

URMELI KATUS

Genetic, behavioural, and environmental
factors in the development of overweight,
obesity and insulin resistance



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Institute of Family Medicine and Public Health, Faculty of Medicine, University of Tartu, Tartu, Estonia

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LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications referred to in the text by their Roman numerals (I–V):

- I. Joost, U., Villa, I., Comasco, E., Orelan, L., Veidebaum, T., Harro, J. (2019) Association between Transcription Factor AP-2B genotype, obesity, insulin resistance and dietary intake in a longitudinal birth cohort study. *International Journal of Obesity*. 43 (10), 2095–2106.
- II. Katus, U., Villa, I., Ringmets, I., Vaht, M., Mäestu, E., Mäestu, J., Veidebaum, T., Harro, J. (2020) Association of FTO rs1421085 with obesity, diet, physical activity, and socioeconomic status: A longitudinal birth cohort study. *Nutrition, Metabolism & Cardiovascular Diseases*. 30 (6), 948–959.
- III. Katus, U., Villa, I., Ringmets, I., Pulver, A., Veidebaum, T., Harro, J. (2020) The role of reward sensitivity in obesity and its association with Transcription Factor AP-2B: A longitudinal birth cohort study. *Neuroscience Letters*. 735, 135158.
- IV. Katus, U., Villa, I., Ringmets, I., Veidebaum, T., Harro, J. (2021) Neuropeptide Y gene variants in obesity, dietary intake, blood pressure, lipid and glucose metabolism: A longitudinal birth cohort study. *Peptides*. 139, 170524.
- V. Katus, U., Villa, I., Ringmets, I., Eensoo, D., Mäestu, J., Veidebaum, T., Harro, J. (2026) Birth cohort effects on obesity, glucose metabolism, diet, and fitness: evidence from a longitudinal study. *Nutrition, Metabolism & Cardiovascular Diseases*. 36 (7), 104638.

Author's contribution to the publication

Contribution of Urmeli Katus (formerly Joost) to the preparation of the original publications.

Papers I–V: contributions to the conception of the work, data analysis and interpretation of results, drafting and revising the manuscripts, final approval of the versions to be published, accountability for all aspects of the work.

LIST OF ABBREVIATIONS

AgRP	agouti-related peptide
ARC	arcuate nucleus
BAS	Behavioural Approach System
BIS	Behavioural Inhibition System
BMI	body mass index
BP	blood pressure
CART	cocaine- and amphetamine-regulated transcript
CHL	cholesterol
CI	confidence interval
CNS	central nervous system
CRF	cardiorespiratory fitness
DALY	disability-adjusted life-year
DEI	daily energy intake
ECPBHS	Estonian Children Personality Behaviour and Health Study
FFS	Fight/Flight System
FTO	fat mass and obesity-associated
GI	gastrointestinal
GLP1	glucagon-like peptide 1
GWAS	genome-wide association study
HC	hip circumference
HDL-C	high-density lipoprotein cholesterol
HIIT	high-intensity interval training
HOMA	Homeostatic Model Assessment
INS	insulin
LDL-C	low-density lipoprotein cholesterol
LHA	lateral hypothalamic area
MC4R	melanocortin-4 receptor-expressing
MD	mean difference
MPO	maximum power output
NCD	noncommunicable disease
NPY	neuropeptide Y
OR	odds ratio
POMC	proopiomelanocortin
PVN	paraventricular nucleus
RNA	ribonucleic acid
ROIS	Reward Openness and Insatiability Scale
RR	relative risk
RST	Reinforcement Sensitivity Theory
SD	standard deviation
SES	socioeconomic status
SIM1	single-minded homolog 1
SNP	single nucleotide polymorphism

TFAP2B	transcription factor AP-2 beta
TRG	triglyceride
UI	uncertainty interval
VMH	ventromedial hypothalamus
VNTR	variable number tandem repeat
WC	waist circumference
WHO	World Health Organization
WHR	waist-to-hip ratio
WHtR	waist-to-height ratio

1. INTRODUCTION

Noncommunicable diseases (NCDs) e.g., cardiovascular diseases, cancer, diabetes and chronic respiratory diseases, are leading causes of death globally (World Health Organization, 2025). Risk factors for NCDs include unhealthy diet, lack of physical activity, alcohol use, tobacco use, overweight and obesity, high blood pressure (BP), and elevated cholesterol (CHL) levels (World Health Organization, 2025). Overweight and obesity are major public health concerns, which affected approximately 2.1 billion adults in year 2021 (GBD 2021 Adult BMI Collaborators, 2025). In 2023, 3.7 million deaths and 136 million disability-adjusted life-years (DALYs) were attributable to high body mass index (BMI) (GBD 2023 Disease and Injury and Risk Factor Collaborators, 2025; Institute for Health Metrics and Evaluation, 2025).

Overweight and obesity are caused by a long-term imbalance between energy intake and expenditure (Blüher, 2019). Obesity displays a wide array of risk factors, such as genetics (e.g., polygenic obesity), biology (e.g., individual differences in physiological processes), psychology (e.g., stress, sensitivity to rewards), physical (built) environment (e.g., food availability, green spaces for physical activity, safety), socioeconomic changes (e.g., economics, policy, education, health awareness, culture), social dynamics (e.g., behaviours of family and friends), and individual behaviours (e.g., diet, level of physical activity) contributing to its development (Lee et al., 2017).

