46(2):90–6.

141. Kanerva N, Harald K, Männistö S, Kaartinen NE, Maukonen M, Haukkala A, et al. Adherence to the healthy Nordic diet is associated with weight change during 7 years of follow-up. Br J Nutr. 2018;120(1):101–10.

142. Esposito K, Kastorini CM, Panagiotakos DB, Giugliano D. Mediterranean diet and weight loss: Meta-analysis of randomized controlled trials. Metab Syndr Relat Disord. 2011;9(1):1–12.

143. Fallaize R, Livingstone KM, Celis-Morales C, Macready AL, San-Cristobal R, Navas-Carretero S, et al. Association between diet-quality scores, adiposity, total cholesterol and markers of nutritional status in european adults: Findings from the Food4Me study. Nutrients. 2018;10(1).

144. Fung TT, Pan A, Hou T, Chiuve SE, Tobias DK, Mozaffarian D, et al. Long-Term Change in Diet Quality Is Associated with Body Weight Change in Men and Women[1–3]. J Nutr. 2015;145(8):1850–6.

145. Wang T, Heianza Y, Sun D, Huang T, Ma W, Rimm EB, et al. Improving adherence to healthy dietary patterns, genetic risk, and long term weight gain: Gene-diet interaction analysis in two prospective cohort studies. BMJ. 2018;360:1–9.

146. Lassale C, Fezeu L, Andreeva VA, Hercberg S, Kengne AP, Czernichow S, et al. Association between dietary scores and 13-year weight change and obesity risk in a French prospective cohort. Int J Obes. 2012;36(11):1455–62.

147. De Oliveira Otto MC, Padhye NS, Bertoni AG, Jacobs DR, Mozaffarian D. Everything in moderation - Dietary diversity and quality, central obesity and risk of diabetes. PLoS One. 2015;10(10):1–13.

148. Sares-Jäske L, Knekt P, Lundqvist A, Heliövaara M, Männistö S. Dieting attempts modify the association between quality of diet and obesity. Nutr Res. 2017;45:63–72.

149. Guo Y, Kopec JA, Cibere J, Li LC, Goldsmith CH. Population Survey Features and Response Rates: A Randomized Experiment. 2016;106(8):1422–6.

150. Sahlqvist S, Song Y, Bull F, Adams E, Preston J, Ogilvie D. Effect of questionnaire length, personalisation and reminder type on response rate to a complex postal survey: Randomised controlled trial. BMC Med Res Methodol. 2011;11(1):62.

151. Calfas KJ, Zabinski MF, Rupp J. Practical Nutrition Assessment in Primary Care Settings.

Am J Prev Med. 2000;18(4).

152. England CY, Andrews RC, Jago R, Thompson JL. A systematic review of brief dietary questionnaires suitable for clinical use in the prevention and management of obesity, cardiovascular disease and type 2 diabetes. Eur J Clin Nutr. 2015;69(9):997–1003.

153. Lafrenière J, Harrison S, Laurin D, Brisson C, Talbot D, Couture P, et al. Development and validation of a Brief Diet Quality Assessment Tool in the French-speaking adults from Quebec. Int J Behav Nutr Phys Act. 2019;16(1):1–10.

154. Schröder H, Benitez Arciniega A, Soler C, Covas MI, Baena-Díez JM, Marrugat J. Validity of two short screeners for diet quality in time-limited Settings. Public Health Nutr. 2012;15(4):618–26.

155. Leppälä J, Lagström H, Kaljonen A, Laitinen K. Construction and evaluation of a self-contained index for assessment of diet quality. Scand J Public Health. 2010;38(8):794–802.

156. Kiely M, Collins A, Lucey AJ, Andersen R, Cashman KD, Hennessy. Development, validation and implementation of a quantitative food frequency questionnaire to assess habitual vitamin D intake. J Hum Nutr Diet. 2016;29(4):495–504.

157. MacDonald HM, Garland A, Burr J, Strachan A, Wood AD, Jamil NA, et al. Validation of a short questionnaire for estimating dietary calcium intakes. Osteoporos Int. 2014;25(6):1765–73.

158. Šatalić Z, Colić Barić I, Cecić I, Keser I. Short food frequency questionnaire can discriminate inadequate and adequate calcium intake in Croatian postmenopausal women. Nutr Res. 2007;27(9):542–7.

159. Greenwood JLJ, Lin J, Arguello D, Ball T, Shaw JM. Healthy Eating Vital Sign: A New Assessment Tool for Eating Behaviors. ISRN Obes. 2012;2012:1–7.

160. Hemiö K, Pölönen A, Ahonen K, Kosola M, Viitasalo K, Lindström J. A simple tool for diet evaluation in primary health care: Validation of a 16-item food intake questionnaire. Int J Environ Res Public Health. 2014;11(3):2683–97.

161. Epel E, Lapidus R, McEwen B, Brownell K. Stress may add bite to appetite in women: A laboratory study of stress-induced cortisol and eating behavior. Psychoneuroendocrinology. 2001;26(1):37–49.

162. Tyrka AR, Walters OC, Price LH, Anderson GM, Carpenter LL. Altered response to neuroendocrine challenge linked to indices of the metabolic syndrome in healthy adults. Horm Metab Res. 2012;44(7):543–9.

163. Zellner DA, Loaiza S, Gonzalez Z, Pita J, Morales J, Pecora D, et al. Food selection changes under stress. Physiol Behav. 2006;87(4):789–93.

164. Appelhans BM, Pagoto SL, Peters EN, Spring BJ. HPA axis response to stress predicts short-term snack intake in obese women. Appetite. 2010;54(1):217–20.

165. Zellner DA, Saito S, Gonzalez J. The effect of stress on men's food selection. Appetite. 2007;49(3):696–9.

166. Macht M. How emotions affect eating: A five-way model. Appetite. 2008;50(1):1–11.

167. Kaplan HI, Kaplan HS. The psychosomatic concept of obesity. J Nerv Ment Dis. 1957;125(2):181–201.

168. Bruch H. Eating disorders. New York: Basic Books; 1973.

169. Schachter S. Obesity and eating. Internal and external cues differentially affect the eating behavior of obese and normal subjects. Science. 1968 Aug;161(3843):751–6.

170. Van Strien T, Roelofs K, De Weerth C. Cortisol reactivity and distress-induced emotional eating. Psychoneuroendocrinology. 2013;38(5):677–84.

171. Schachter S, Rodin J. Obese humans and rats. Obese humans and rats. Oxford, England: Lawrence Erlbaum; 1974. ix, 182–ix, 182.

172. Ferriday D, Brunstrom JM. I just can't help myself: Effects of food-cue exposure in

overweight and lean individuals. Int J Obes. 2011;35(1):142–9.