Usually, genetic reasons behind common obesity are polygenic, expressed in hundreds of obesogenic polymorphisms having a small effect (Loos & Yeo, 2022). Gene discovery for polygenic obesity accelerated rapidly with the introduction of genome-wide association studies (GWAS) approximately 20 years ago (Frayling et al., 2007; Visscher et al., 2017). GWAS have identified hundreds of genetic variants associated with obesity, however, the causality of these genetic variants and the underlying mechanisms remain unclear. Further, the effect of genetic variants may be influenced by demographic factors (e.g., sex, age), the environment (e.g., built environment, the birth cohort), and individual behaviours (e.g., diet, physical activity, smoking) (Loos & Yeo, 2022). Genotype-age, genotype-environment (Robinson et al., 2017), and genotype-birth cohort (Rosenquist et al., 2015) interactions in BMI variation have been observed. However, genotype-environment interaction analyses are challenging to consider in GWAS.

As obesity is a multifactorial condition, several other factors e.g., cognitive control, regulation of motivation, and sensitivity to reward, contribute to its development. As an example, sensitivity to reward, a psychobiological trait to seek rewarding substances or enjoyment with high reward potential, has been associated with overeating (Davis, 2013; Loxton & Tipman, 2017; Volkow et al., 2011), preference for foods high in fat and sugar (Davis et al., 2007; De Decker et al., 2016), varying levels of physical activity and fitness (Kiive et al., 2025), and use of addictive substances (Emery & Simons, 2017; Jonker et al., 2014; Tatnell et al., 2019).

The current dissertation analyses the association between selected genetic (i.e., transcription factor AP-2 beta [*TFAP2B*], fat mass and obesity-associated [*FTO*], neuropeptide Y [*NPY*]), and psychobiological factors (i.e., reward sensitivity) with overweight, obesity, and its related conditions (i.e., insulin resistance) while considering interactions with age, sex, diet, physical activity, socioeconomic status (SES), and the birth cohort during adolescence and young adulthood.

2. LITERATURE REVIEW

2.1. Overweight, obesity and its related conditions

Rates of overweight and obesity have increased at the global, regional, and national levels from 1990 to 2021 (GBD 2021 Adult BMI Collaborators, 2025), and as such, have become a major public health concern. In 2021, approximately 2.11 billion (95% uncertainty interval [UI] 2.09, 2.13) adults aged ≥ 25 years were overweight or obese, representing 45.1% (95% UI 44.7, 45.4) of the global adult population (GBD 2021 Adult BMI Collaborators, 2025). From 1990 to 2021, the combined prevalence of overweight and obesity in children and adolescents aged 5–24 years has increased twofold, while the prevalence of obesity alone has tripled. In 2021, 18.1% (95% UI 17.5, 18.7) of children aged 5–14 years and 20.3% (95% UI 19.7, 21.0) of adolescents aged 15–24 years were overweight or obese, corresponding to an estimated 493 million (95% UI 483, 505 million) individuals (GBD 2021 Adolescent BMI Collaborators, 2025).

According to the Health Behaviour among Estonian Adult Population 2024 study, the prevalence of overweight among individuals aged 16–64 years was 42.0% among men and 32.8% among women, the prevalence of obesity was 20.3% and 19.9%, respectively (Reile et al., 2025). The World Health Organization (WHO) Childhood Obesity Surveillance Initiative in Estonia demonstrated that, during the 2021/22 academic year, the prevalence of overweight and obesity among first-grade children (aged 7–8 years) was 16.6% and 11.5%, among fourth-grade children (aged 10–11 years) 20.3% and 14.1%, and among seventh-grade children (aged 13–14 years) 18.9% and 10.5%, respectively (National Institute for Health Development, 2023). The 2021/22 Estonian Health Behaviour in School-aged Children study reported a prevalence of overweight and obesity of 19.3% for children aged 11 years, 21.1% for children aged 13 years, and 19.2% for children aged 15 years (Piksööt & Oja, 2023).

Overweight and obesity are complex conditions with no single linear cause-effect relationship, and the interaction between partially overlapping and synergistic factors such as genetics, biology, behaviour, SES, cultural differences, and the environment contributing to an imbalance between energy intake and expenditure, leading to excessive weight gain (Bray et al., 2016; Hruby & Hu, 2015; Lee et al., 2017). The prevalence of overweight and obesity varies across sex, race and ethnicity, increasing with age (Hales et al., 2018). In Central and Eastern Europe, the prevalence of overweight and obesity was higher in males than females before 40 years of age, with the prevalence in females surpassing that in males thereafter. In males, the prevalence of overweight and obesity peaked at approximately 55–59 years of age, whereas in females it peaked later, at approximately 60–64 years of age (GBD 2021 Adult BMI Collaborators, 2025).

Currently, the most widely used criterion for defining overweight and obesity in adults is the BMI. The WHO defines individuals with $\text{BMI} \geq 25 \text{ kg/m}^2$ as overweight and with $\text{BMI} \geq 30 \text{ kg/m}^2$ as obese (**Table 1**) (World Health Organization, 2000). However, it should be noted that the optimal BMI might differ between

younger and older people. Current available evidence is insufficient to provide a recommendation for optimal BMI amongst the elderly. It has been suggested that it may be between 23–29 kg/m² (Cloetens and Ellegård, 2023).

Table 1. The WHO classification according to the BMI (World Health Organization, 2000).

Classification	BMI (kg/m ²)	Risk of comorbidities
Underweight	< 18.5	Low
Normal weight	18.5–24.9	Average
Overweight	25.0–29.9	Increased
Obesity class I	30.0–34.9	Moderate
Obesity class II	35.0–39.9	Severe
Obesity class III	≥ 40.0	Very severe

BMI, body mass index; kg/m², kilogram per square metre; WHO, World Health Organization

Obesity is characterised by excessive adiposity (Rubino et al., 2025), however, the BMI does not differentiate between weight associated with muscle and weight associated with fat, and thus may not correctly distinguish individuals with normal weight from people with overweight or obesity (World Health Organization, 2000). Thus, it has been suggested that excess adiposity should be confirmed by either direct measurement of body fat, or at least one anthropometric criterion in addition to BMI (Rubino et al., 2025). The WHO has recommended to use the waist circumference (WC) and waist-to-hip ratio (WHR) as indicators of abdominal obesity (World Health Organization, 2008, 2000). Another widely used proxy for characterising abdominal obesity is the waist-to-height ratio (WHtR) with a cut-off value of 0.5 (**Table 2**) (Ashwell et al., 2012; Ashwell & Gibson, 2016; Savva et al., 2013). Although newer tools are available to assess the presence of excessive adiposity e.g., body roundness index (Thomas et al., 2013) and relative fat mass (Woolcott & Bergman, 2018), the BMI has remained the main component in assessing the presence of overweight and obesity in both population and individual level.

Table 2. Classification of adults into risk of metabolic complication categories according to WC, WHR and WHtR (Ashwell et al., 2012; Ashwell & Gibson, 2016; Savva et al., 2013; World Health Organization, 2008, 2000).

Indicator	Cut-off points		Risk of metabolic complications
	Male	Female	
WC	≥ 94 cm	≥ 80 cm	Increased
WC	≥ 102 cm	≥ 88 cm	Substantially increased
WHR	≥ 0.90 units	≥ 0.85 units	Substantially increased
WHtR	≥ 0.5 units	≥ 0.5 units	Increased

WC, waist circumference; WHR, waist-to-hip ratio; WHtR, waist-to-height ratio; cm, centimetre

There is more variability in criterion used to define overweight and obesity in children and adolescents (World Health Organization, 2000). Many countries, including Estonia, have developed local, country specific reference growth charts based on weight-for-age and height-for-age. The growth charts currently used in Estonia were developed using data collected in 1996 and include percentile curves spanning from the 3rd to the 97th percentile (Grünberg et al., 1998). However, during the interim period, the rate of growth of Estonian children has changed. Comparative analysis by Salm et al. (2013) demonstrated that already between 2006–2009, school-aged children were significantly taller and heavier, with a significantly increased BMI, compared to children in 1996 (Salm et al., 2013). The Estonian growth charts need updating, nevertheless, in the meantime, they remain the most suitable reference for clinical growth assessment reflecting best the population-specific determinants of growth e.g., genetic background, environmental exposures, and nutritional status. In addition, WHO has developed international child growth standards, including weight-for-age, height-for-age, weight-for-height, and BMI-for-age (World Health Organization, 2009), that are derived from the WHO Multicentre Growth Reference Study (de Onis et al., 2004), yet these only apply to children up to 5 years of age. A study by Cole et al. (2000) developed a definition of child overweight and obesity for children aged 2–18 years for international use by analysing data on BMI from six large nationally representative cross-sectional surveys on growth from Brazil, United Kingdom, Hong Kong, Netherlands, Singapore, and United States (**Table 3**). Nevertheless, because these cut off points have been developed using cross-sectional data, they are limited by describing the population at only one point in time and thus do not represent individual growth trajectories, account for birth-cohort effects, or capture secular trends (Cole et al., 2000).

Table 3. Cut off points for BMI for overweight and obesity by sex from age 2–18 years (Cole et al., 2000).

Age (years)	BMI 25 kg/m ²		BMI 30 kg/m ²	
	Male	Female	Male	Female
2	18.41	18.02	20.09	19.81
3	17.89	17.56	19.57	19.36
4	17.55	17.28	19.29	19.15
5	17.42	17.15	19.30	19.17
6	17.55	17.34	19.78	19.65
7	17.92	17.75	20.63	20.51
8	18.44	18.35	21.60	21.57
9	19.10	19.07	22.77	22.81
10	19.84	19.86	24.00	24.11
11	20.55	20.74	25.10	25.42
12	21.22	21.68	26.02	26.67
13	21.91	22.58	26.84	27.76
14	22.62	23.34	27.63	28.57
15	23.29	23.94	28.30	29.11
16	23.90	24.37	28.88	29.43
17	24.46	24.70	29.41	29.69
18	25	25	30	30

BMI, body mass index; kg/m², kilogram per square metre

Obesity is a critical risk factor for morbidity and mortality (GBD 2023 Disease and Injury and Risk Factor Collaborators, 2025) particularly in regards to glucose (GLC) regulation and metabolic disease (Kahn et al., 2006). Insulin resistance, a defect in insulin-mediated control of GLC metabolism in muscle, fat and liver tissue, plays a key role in the early manifestation of type 2 diabetes and cardiovascular disease (James et al., 2021). Although normal fluctuations in insulin sensitivity occur during the life cycle e.g., during puberty, pregnancy and with ageing (Kahn et al., 2006), the expansion of adipose tissue is a risk factor for the development of insulin resistance (James et al., 2021). Intrinsically, obesity increases the risk of NCDs such as type 2 diabetes, non-alcoholic fatty liver disease, cardiovascular disease, musculoskeletal disease, mood disorders, and some types of cancer (Blüher, 2019). In 2023, high BMI, defined as BMI ≥ 25 kg/m², contributed to 3.7 million (95% UI 2.0, 5.2) deaths, and led to 135.8 million (95% UI 66.1, 199.7) DALYs (Institute for Health Metrics and Evaluation, 2025).

2.2. Environmental factors in overweight and obesity

2.2.1. The living environment

The immediate living environment within a country or a geographic region such as the built environment, transport systems, availability of low-cost, high-calorie, high-fat foods, opportunities for physical activity, sociocultural determinants of food choices and body-size perception have been associated with overweight and obesity (Swinburn et al., 2011). Twin studies have indicated the importance of shared environment on fast food intake, sedentary lifestyle and obesity (Nelson et al., 2006). Some authors suggest that overweight and obesity are the result of a normal reaction to the surrounding obesogenic environment, which imposes a wide range of barriers to maintaining a healthy weight (Jackson et al., 2020; Swinburn et al., 2011).