173. Halford JCG, Boyland EJ, Hughes GM, Stacey L, McKean S, Dovey TM. Beyond-brand effect of television food advertisements on food choice in children: The effects of weight status. Public Health Nutr. 2008;11(9):897–904.

174. Anschutz DJ, Engels RCME, Van Strien T. Side effects of television food commercials on concurrent nonadvertised sweet snack food intakes in young children. Am J Clin Nutr. 2009;89(5):1328–33.

175. Anderson GH, Khodabandeh S, Patel B, Luhovyy BL, Bellissimo N, Mollard RC. Mealtime exposure to food advertisements while watching television increases food intake in overweight and obese girls but has a paradoxical effect in boys. Appl Physiol Nutr Metab. 2014;40(2):162–7.

176. Herman CP, Polivy J. Anxiety, restraint, and eating behavior. J Abnorm Psychol. 1975 Dec;84(6):66–72.

177. Herman CP, Mack D. Restrained and unrestrained eating. Vol. 43, Journal of Personality. United Kingdom: Blackwell Publishing; 1975. p. 647–60.

178. Heatherton TF, Herman CP, Polivy J, King GA, McGree ST. The (mis)measurement of restraint: An analysis of conceptual and psychometric issues. Vol. 97, Journal of Abnormal Psychology. US: American Psychological Association; 1988. p. 19–28.

179. Stunkard AJ, Messick S. The three-factor eating questionnaire to measure dietary restraint, disinhibition and hunger. J Psychosom Res. 1985;29(1):71–83.

180. Van Strien T, Frijters JE, Bergers GP, Defares PB. The Dutch Eating Behavior Qusetionnaires (DEBQ) for assesmment of Restraint, Emotional, and External Eating Behavior. Int J Eat Disord. 1986;5(2):295–315.

181. Karlsson J, Persson L-O, Sjöström L, Sullivan M. Psychometric properties and factor structure of the Three-Factor Eating Questionnaire (TFEQ) in obese men and women. Results from the Swedish Obese Subjects (SOS) study. Int J Obes. 2000;24:1715–25.

182. Braet C, van Strien T. Assessment of emotional, externally induced and restrained eating behaviour in nine to twelve-year-old obese and non-obese children. Behav Res Ther. 1997;35(9):863–73.

183. Van Strien T, Oosterveld P. The Children's DEBQ for Assessment of Restrained, Emotional, and External Eating in 7- to 12-Year-Old Children. Int J Eat Disord. 2008;41(1):72–81.

184. Wardle J, Guthrie CA, Sanderson S, Rapoport L. Development of the children's eating behaviour questionnaire. J Child Psychol Psychiatry Allied Discip. 2001;42(7):963–70.

185. Snoek HM, Engels RCME, van Strien T, Otten R. Emotional, external and restrained eating behaviour and BMI trajectories in adolescence. Appetite. 2013;67:81–7.

186. Van Strien T, Peter Herman C, Verheijden MW. Eating style, overeating and weight gain. A prospective 2-year follow-up study in a representative Dutch sample. Appetite. 2012;59(3):782–9.

187. De Lauzon-Guillain B, Basdevant A, Romon M, Karlsson J, Borys JM, Charles MA. Is restrained eating a risk factor for weight gain in a general population? Am J Clin Nutr. 2006;83(1):132–8.

188. Croker H, Cooke L, Wardle J. Appetitive behaviours of children attending obesity treatment. Appetite. 2011;57(2):525–9.

189. Sleddens EFC, Kremers SPJ, Thijs C. The Children's Eating Behaviour Questionnaire: Factorial validity and association with Body Mass Index in Dutch children aged 6-7. Int J Behav Nutr Phys Act. 2008;5:1–9.

190. Vandeweghe L, Verbeken S, Vervoort L, Moens E, Braet C. Reward sensitivity and body weight: the intervening role of food responsive behavior and external eating. Appetite. 2017;112:150–6.

191. Van Jaarsveld CHM, Llewellyn CH, Johnson L, Wardle J. Prospective associations between appetitive traits and weight gain in infancy. Am J Clin Nutr. 2011;94(6):1562–7.

192. Van Jaarsveld CHM, Boniface D, Llewellyn CH, Wardle J. Appetite and growth a longitudinal sibling analysis. JAMA Pediatr. 2014;168(4):345–50.

193. Quah PL, Chan YH, Aris IM, Pang WW, Toh JY, Tint MT, et al. Prospective associations of appetitive traits at 3 and 12 months of age with body mass index and weight gain in the first 2 years of life. BMC Pediatr. 2015;15(1):1–10.

194. Derks IPM, Sijbrands EJG, Wake M, Qureshi F, van der Ende J, Hillegers MHJ, et al. Eating behavior and body composition across childhood: a prospective cohort study. Int J Behav Nutr Phys Act. 2018;15(1):1–9.

195. Costa A, Severo M, Vilela S, Fildes A, Oliveira A. Bidirectional relationships between appetitive behaviours and body mass index in childhood: a cross-lagged analysis in the Generation XXI birth cohort. Eur J Nutr. 2021;60(1):239–47.

196. Steinsbekk S, Wichstrøm L. Predictors of change in BMI from the age of 4 to 8. J Pediatr Psychol. 2015;40(10):1056–64.

197. Snoek HM, van Strien T, Janssens JMAM, Engels RCME. Restrained Eating and BMI: A Longitudinal Study Among Adolescents. Heal Psychol. 2008;27(6):753–9.

198. Konttinen H, Llewellyn C, Silventoinen K, Joensuu A, Männistö S, Salomaa V, et al. Genetic predisposition to obesity, restrained eating and changes in body weight: a population-based prospective study. Int J Obes. 2018;42(4):858–65.

199. Booth DA. Mechanisms from models—actual effects from real life: The zero-calorie drink-break option. Appetite. 1988;11:94–102.

200. Zizza C, Siega-Riz AM, Popkin BM. Significant increase in young adults' snacking between 1977-1978 and 1994-1996 represents a cause for concern! Prev Med (Baltim). 2001;32(4):303–10.

201. Piernas C, Popkin BM. Trends in snacking among U.S. children. Health Aff. 2010;29(3):398–404.

202. Vatanparast H, Islam N, Patil RP, Shafiee M, Smith J, Whiting S. Snack consumption patterns among canadians. Nutrients. 2019;11(5):1–12.

203. Hampl JS, Heaton CLB, Taylor CA. Snacking patterns influence energy and nutrient intakes but not body mass index. J Hum Nutr Diet. 2003;16(1):3–11.

204. Ovaskainen ML, Reinivuo H, Tapanainen H, Hannila ML, Korhonen T, Pakkala H. Snacks as an element of energy intake and food consumption. Eur J Clin Nutr. 2006;60(4):494–501.