The association between the built environment and obesity has been extensively investigated. Mixed land use, pleasant aesthetics, environment with healthy food options and greater access to parks and playgrounds have been associated with lower weight status (Dixon et al., 2021). An analysis of 11,562 children aged 3–5 years revealed a link between a higher density of street trees and a lower prevalence of obesity (Lovasi et al., 2013). In addition, access to bike lanes have been significantly associated with physical activity (Pan et al., 2021). In contrast, lack of green spaces in the urban environment has been associated with higher risk of obesity. Poulain et al. (2020) analysed the association between the proportion of streets (sum of railways and streets) and green spaces (sum of agriculture, lawn, bushes/young trees and trees) in the immediate urban living area and the risk of overweight and obesity. The authors observed a positive link between higher percentage of streets within 100 meters of home and increased odds for overweight and obesity in adolescents (aged 10–19 years) (Poulain et al., 2020). Further, neighbourhood walkability, defined by residential density, proximity of shops and services, street connectivity, and proximity to parks and recreation facilities, and safety have been studied in regards to physical activity (Hermosillo-Gallardo et al., 2020; Sallis et al., 2018, 2011). Sallis et al. (2018) reported greater physical activity and less sedentary time and TV time among adolescents aged 12–16 years ($n = 928$) living in walkable neighbourhoods (Sallis et al., 2018). In a study of 4,079 adolescents aged 15–18 years, low perception of pedestrian safety was associated with lower physical activity, among female subjects ($n = 2074$) (Hermosillo-Gallardo et al., 2020). However, most evidence on the effects of the built environment comes from urban populations in high-income countries. Corsi et al. (2024) recently analysed 143,338 participants across 530 communities in countries spanning all income levels. Higher pedestrian safety (e.g., sidewalks, crosswalks) and community beautification (e.g., trees, benches, streetlamps) was associated with lower obesity overall and in urban areas, but not in rural areas. However, bike lanes were associated with lower obesity in both urban and rural settings. Community disorder (e.g.,

derelict buildings, graffiti) was associated with higher obesity overall, with similar associations across urban and rural areas (Corsi et al., 2024).

Furthermore, it has been hypothesised that SES may modify the effect of living environment on overweight and obesity. A trend for effect modification by income, demonstrating that lower walkable/lower income neighbourhoods had the highest percent of obese adolescents (16.7%) whereas lower walkable/higher income neighbourhoods had the lowest percent of obese adolescents (8.8%), has been noted (Sallis et al., 2018).

2.2.2. Socioeconomic status

Stunkard (1972) was one of the first to report the inverse relationship between SES and obesity (Stunkard et al., 1972). Over the years, the same phenomenon has been reported among both children and adults in other high-income developed countries, where the highest prevalence of overweight and obesity has been observed in groups with the lowest SES (Chung et al., 2016; Devaux & Sassi, 2013; McLaren, 2007; Shrewsbury & Wardle, 2008). Moreover, residing in low SES neighbourhood has been associated with a higher risk of overweight and obesity regardless of the individual-level SES (Wang et al., 2007). A systematic review and a meta-analysis by Mohammed et al. (2019) demonstrated that low SES neighbourhood was associated with a 31% higher odds of overweight, a 45% higher odds of obesity and a higher mean BMI (by 1.09 kg/m²; 95% confidence interval [CI] 0.67, 1.50) (Mohammed et al., 2019).

Various mechanisms exist through which individual, and neighbourhood SES can influence a person's weight status. Thomas et al. (2019) investigated the association between area-based SES index and consumption of foods high in fat, salt and sugar, screen time and health knowledge among 3,348 adolescents (aged 11–19 years) across the United Kingdom. Subjects in the upper quintile of the deprivation index had greater consumption of foods high in fat, salt and sugar and lower intake of fruits and vegetables. In addition, deprivation was associated with greater consumption of sugar-sweetened beverages and higher weekly screen time, but lower awareness of the associations between obesity and chronic diseases such as type 2 diabetes, cardiovascular disease and cancer (Thomas et al., 2019). Schneider and Gruber (2013) observed a higher density of alcohol, tobacco and fast food outlets in residential areas with low income and high deprivation (Schneider & Gruber, 2013).

2.3. Behavioural factors in obesity

2.3.1. Diet

Energy requirement has been defined as the amount of energy from food needed to keep a balance between energy intake and expenditure with the aim of maintaining body size and composition while getting a desirable amount of physical activity consistent with long-term good health. Energy requirement consists of

the following components (Food and Agriculture Organization of the United Nations et al., 2004):

- basal metabolism;
- metabolic response to food;
- physical activity;
- growth.

Overweight and obesity are a consequence of net positive energy balance i.e., to gain weight, energy intake must exceed expenditure and vice versa; to lose weight, energy expenditure must exceed intake. Factors that influence energy balance can be considered as relating to the host (individual factors), the environment (external factors) and the vector (food and drink) (Romieu et al., 2017). A healthy and a balanced diet is an important factor in maintaining good health, and prevention or delay of chronic disease. Therefore, most countries or regions develop national nutrition recommendations. Since Estonian restoration of independence in 1991, four versions of national nutrition recommendations have been published (**Table 4**) (Kuivjõgi et al., 1995; Pitsi et al., 2025, 2017; Vaask et al., 2006).

Macronutrients i.e., proteins, fats, and carbohydrates, are the energy contributing components of a diet. According to the recent Estonian Nutrition, Physical Activity, and Sleep Recommendations 2025, proteins should contribute between 10–20%, fats 25–40% and carbohydrates 45–60% of the total daily energy intake (DEI) (Pitsi et al., 2025). The recommendations are based on the following average values (Blomhoff et al., 2023):

- 1 gram of protein has an energetic value of 4 kilocalories (kcal) or 16.7 kilojoules (kJ);
- 1 gram of fats has an energetic value of 9 kcal or 37.7 kJ;
- 1 gram of carbohydrates has an energetic value of 4 kcal or 16.7 kJ.

Table 4. Recommended intake of macronutrients and fatty acids from total DEI according to the Estonian national nutrition recommendations published in years 1995, 2006, 2017, and 2025 (Kuivjõgi et al., 1995; Pitsi et al., 2025, 2017; Vaask et al., 2006)

Macronutrients and fatty acids	Recommended intake as %E			
	Year 1995	Year 2006	Year 2017	Year 2025
Proteins	10–15	10–15	10–20	10–20
Fats	30–32	25–30	25–35	25–40
Saturated fatty acids	10–12	up to 10	up to 10	up to 10
Monounsaturated fatty acids	10	10–15	10–20	10–20
Polyunsaturated fatty acids	10	5–10	5–10	5–10
Carbohydrates	52–60	55–60	50–60	45–60

DEI, daily energy intake; %E, percentage from DEI.

High protein intake in young children has been associated with excess weight gain (Gruszfeld et al., 2016; Pimpin et al., 2016) although the source of proteins also plays a role (Pimpin et al., 2018). A twin study in children up to 5 years of age observed that the intake of protein from milk, cheese, and yogurt products, was associated with greater weight and higher BMI compared to a diet composed of plant-based milks, pulses, fruit, bread, vegetables, potatoes, pasta, rice and white meat (Pimpin et al., 2018). Similar findings have been reported in adults. Moon et al. (2021) observed a positive association between BMI and total protein intake and protein intake from animal sources among German adults ($n = 9,214$; aged 18–80 years). Every additional one percent intake of energy from animal protein was associated with a 0.19 kg/m^2 higher BMI in men and 0.06 kg/m^2 higher BMI in women at the lowest BMI quantiles and with a 0.32 kg/m^2 higher BMI in men and 0.40 kg/m^2 higher BMI in women at the highest BMI quantiles (Moon et al., 2021).

Wang et al. (2020) demonstrated that overall fat intake, percentage of DEI from fats and a high-fat diet were positively associated with weight and BMI. Further, a high-fat diet increased the risk of overweight and obesity by 13.2% (relative risk [RR] 1.13; 95% CI 1.04, 1.23) (Wang et al., 2020). Dietary fat composition may also play a role. Raatz et al. (2017) observed a positive association between BMI and total fat intake, intake of saturated fatty acids, and mono-unsaturated fatty acids, whereas no association was observed between BMI and polyunsaturated fatty acids (Raatz et al., 2017). Moreover, a systematic review and a meta-analysis by Hooper et al. (2020) demonstrated that reducing total fat intake to $\leq 30\%$ from DEI resulted in reduction of weight (mean difference [MD] -1.4 kg ; 95% CI $-1.7, -1.1$) that also reflected in a reduction of BMI (MD -0.5 kg/m^2 ; 95% CI $-0.6, -0.3$) and WC (MD -0.5 cm ; 95% CI $-0.7, -0.2$) (Hooper et al., 2020).

Sartorius et al. (2018) did not find any significant association between high-carbohydrate intake and obesity (odds ratio [OR] 1.04; 95% CI 0.93, 1.15). Further, no association between total calorie intake from carbohydrates and the odds of obesity (OR 0.98; 95% CI 0.93, 1.04) was observed (Sartorius et al., 2018). In recent years, low-carbohydrate diets have been suggested as being more effective for weight loss, than balanced-carbohydrate diets. A systematic review and a meta-analysis by Naude et al. (2022) observed that low-carbohydrate weight-reducing diets compared to balanced-carbohydrate weight-reducing diets resulted in little to no difference in change in weight over 3–8.5 months (MD -1.07 kg ; 95% CI $-1.55, -0.59$) and over 1–2 years (MD -0.93 kg ; 95% CI $-1.81, -0.04$) (Naude et al., 2022).

Measuring DEI and macronutrient composition is challenging; thus, several dietary habits have been independently identified as obesogenic. These include, but are not limited to, intake of high energy density foods, daily consumption of sugar-sweetened beverages and intake of red and processed meats. In contrast, higher consumption of legumes, wholegrain foods and nuts have been associated with a lower risk of obesity and weight gain (Romieu et al., 2017). A systematic review and a meta-analysis by Schlesinger et al. (2019) observed a significantly

higher risk for overweight and obesity with high consumption of red meat (RR 1.23; 95% CI 1.07, 1.41), processed meat (RR 8.80; 95% CI 1.20, 64.28) and sugar-sweetened beverages (RR 1.20; 95% CI 1.01, 1.43), compared to low consumption. Further, lower risk for overweight and obesity was noted with high consumption of whole grains (RR 0.85; 95% CI 0.79, 0.91), fruits (RR 0.88; 95% CI 0.80, 0.96), legumes (RR 0.87; 95% CI 0.81, 0.94) and fish (0.75; 95% CI 0.62, 0.89) (Schlesinger et al., 2019). Frequency of fast-food consumption has also been shown to increase the odds for obesity in a dose-dependent manner (Anderson et al., 2011).