205. Murakami K, Livingstone MBE. Eating frequency is positively associated with overweight and central obesity in US adults. J Nutr. 2015;145(12):2715–24.

206. Murakami K, Livingstone MBE. Associations between meal and snack frequency and overweight and abdominal obesity in US children and adolescents from National Health and Nutrition Examination Survey (NHANES) 2003-2012. Br J Nutr. 2016;115(10):1819–29.

207. Bertéus Forslund H, Torgerson JS, Sjöström L, Lindroos AK. Snacking frequency in relation to energy intake and food choices in obese men and women compared to a reference population. Int J Obes. 2005;29(6):711–9.

208. Tripicchio GL, Kachurak A, Davey A, Bailey RL, Dabritz LJ, Fisher JO. Associations between snacking and weight status among adolescents 12–19 years in the United States. Nutrients. 2019;11(7):1–11.

209. Keast DR, Nicklas TA, O'Neil CE. Snacking is associated with reduced risk of overweight and reduced abdominal obesity in adolescents: National Health and Nutrition Examination Survey (NHANES) 1999-2004. Am J Clin Nutr. 2010;92(2):428–35.

210. Phillips SM, Bandini LG, Naumova EN, Cyr H, Colclough S, Dietz WH, et al. Energy-

dense snack food intake in adolescence: Longitudinal relationship to weight and fatness. Obes Res. 2004;12(3):461–72.

211. Marangoni F, Martini D, Scaglioni S, Sculati M, Donini LM, Leonardi F, et al. Snacking in nutrition and health. Int J Food Sci Nutr. 2019;70(8):909–23.

212. Njike VY, Smith TM, Shuval O, Shuval K, Edshteyn I, Kalantari V, et al. Snack Food, Satiety, and Weight. Adv Nutr. 2016;7:866–78.

213. Savige G, MacFarlane A, Ball K, Worsley A, Crawford D. Snacking behaviours of adolescents and their association with skipping meals. Int J Behav Nutr Phys Act. 2007;4:1–9.

214. Kelishadi R, Mozafarian N, Qorbani M, Motlagh ME, Safiri S, Ardalan G, et al. Is snack consumption associated with meal skipping in children and adolescents? The CASPIAN-IV study. Eat Weight Disord. 2017;22(2):321–8.

215. Holmbäck I, Ericson U, Gullberg B, Wirflt E. A high eating frequency is associated with an overall healthy lifestyle in middle-aged men and women and reduced likelihood of general and central obesity in men. Br J Nutr. 2010;104(7):1065–73.

216. Schoenfeld BJ, Aragon AA, Krieger JW. Effects of meal frequency on weight loss and body composition: A meta-analysis. Nutr Rev. 2015;73(2):69–82.

217. Leidy HJ, Armstrong CLH, Tang M, Mattes RD, Campbell WW. The influence of higher protein intake and greater eating frequency on appetite control in overweight and obese men. Obesity. 2010;18(9):1725–32.

218. Ohkawara K, Cornier MA, Kohrt WM, Melanson EL. Effects of increased meal frequency on fat oxidation and perceived hunger. Obesity. 2013;21(2):336–43.

219. Farshchi HR, Taylor MA, Macdonald IA. Deleterious effects of omitting breakfast on insulin sensitivity and fasting lipid profiles in healthy lean women. Am J Clin Nutr. 2005;81(2):388–96.

220. Farshchi HR, Taylor M, Macdonald IA. Decreased thermic effect of food after an irregular compared with a regular meal pattern in healthy lean women. Int J Obes. 2004;28(5):653–60.

221. Alhussain MH, Macdonald IA, Taylor MA. Irregular meal-pattern effects on energy expenditure, metabolism, and appetite regulation: A randomized controlled trial in healthy normal-weight women. Am J Clin Nutr. 2016;104(1):21–32.

222. Kahleova H, Lloren JI, Mashchak A, Hill M, Fraser GE. Meal Frequency and Timing Are Associated with Changes in Body Mass Index in Adventist Health Study 2. J Nutr. 2017;147:1722–8.

223. O'Neil CE, Byrd-Bredbenner C, Hayes D, Jana L, Klinger SE, Stephenson-Martin S. The role of breakfast in health: Definition and criteria for a quality breakfast. J Acad Nutr Diet. 2014;114(12):S8–26.

224. Timlin MT, Pereira MA. Breakfast frequency and quality in the etiology of adult obesity and chronic diseases. Nutr Rev. 2007;65(6):268–81.

225. Kant AK, Graubard BI. Within-person comparison of eating behaviors, time of eating, and dietary intake on days with and without breakfast: NHANES 2005-2010[1-3]. Am J Clin Nutr. 2015;102(3):661–70.

226. Sievert K, Hussain SM, Page MJ, Wang Y, Hughes HJ, Malek M, et al. Effect of breakfast on weight and energy intake: Systematic review and meta-analysis of randomised controlled trials. BMJ. 2019;364:15–7.

227. Szajewska H, Ruszczyński M. Systematic review demonstrating that breakfast consumption influences body weight outcomes in children and adolescents in Europe. Crit Rev Food Sci Nutr. 2010;50(2):113–9.

228. Ardeshirlarijani E, Namazi N, Jabbari M, Zeinali M, Gerami H, Jalili RB, et al. The link between breakfast skipping and overweight/obesity in children and adolescents: a meta-

analysis of observational studies. J Diabetes Metab Disord. 2019;18(2):657–64.

229. Ma X, Chen Q, Pu Y, Guo M, Jiang Z, Huang W, et al. Skipping breakfast is associated with overweight and obesity: A systematic review and meta-analysis. Obes Res Clin Pract. 2020;14(1):1–8.

230. Elks CE, Hoed M Den, Zhao JH, Sharp SJ, Wareham NJ, Loos RJF, et al. Variability in the heritability of body mass index: a systematic review and meta-regression. Front Endocrinol (Lausanne). 2012;3:29.

231. Konttinen H, Llewellyn C, Wardle J, Silventoinen K, Joensuu A, Männistö S, et al. Appetitive traits as behavioural pathways in genetic susceptibility to obesity: A population-based cross-sectional study. Sci Rep. 2015;5:1–10.

232. De Lauzon-Guillain B, Clifton EAD, Day FR, Clément K, Brage S, Forouhi NG, et al. Mediation and modification of genetic susceptibility to obesity by eating behaviors. Am J Clin Nutr. 2017;106(4):996–1004.

233. Jacob R, Drapeau V, Tremblay A, Provencher V, Bouchard C, Pérusse L. The role of eating behavior traits in mediating genetic susceptibility to obesity. Am J Clin Nutr. 2018;108(3):445–52.