Several diet patterns and overall diet quality have been studied regarding overweight and obesity. Li et al. (2022) evaluated the association between diet quality, BMI, and WC, using the Healthy Eating Index-2015 score. Odds for overall obesity (BMI ≥ 30 kg/m²) and abdominal obesity (WC of ≥ 102 cm) were lower in the higher quartiles of the Healthy Eating Index-2015 score (Li et al., 2022). Fung et al. (2015) used the alternate Mediterranean Diet, the alternate Healthy Eating Index-2010, and the Dietary Approaches to Stop Hypertension scores to assess the relationship between diet quality and weight gain among 50,603 women in the Nurses' Health Study, 22,973 men in the Health Professionals Follow-Up Study and 72,495 younger women from the Nurses' Health Study II. The three diet quality scores moderately and significantly correlated with each other. During the study period (follow-up of 20 years in Nurses' Health Study and Health Professionals Follow-Up Study, and 16 years in Nurses' Health Study II), mean weight increased in all three cohorts. Each 1-standard deviation (SD) increase in the alternate Mediterranean Diet, alternate Healthy Eating Index-2010 or Dietary Approaches to Stop Hypertension score over a 4 year period was associated with less weight gain in the same period (Fung et al., 2015).

2.3.2. Physical activity and cardiorespiratory fitness

Physical activity has been defined as “any bodily movement produced by skeletal muscles that requires energy expenditure” (World Health Organization, 2020a). Various types of exercise (e.g., aerobic training, resistance training, combined aerobic plus resistance training, and high-intensity interval training [HIIT]) have demonstrated positive effects on the cardiometabolic health. A systematic review and meta-analysis by van Baak et al. (2021) noted that all different training types (aerobic, resistance, combined aerobic plus resistance, and HIIT) increased cardiorespiratory fitness (CRF), compared to no exercise. Further, aerobic training, resistance training and combined aerobic plus resistance training increased muscle strength; resistance training or combined aerobic plus resistance training increased overall physical fitness (**Figure 1**) (van Baak et al., 2021).

CRF reflects the ability of the cardiovascular and respiratory systems to deliver oxygen to skeletal muscles during exercise and is an independent predictor of cardiometabolic health and cardiovascular disease. CRF is influenced by both genetic and modifiable factors. In addition to age and sex, engagement in vigorous physical activity is a key determinant of CRF, with its effects likely

dependant by the duration, frequency, and intensity of physical activity (Raghuveer et al., 2020).

Although physical activity has beneficial effects independent of weight control, in both obese and non-obese individuals (An et al., 2019; Pojednic et al., 2022; van Baak et al., 2021), increased physical activity is a common strategy to create negative energy balance and achieve weight loss (Chin et al., 2016). A systematic review and network meta-analysis by Song et al. (2026) found that combined aerobic and resistance exercise, HIIT, and moderate-to-vigorous aerobic exercise were associated with significant reductions in BMI and body fat percentage (BF%) among women with overweight or obesity (Song et al., 2026). Furthermore, aerobic exercise, resistance exercise, combined aerobic and resistance exercise, and HIIT all significantly reduced BMI and BF% among young adults with overweight or obesity (**Figure 1**) (Lv et al., 2026).

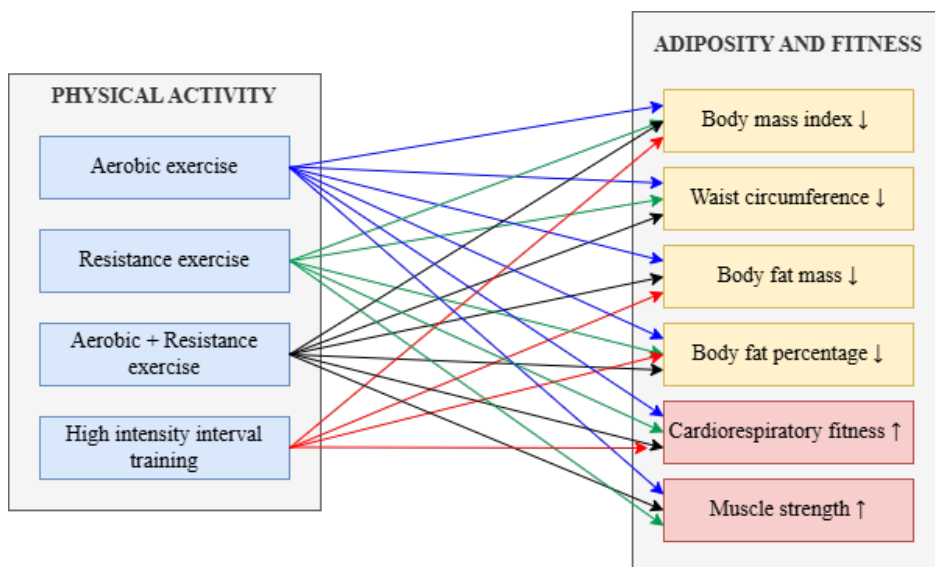


Figure 1. The effect of physical activity to adiposity and fitness (Lv et al., 2026; van Baak et al., 2021).

The overall beneficial effect of physical activity to health and wellbeing have led to the development of recommendations for optimal physical activity and sedentary behaviour (**Table 5**) (World Health Organization, 2020b). Recommendations regarding physical activity are also incorporated to the latest version of Estonian Nutrition, Physical Activity, and Sleep Recommendations 2025, published in year 2025 (**Table 5**) (Pitsi et al., 2025).

Table 5. Physical activity recommendations according to the WHO Guidelines on Physical Activity and Sedentary Behaviour and Estonian Nutrition, Physical Activity, and Sleep Recommendations 2025 (Pitsi et al., 2025; World Health Organization, 2020b).