234. Fisher R. The Correlation between relatives on the supposition of Mendelian inheritance. Trans Roy Soc Edin. 1918;(52):399–433.

235. Wright S. The Relative Importance of Heredity and Environment in Determining the Piebald Pattern of Guinea-Pigs. Proc Natl Acad Sci. 1920 Jun 1;6(6):320 LP – 332.

236. Neale MC, Maes HH. Methodology for Genetic Studies of Twins and Families. Vol. 30, Journal of Medical Genetics. 1993. 800–800 p.

237. Williams PT. Quantile-dependent heritability of computed tomography, dual-energy x-ray absorptiometry, anthropometric, and bioelectrical measures of adiposity. Int J Obes. 2020;44(10):2101–12.

238. Rose KM, Newman B, Mayer-Davis EJ, Selby J V. Genetic and behavioral determinants of waist-hip ratio and waist circumference in women twins. Obes Res. 1998;6(6):383–92.

239. Benyamin B, Sørensen TIA, Schousboe K, Fenger M, Visscher PM, Kyvik KO. Are there common genetic and environmental factors behind the endophenotypes associated with the metabolic syndrome? Diabetologia. 2007;50(9):1880–8.

240. Nelson TL, Brandon DT, Wiggins SA, Whitfield KE. Genetic and environmental influences on body-fat measures among African-American twins. Obes Res. 2002;10(8):733–9.

241. Schousboe K, Visscher PM, Erbas B, Kyvik KO, Hopper JL, Henriksen JE, et al. Twin study of genetic and environmental influences on adult body size, shape, and composition. Int J Obes. 2004;28(1):39–48.

242. Hasselbalch AL, Benyamin B, Visscher PM, Heitmann BL, Kyvik KO, Sørensen TIA. Common genetic components of obesity traits and serum leptin. Obesity. 2008;16(12):2723–9.

243. Mamtani M, Kulkarni H, Dyer TD, Almasy L, Mahaney MC, Duggirala R, et al. Waist circumference is genetically correlated with incident Type 2 diabetes in Mexican-American families. Diabet Med. 2014;31(1):31–5.

244. Man T, Nolte IM, Jaju D, Al-Anqoudi ZA, Muñoz ML, Hassan MO, et al. Heritability and genetic correlations of obesity indices with ambulatory and office beat-to-beat blood pressure in the Oman Family Study. J Hypertens. 2020;38(8):1474–80.

245. Llewellyn CH, Van Jaarsveld CHM, Johnson L, Carnell S, Wardle J. Nature and nurture in infant appetite: Analysis of the Gemini twin birth cohort. Am J Clin Nutr. 2010;91(5):1172–9.

246. Carnell S, Haworth CMA, Plomin R, Wardle J. Genetic influence on appetite in children. Int J Obes. 2008;32(10):1468–73.

247. Llewellyn CH, Van Jaarsveld CHM, Boniface D, Carnell S, Wardle J. Eating rate is a heritable phenotype related to weight in children. Am J Clin Nutr. 2008;88(6):1560–6.

248. Keskitalo K, Tuorila H, Spector TD, Cherkas LF, Knaapila A, Kaprio J, et al. The Three-Factor Eating Questionnaire, body mass index, and responses to sweet and salty fatty foods: A twin study of genetic and environmental associations. Am J Clin Nutr. 2008;88(2):263–71.

249. Tholin S, Rasmussen F, Tynelius P, Karlsson J. Genetic and environmental influences on eating behavior : the Swedish Young Male Twins Study[1–3]. Am J Clin Nutr. 2005;81:564–9.

250. Schur E, Noonan C, Polivy J, Goldberg J, Buchwald D. Genetic and Environmental Influences on Restrained Eating Behavior. Int J Eat Disord. 2009;42(8):765–72.

251. Bouchard C, Tremblay A, Nadeau A, Després JP, Thériault G, Boulay MR, et al. Genetic effect in resting and exercise metabolic rates. Metabolism. 1989;38(4):364–70.

252. Cai G, Cole SA, Butte NF, Voruganti VS, Comuzzie AG. Genome-wide scan revealed genetic loci for energy metabolism in Hispanic children and adolescents. Int J Obes. 2008;32(4):579–85.

253. Teucher B, Skinner J, Skidmore PML, Cassidy A, Fairweather-Tait SJ, Hooper L, et al. Dietary Patterns and Heritability of Food Choice in a UK Female Twin Cohort. Twin Res Hum Genet. 2007;10(5):734–48.

254. Llewellyn CH, Van Jaarsveld CHM, Plomin R, Fisher A, Wardle J. Inherited behavioral susceptibility to adiposity in infancy: A multivariate genetic analysis of appetite and weight in the Gemini birth cohort. Am J Clin Nutr. 2012;95(3):633–9.

255. Day FR, Loos RJF. Developments in obesity genetics in the era of genome-wide association studies. J Nutrigenet Nutrigenomics. 2011;4(4):222–38.

256. Loos RJF. Recent progress in the genetics of common obesity. Br J Clin Pharmacol. 2009;68(6):811–29.

257. Ioannidis JPA, Ntzani EE, Trikalinos TA, Contopoulos-Ioannidis DG. Replication validity of genetic association studies. Nat Genet. 2001;29(3):306–9.

258. Saunders CL, Chiodini BD, Sham P, Lewis CM, Abkevich V, Adeyemo AA, et al. Meta-analysis of genome-wide linkage studies in BMI and obesity. Obesity. 2007;15(9):2263–75.

259. Visscher PM, Brown MA, McCarthy MI, Yang J. Five years of GWAS discovery. Am J Hum Genet. 2012;90(1):7–24.

260. Frayling TM, Timpson NJ, Weedon MN, Freathy RM, Lindgren CM, Perry JRB, et al. Index and Predisposes to Childhood and Adult Obesity. Science. 2007;316(5826):889–94.

261. Manolio TA, Collins FS, Cox NJ, Goldstein DB, Hindorff LA, Hunter DJ, et al. Finding the missing heritability of complex diseases. Nature. 2009;461(7265):747–53.

262. Lim ET, Würtz P, Havulinna AS, Palta P, Tukiainen T, Rehnström K, et al. Distribution and Medical Impact of Loss-of-Function Variants in the Finnish Founder Population. PLoS Genet. 2014;10(7).

263. Vinkhuyzen AAE, Pedersen NL, Yang J, Lee SH, Magnusson PKE, Iacono WG, et al. Common SNPs explain some of the variation in the personality dimensions of neuroticism and extraversion. Transl Psychiatry. 2012;2(4):e102-7.