WHO Guidelines on Physical Activity and Sedentary Behaviour (2020)	Estonian Nutrition, Physical Activity, and Sleep Recommendations 2025 (2025)
Children (aged 5–17 years) At least an average of 60 min per day of moderate to vigorous-intensity, mostly aerobic, physical activity. Vigorous-intensity aerobic activities, as well as those that strengthen muscle and bone at least 3 days per week. Limit the amount of time spent being sedentary, particularly the amount of recreational screen time.	Children (aged 7–18 years) At least an average of 60 min per day of moderate to vigorous-intensity physical activity. Muscle- and bone-strengthening activities at least 3 days per week. Limit non-school-related screen time to less than 2 hours per day.
Adults (aged 18–64 years) Physical activity should be performed regularly. At least 150–300 min of moderate-intensity aerobic physical activity per week; or at least 75–150 min of vigorous-intensity aerobic physical activity per week; or an equivalent combination of moderate- and vigorous-intensity activity per week. Muscle strengthening activities at moderate or greater intensity involving all major muscle groups on 2 or more days per week. Moderate intensity aerobic physical activity may be increased to more than 300 min per week; or more than 150 min of vigorous-intensity aerobic physical activity per week; or an equivalent combination of moderate- and vigorous-intensity activity per week. Limit sedentary time. Replace sedentary time with physical activity of any intensity (including light intensity). Aim for more than the recommended levels of moderate- to vigorous-intensity physical activity.	Adults (from age 19 years) Physical activity should be performed regularly, preferably for at least 30 min every day. At least 150–300 min of moderate-intensity physical activity per week; or 75–150 min of vigorous-intensity physical activity per week; or an equivalent combination of moderate- and vigorous-intensity physical activity per week. Muscle strengthening activities involving all major muscle groups at least 2 days per week and balance and flexibility exercises at least 3 days per week. Limit sedentary and screen time. Standing and stretching breaks should be performed at least once every hour.

h, hour; min, minute; WHO, World Health Organization

2.4. Birth cohort effects

A birth cohort consists of individuals born at a specific point in time or roughly in a similar time period (Canizares et al., 2018; Yoo, 2023). It should not be confused with age effect, which is the effect of growing older, or period effect, the variations across time periods that simultaneously affect all age groups (Canizares et al., 2018). Birth cohort effects have been noticed in several areas e.g., psychological dimensions such as agreeableness, perceived distress, and depression (Keyes et al., 2014; Kiive et al., 2023; Yoo, 2023), but also on BMI, overweight, obesity (Allman-Farinelli et al., 2008; Keyes et al., 2010; Robinson et al., 2013; Schramm et al., 2023; Yoo & Chung, 2020), and alcohol consumption (Pabst et al., 2010; Vaht et al., 2014; Virtanen et al., 2019). Individual birth cohorts experience different social and environmental factors, which may lead to differences in psychological and social development, and health related behaviour (Yoo, 2023). However, the differentiation of independent effects of the birth cohort, age, and time period is complex, because they are linearly dependent (Canizares et al., 2018).

The effects of the birth cohort may be especially relevant during a period of rapid change in societies, e.g., transitioning from the Soviet era. In the 1990-ies Estonia possibly experienced the fastest transition among the Countries of Central and Eastern Europe. The post-Soviet era was characterised by moving towards a meritocratic society, rapid changes in economy, equal access to education and occupation, and gender equality (Rimfeld et al., 2018). Many other changes, from value systems to customary food and eating habits, were also to change.

2.5. Central and peripheral regulators of appetite and energy homeostasis

Energy intake and expenditure is a homeostatic process where the regulation of appetite and feeding is controlled by the central nervous system (CNS) via integration of external signals from the environment together with internal signals from peripheral regulators such as leptin, insulin (INS) and several gastrointestinal (GI) hormones in a rather complex manner (Hall et al., 2022). The main central and peripheral regulators of appetite have been presented in **Figure 2** (Austin & Marks, 2009; Lean & Malkova, 2016).

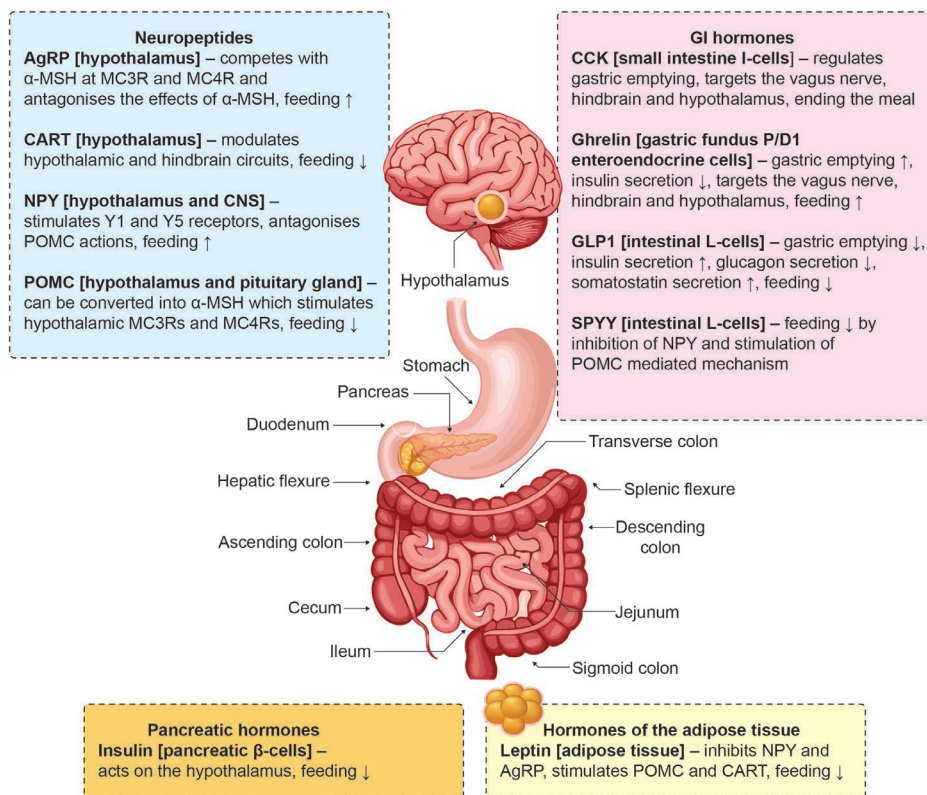


Figure 2. Main central and peripheral regulators of appetite (Austin & Marks, 2009; Lean & Malkova, 2016). AgRP, agouti-related peptide; α -MSH, melanocyte-stimulating hormone; CART, cocaine- and amphetamine regulated transcript; CCK, cholecystikinin; GI, gastrointestinal; GLP1, glucagon-like peptide-1; INS, insulin; MC3R, melanocortin-3 receptor; MC4R, melanocortin-4 receptor; NPY, neuropeptide Y; POMC, proopiomelanocortin; PYY, peptide tyrosine tyrosine (Figure design by Mette Mari Kaljas)