264. Wainschtein P, Jain DP, Yengo L, Zheng Z, Group TopmAW, Consortium T-O for PM, et al. Recovery of trait heritability from whole genome sequence data. Preprint. Available from: bioRxiv 588020

265. Kaprio J. Twins and the mystery of missing heritability: The contribution of gene-environment interactions. J Intern Med. 2012;272(5):440–8.

266. Zuk O, Hechter E, Sunyaev SR, Lander ES. The mystery of missing heritability: Genetic interactions create phantom heritability. Proc Natl Acad Sci USA. 2012;109(4):1193–8.

267. Loos RJF, Bouchard C. Obesity - Is it a genetic disorder? J Intern Med. 2003;254(5):401–25.

268. Huvenne H, Dubern B, Clément K, Poitou C. Rare Genetic Forms of Obesity: Clinical Approach and Current Treatments in 2016. Obes Facts. 2016;9:158–73.

269. Turcot V, Lu Y, Highland HM, Schurmann C, Justice AE, Fine RS, et al. Protein-altering variants associated with body mass index implicate pathways that control energy intake and expenditure in obesity. Nat Genet. 2018;50(1):26–35.

270. Ndiaye FK, Huyvaert M, Ortalli A, Canouil M, Lecoeur C, Verbanck M, et al. The expression of genes in top obesity-associated loci is enriched in insula and substantia nigra brain regions involved in addiction and reward. Int J Obes. 2020;44(2):539–43.

271. O'Brien PD, Hinder LM, Callaghan BC, Feldman EL. Neurological consequences of obesity. Lancet Neurol. 2017;16(6):465–77.

272. Ahn J, Wu H, Lee K. Integrative Analysis Revealing Human Adipose-Specific Genes and Consolidating Obesity Loci. Sci Rep. 2019;9(1):1–13.

273. Heianza Y, Qi L. Gene-diet interaction and precision nutrition in obesity. Int J Mol Sci. 2017;18(4).

274. Muller D, Judd CM, Yzerbyt VY. When moderation is mediated and mediation is moderated. J Pers Soc Psychol. 2005;89(6):852–63.

275. Llewellyn CH, Trzaskowski M, van Jaarsveld CHM, Plomin R, Wardle J. Satiety Mechanisms in Genetic Risk of Obesity. JAMA Pediatr. 2014;168(4):338–44.

276. de Lauzon-Guillain B, Koudou YA, Botton J, Forhan A, Carles S, Pelloux V, et al. Association between genetic obesity susceptibility and mother-reported eating behaviour in children up to 5 years. Pediatr Obes. 2019;14(5):1–8.

277. Steinsbekk S, Belsky D, Guzey IC, Wardle J, Wichstrom L. Polygenic risk, appetite traits, and weight gain in middle childhood a longitudinal study. JAMA Pediatr. 2016;170(2).

278. Opel N, Redlich R, Kaehler C, Grotegerd D, Dohm K, Heindel W, et al. Prefrontal gray matter volume mediates genetic risks for obesity. Mol Psychiatry. 2017;22(5):703–10.

279. Barker ED, Ing A, Biondo F, Jia T, Pingault JB, Du Rietz E, et al. Do ADHD-impulsivity and BMI have shared polygenic and neural correlates? Mol Psychiatry. 2019;1019–28.

280. Belsky DW, Moffitt TE, Houts R, Bennett GG, Biddle AK, Blumenthal JA, et al. Polygenic risk, rapid childhood growth, and the development of obesity: Evidence from a 4-decade longitudinal study. Arch Pediatr Adolesc Med. 2012;166(6):515–21.

281. Fu J, Wang Y, Li G, Han L, Li Y, Li L, et al. Childhood sleep duration modifies the polygenic risk for obesity in youth through leptin pathway: the Beijing Child and Adolescent Metabolic Syndrome cohort study. Int J Obes. 2019;43(8):1556–67.

282. Stephan Y, Sutin AR, Luchetti M, Caille P, Terracciano A. An examination of potential mediators of the relationship between polygenic scores of BMI and waist circumference and phenotypic adiposity. Psychol Heal. 2020;35(9):1151–61.

283. Avinun R, Hariri AR. A Polygenic Score for Body Mass Index is Associated with Depressive Symptoms via Early Life Stress: Evidence for Gene- Environment Correlation. J Psychiatr Res. 2019;118:9–13.

284. Abdulkadir M, Herle M, De Stavola BL, Hübel C, Santos Ferreira DL, Loos RJF, et al. Polygenic Score for Body Mass Index Is Associated with Disordered Eating in a General Population Cohort. J Clin Med. 2020;9(4):1187.

285. Nagata JM, Braudt DB, Domingue BW, Bibbins-Domingo K, Garber AK, Griffiths S, et al. Genetic risk, body mass index, and weight control behaviors: Unlocking the triad. Int J Eat Disord. 2019;52(7):825–33.

286. Flores-Dorantes MT, Díaz-López YE, Gutiérrez-Aguilar R. Environment and Gene Association With Obesity and Their Impact on Neurodegenerative and Neurodevelopmental Diseases. Front Neurosci. 2020;14.

287. Kaidesoja M, Aaltonen S, Bogl LH, Heikkilä K, Kaartinen S, Kujala UM, et al. FinnTwin16: A Longitudinal Study from Age 16 of a Population-Based Finnish Twin Cohort. Twin Res Hum Genet. 2019;22(6):1–10.

288. Naukkarinen J, Rissanen A, Kaprio J, Pietiläinen KH. Causes and consequences of obesity: The contribution of recent twin studies. Int J Obes. 2012;36(8):1017–24.

289. Rottensteiner M, Leskinen T, Niskanen E, Aaltonen S, Mutikainen S, Wikgren J, et al. Physical activity, fitness, glucose homeostasis, and brain morphology in twins. Med Sci Sports Exerc. 2014;47(3):509–18.

290. Ahrens W, Siani A, Adan R, De Henauw S, Eiben G, Gwozdz W, et al. Cohort Profile: The transition from childhood to adolescence in European children-how I.Family extends the IDEFICS cohort. Int J Epidemiol. 2017;46(5):1394–5.

291. Nagy P, Kovacs E, Moreno LA, Veidebaum T, Tornaritis M, Kourides Y, et al. Percentile reference values for anthropometric body composition indices in European children from the IDEFICS study. Int J Obes. 2014;38:S15–25.

292. Nordic Council of Ministers. Nordic Nutrition Recommendations 2012; Nordisk Ministerråd: Kopenhagen, Denmark, 2012; Volume 5

293. National Nutrition Council. Terveyttä Ruoasta. Suomalaiset Ravitsemussuositukset 2014 [Health From Food The Finnish Nutrition Recommendations 2014]; Valtion Ravitsemusneuvottelukunta/National Nutrition Council: Helsinki, Finland, 2014 (In Finnish)

294. Huybrechts I, Börnhorst C, Pala V, Moreno LA, Barba G, Lissner L, et al. Evaluation of the children's eating habits questionnaire used in the IDEFICS study by relating urinary calcium and potassium to milk consumption frequencies among european children. Int J Obes. 2011;35:S69–78.

295. Baughcum AE, Powers SW, Johnson SB, Chamberlin LA, Deeks CM, Jain A, et al. Maternal feeding practices and beliefs and their relationships to overweight in early childhood. J Dev Behav Pediatr. 2001;22(6):391–408.

296. Jelenkovic A, Ortega-Alonso A, Rose RJ, Kaprio J, Rebato E, Silventoinen K. Genetic and environmental influences on growth from late childhood to adulthood: A longitudinal study of two Finnish twin cohorts. Am J Hum Biol. 2011;23(6):764–73.

297. Vilhjálmsson BJ, Yang J, Finucane HK, Gusev A, Lindström S, Ripke S, et al. Modeling Linkage Disequilibrium Increases Accuracy of Polygenic Risk Scores. Am J Hum Genet. 2015;97(4):576–92.

298. Borodulin K, Vartiainen E, Peltonen M, Jousilahti P, Juolevi A, Laatikainen T, et al. Forty-year trends in cardiovascular risk factors in Finland. Eur J Public Health. 2015;25(3):539–46.

299. Kujala UM, Kaprio J, Sarna S, Koskenvuo M. Relationship of Leisure-Time Physical Activity and Mortality. 1998;279(6).

300. Latvala A, Dick DM, Tuulio-Henriksson A, Suvisaari J, Viken RJ, Rose RJ, et al. Genetic Correlation and Gene–Environment Interaction Between Alcohol Problems and Educational Level in Young Adulthood*. J Stud Alcohol Drugs. 2011;72(2):210–20.

301. UNESCO. The International Standard Classification of Education (ISCED). ISCED 2011. Montreal: UNESCO Institute for Statistics; 2012.

302. Iguacel I, Michels N, Fernández-Alvira JM, Bammann K, De Henauw S, Felső R, et al. Associations between social vulnerabilities and psychosocial problems in European children. Results from the IDEFICS study. Eur Child Adolesc Psychiatry. 2017;26(9):1105–17.

303. Peplies J, Günther K, Bammann K, Fraterman A, Russo P, Veidebaum T, et al. Influence of sample collection and preanalytical sample processing on the analyses of biological markers in the European multicentre study IDEFICS. Int J Obes. 2011;35:S104–12.

304. Williams RL. A Note on Robust Variance Estimation for Cluster-Correlated Data.

Biometrics. 2000;56(June):645–6.

305. Hu LT, Bentler PM. Cutoff criteria for fit indexes in covariance structure analysis: Conventional criteria versus new alternatives. Struct Equ Model. 1999;6(1):1–55.

306. Bentler PM. Comparative fit indexes in structural models. Psychol Bull. 1990 Mar;107(2):238–46.

307. VanderWeele T. Explanation in Causal inference: Methods for Mediation and Interaction. New York, NY: Oxford University Press; 2015.

308. Discacciati A, Bellavia A, Lee JJ, Mazumdar M, Valeri L. Med4way: A Stata command to investigate mediating and interactive mechanisms using the four-way effect decomposition. Int J Epidemiol. 2019;48(1):15–20.

309. Cena H, Calder PC. Defining a Healthy Diet: Evidence for the Role of Contemporary Dietary Patterns in Health and Disease. Nutrients. 2020;12(334):1–15.

310. Sluik D, Geelen A, De Vries JHM, Eussen SJPM, Brants HAM, Meijboom S, et al. A national FFQ for the Netherlands (the FFQ-NL 1.0): Validation of a comprehensive FFQ for adults. Br J Nutr. 2016;116(5):913–23.

311. Marshall SJ, Livingstone KM, Celis-Morales C, Forster H, Fallaize R, O'Donovan CB, et al. Reproducibility of the online Food4Me food-frequency questionnaire for estimating dietary intakes across Europe. J Nutr. 2016;146(5):1068–75.

312. Verger EO, Mariotti F, Holmes BA, Paineau D, Huneau JF. Evaluation of a diet quality index based on the probability of adequate nutrient intake (PANDiet) using national french and US dietary surveys. PLoS One. 2012;7(8).

313. Van Lee L, Feskens EJM, Meijboom S, Hooft Van Huysduynen EJC, Van'T Veer P, De Vries JHM, et al. Evaluation of a screener to assess diet quality in the Netherlands. Br J Nutr. 2016;115(3):517–26.

314. Gicevic S, Mou Y, Bromage S, Fung TT, Willett W. Development of a Diet Quality Screener for Global Use: Evaluation in a Sample of US Women. J Acad Nutr Diet. 2021;

315. Cade JE, Burley VJ, Warm DL, Thompson RL, Margetts BM. Food-frequency questionnaires: a review of their design, validation and utilisation. Nutr Res Rev. 2004;17(1):5–22.

316. Sung J, Lee K, Song YM, Lee MK, Lee DH. Heritability of eating behavior assessed using the DEBQ (Dutch Eating Behavior Questionnaire) and weight-related traits: The healthy twin study. Obesity. 2010;18(5):1000–5.

317. Herle M, Madrid-Valero JJ, Morosoli JJ, Colodro-Conde L, Ordoñana J. The Role of the Environment in Overweight and Eating Behavior Variability: Insights from a Multivariate Twin Study. Twin Res Hum Genet. 2020;23(6):338–44.

318. Van den Berg L, Henneman P, van Dijk KW, Delemarre-van de Waal HA, Oostra BA, van Duijn CM, et al. Heritability of dietary food intake patterns. Acta Diabetol. 2013;50:721–6.

319. Li J, Liu H, Beaty TH, Chen H, Caballero B, Wang Y. Heritability of Children's Dietary Intakes: A Population-Based Twin Study in China. Twin Res Hum Genet. 2019;19(5):472–84.

320. Vink JM, Van Hooijdonk KJM, Willemsen G, Feskens EJM, Boomsma DI. Causes of Variation in Food Preference in the Netherlands. Twin Res Hum Genet. 2020;23(4):195–203.

321. Keski-Rahkonen A, Viken RJ, Kaprio J, Rissanen A, Rose RJ. Genetic and environmental factors in breakfast eating patterns. Behav Genet. 2004;34(5):503–14.

322. Lopez-Minguez J, Dashti HS, Madrid-Valero JJ, Madrid JA, Saxena R, Scheer FAJL, et al. Heritability of the timing of food intake. Clin Nutr. 2019;38(2):767–73.

323. Cohen-Cline H, Lau R, Moudon A V., Turkheimer E, Duncan GE. Associations Between Fast-Food Consumption and Body Mass Index: A Cross-Sectional Study in Adult Twins.

Twin Res Hum Genet. 2015;18(4):375–82.

324. Eney AE, Tsang S, Delaney JA, Turkheimer E, Duncan GE. Cross-sectional association between soda consumption and body mass index in a community-based sample of twins. Nutr J. 2017;16(1):48.

325. Herle M, Stavola B De, Hübel C, Ferreira DLS, Abdulkadir M, Yilmaz Z, et al. Eating behavior trajectories in the first 10 years of life and their relationship with BMI. Int J Obes. 2020;44(8):1766–75.

326. Herle M, Stavola B De, Hübel C, Abdulkadir M, Ferreira DiS, Loos RJF, et al. A longitudinal study of eating behaviours in childhood and later eating disorder behaviours and diagnoses. Br J Psychiatry. 2020;216(2):113–9.

327. Yilmaz Z, Gottfredson NC, Zerwas SC, Bulik CM, Micali N. Developmental Premorbid Body Mass Index Trajectories of Adolescents With Eating Disorders in a Longitudinal Population Cohort. J Am Acad Child Adolesc Psychiatry. 2019;58(2):191–9.

328. Hüls A, Wright MN, Bogl LH, Kaprio J, Lissner L, Molnár D, et al. Polygenic risk for obesity and its interaction with lifestyle and sociodemographic factors in European children and adolescents. Int J Obes. 2021;45:1321–1330

329. Richardson TG, Sanderson E, Elsworth B, Tilling K, Smith GD. Use of genetic variation to separate the effects of early and later life adiposity on disease risk: Mendelian randomisation study. BMJ. 2020;369:1–12.

330. Brandkvist M, Bjørngaard JH, Ødegård RA, Åsvold BO, Smith GD, Brumpton B, et al. Separating the genetics of childhood and adult obesity: a validation study of genetic scores for body mass index in adolescence and adulthood in the HUNT Study. Hum Mol Genet. 2021;29(24):3966–73.

331. Alves AC, De Silva NMG, Karhunen V, Sovio U, Das S, Rob Taal H, et al. GWAS on longitudinal growth traits reveals different genetic factors influencing infant, child, and adult BMI. Sci Adv. 2019;5(9):1–18.

332. Davis LL, Broome ME, Cox RP. Maximizing retention in community-based clinical trials. J Nurs Scholarsh. 2002;34(1):47–53.

333. Hense S, Pohlabeln H, Michels N, Mårild S, Lissner L, Kovacs E, et al. Determinants of Attrition to Follow-Up in a Multicentre Cohort Study in Children-Results from the IDEFICS Study. Epidemiol Res Int. 2013;2013:1–9.

334. Hernán MA, Robins JM. Causal Inference - What if. Boca Raton: Chapman & Hall/CRC. 2020.

335. Heitmann BL, Lissner L. Dietary underreporting by obese individuals-is it specific or non-specific? BMJ. 1995;311:986–9.

336. Hebert JR, Ma Y, Clemow L, Ockene IS, Saperia G, Stanek III EJ, et al. Gender Differences in Social Desirability and Social Approval Bias in Dietary Self-report. Am J Epidemiol. 1997;146(12):1046–55.

337. Gorber SC, Tremblay M, Moher D, Gorber B. A comparison of direct vs. self-report measures for assessing height, weight and body mass index: A systematic review. Obes Rev. 2007;8(4):307–26.

338. Park JY, Mitrou PN, Keogh RH, Luben RN, Wareham NJ, Khaw KT. Effects of body size and sociodemographic characteristics on differences between self-reported and measured anthropometric data in middle-aged men and women: The EPIC-Norfolk study. Eur J Clin Nutr. 2011;65(3):357–67.

339. Poínhos R, Oliveira BMPM, Correia F. Eating behavior in Portuguese higher education students: The effect of social desirability. Nutrition. 2015;31(2):310–4.

340. Nemecek D, Sebelefsky C, Woditschka A, Voitl P. Overweight in children and its perception by parents: Cross-sectional observation in a general pediatric outpatient clinic. BMC Pediatr. 2017;17(1):1–10.

APPENDICES

Apendix 1. Diet Quality Score from FinnTwin16 - wave 5

Food frequency questions:

How many slices of bread do you usually eat in a day? Mark 0 if none.

rye bread (rye, ryecrisp) _____ slices

brown, yeast, oatmeal or graham bread _____ slices

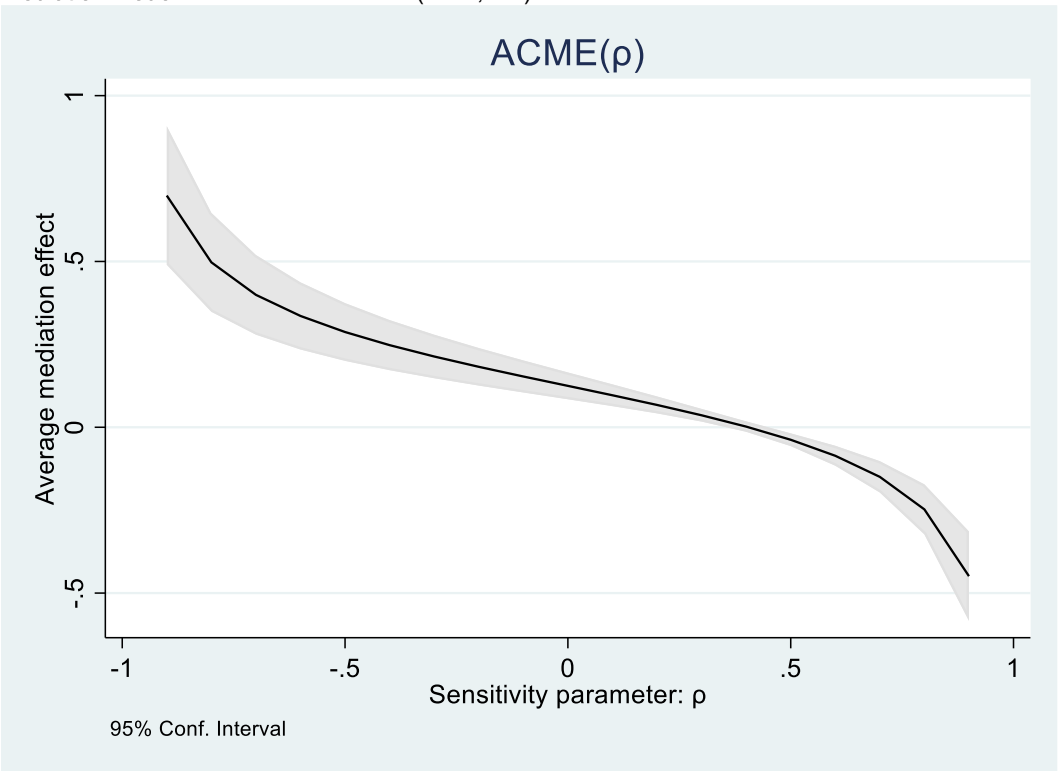
white, French bread or toast etc. _____ slices

How often do you usually use these ingredients? Please, think of the past 12 months.

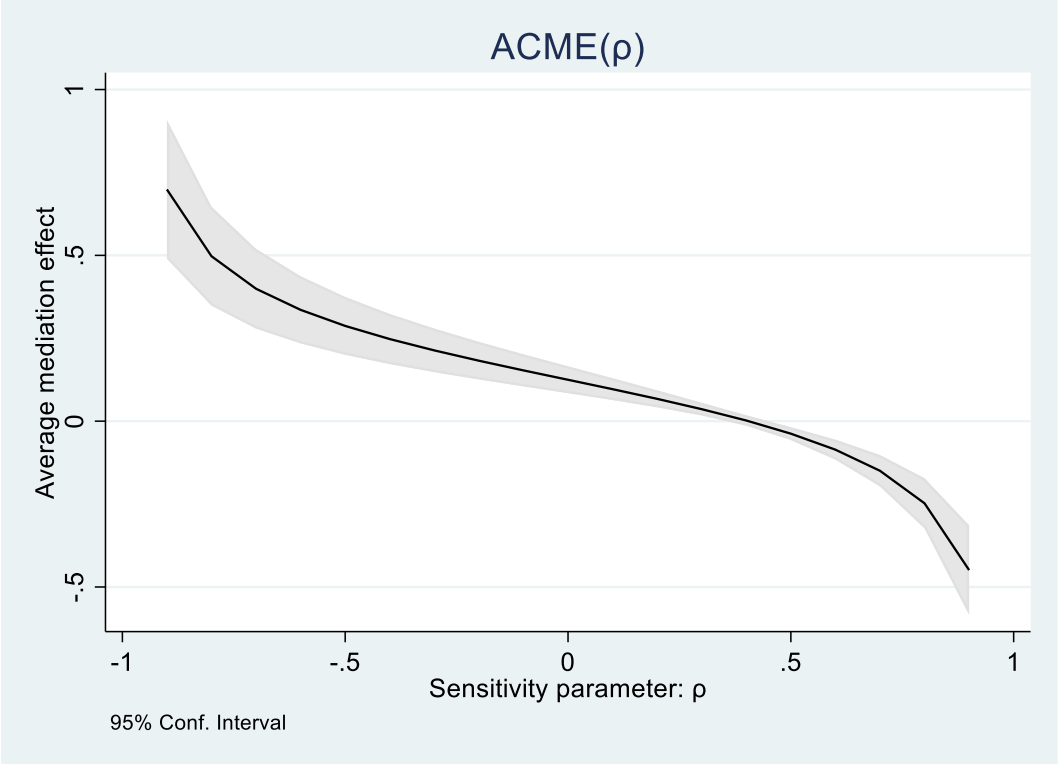
	Not at all	Few times per month	Few times per week	Once a day	Many times per day
Fruits or berries					
Vegetables					
Fish					
High fibrous grain products (porridge, muesli, brown pasta or rice, whole grain rice crispies, etc.)					
Fast food (hamburguers, pizza, etc.)					
Fat free or low fat milk, sour milk or yogurt					
Juice or soft drinks with sugar					
Energy drinks					
Butter					
Margarine					
Vegetable oil					

Apendix 2. Sensitivity plots from causal mediation analyses

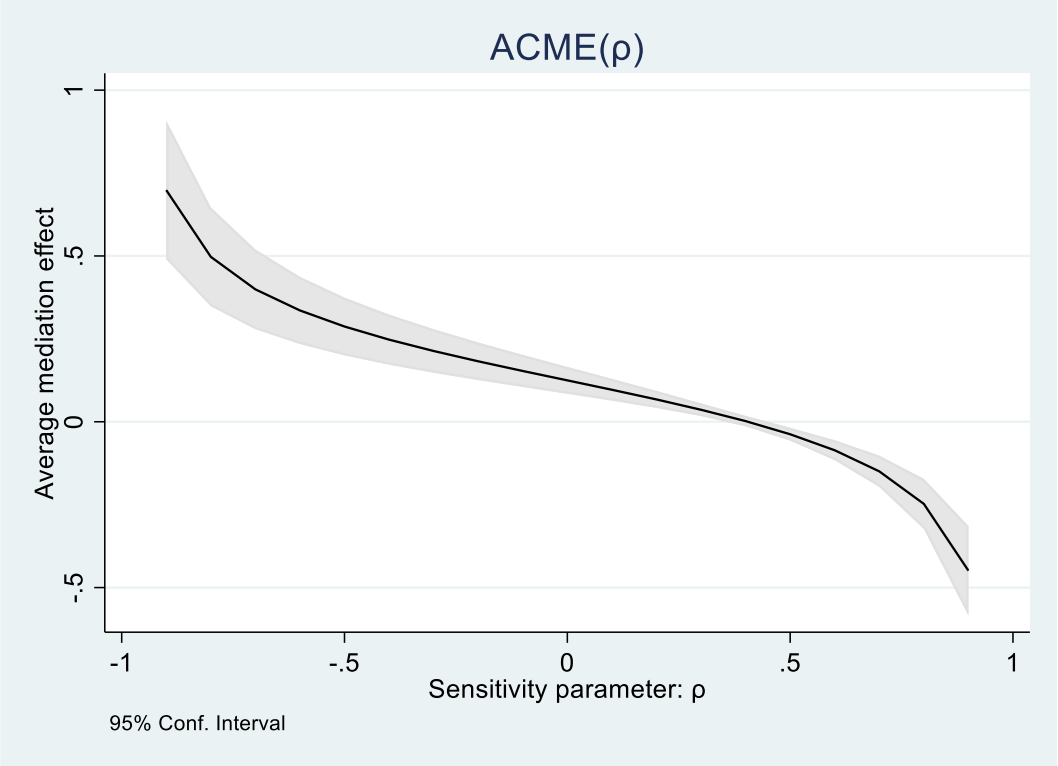
Mediation Model 2 for z-BMI at wave 3 (n = 2,386)



Mediation Model 2 for z-WC at wave 3 (n = 1,983)



Mediation Model 3 through z-BMI at wave 1 (n = 1,246)



Mediation Model 3 through z-WC at wave 1 (n = 1,134)