Hypothalamus, a small area of the brain located just below the thalamus, is a centre for appetite and energy homeostasis (Timper & Brüning, 2017). A key region involved in the central regulation of appetite and feeding is the arcuate nucleus (ARC) of the hypothalamus, where the appetite-inhibiting (i.e., anorexiogenic) proopiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript (CART) expressing neurons, and the appetite-stimulating (i.e., orexiogenic) NPY and agouti-related peptide (AgRP) co-expressing neurons are located (Farr et al., 2016; Timper & Brüning, 2017). Both POMC/CART and AgRP/NPY neurons express receptors for peripheral regulators e.g., INS and leptin (Timper & Brüning, 2017) which act in the hypothalamus to inhibit or excite these neurons and modify appetite (Farr et al., 2016).

The anorexigenic cells in the ARC activate the paraventricular nucleus (PVN) (Yu & Kim, 2012). PVN has an inhibitory role on food intake by inhibiting the lateral hypothalamic area (LHA). PVN neuron groups, particularly the PVN single-minded homolog 1 (SIM1) neurons, play an important role in satiety. PVN melanocortin-4 receptor-expressing (MC4R) neurons together with PVN prodynorphin-expressing neurons comprise the totality of PVN SIM1 neuron-mediated satiety. Thus, silencing the PVN MC4R or PVN prodynorphin-expressing neurons promotes food intake (Li et al., 2019). One of the most frequent genetic causes of obesity is the loss of MC4R function (Obradovic et al., 2021). Further, it has been demonstrated that PVN lesions (Leibowitz et al., 1981) and haploinsufficiency of SIM1 transcription factor, which is necessary for the development of PVN, cause hyperphagia and obesity (Holder et al., 2000; Michaud et al., 2001).

LHA acts as a feeding centre that contains two neuronal populations producing orexigenic neuropeptides, the melanin concentrating hormone and orexin. Damage to the LHA leads to hypophagia and weight loss (Yu & Kim, 2012). Ventromedial hypothalamus (VMH) plays a role in GLC homeostasis, where it is involved in the release of gluconeogenic hormones during INS-induced hypoglycaemia, but also in hepatic GLC production during euglycaemia (Hirschberg et al., 2020). VMH inhibits feeding, and damage to the VMH causes hyperphagia and obesity (Shimizu et al., 1987).

FTO protein is a ribonucleic acid (RNA) demethylase that belongs to a non-heme iron(II) and α -ketoglutarate dependent dioxygenase AlkB family (Gerken et al., 2007; Jia et al., 2011, 2008). FTO can bind to multiple RNA types and demethylate internal N⁶-methyladenosine (m⁶A) and cap 2-O-dimethyladenosine (m⁶A_m) in mRNA, internal m⁶A in U6 RNA, internal and cap m⁶A_m in snRNAs, and N1-methyladenosine (m¹A) in tRNA (Wei et al., 2018). However m⁶A, the most common modification of mRNA, is the most favourable nucleobase substrate of FTO (Zhang et al., 2019) and modulates several cellular processes such as RNA splicing, stability, translation, transportation and degradation (Azzam et al., 2022; Lan et al., 2020). Studies have demonstrated the potential role of FTO in the regulation of ghrelin (Karra et al., 2013), lipid accumulation (Tuck et al., 1999; Wang et al., 2015), adipogenesis and pre-adipocyte differentiation (Wu et al., 2018b, 2018a; Zhang et al., 2015; Zhao et al., 2014).

The more specific feeding control circuits are moderated by the monoaminergic systems that originate from the brainstem. Dopaminergic neurotransmission provides general motivating force, and the net effect of serotonin appears to be inhibition of feeding as depletion of serotonin generally increases food intake. The TFAP2B is a member of the AP-2 family of transcription factors (Raap et al., 2021). TFAP2B has an effect on both the serotonin and dopamine systems: we have previously demonstrated a strong correlation between TFAP2B levels in the raphe, where the serotonergic perikarya are located, and serotonin turnover in the frontal cortex (Damberg et al., 2001). Further, *TFAP2B* genotype has been associated with striatal dopamine D2-receptor availability as measured

by positron emission tomography as well as with the cerebrospinal fluid levels of homovanillic acid, a major metabolite of dopamine (Damberg et al., 2004).

Both the GI tract and adipose tissue have endocrine functions (Alhabeeb et al., 2021; Lean & Malkova, 2016). The gut-brain axis, a bidirectional communication network between the GI tract and CNS, is the physiological driver of satiation. GI and adipose tissue hormones are important peripheral regulators of energy control and interaction between the peripheral regulators and hypothalamic and brainstem centres represents a collective regulatory system for appetite, feeding and energy balance (Lean & Malkova, 2016).

Ghrelin, an orexigenic gut hormone, mostly secreted from the stomach during a period of food deprivation, increases appetite and feeding via direct effects on PVN and by activating AgRP/NPY neurons and inhibiting POMC neurons (Alhabeeb et al., 2021; Timper & Brüning, 2017). Other GI hormones, such as cholecystokinin, glucagon-like peptide 1 (GLP1), and peptide tyrosine tyrosine are released from the intestine and wield anorexigenic effects in various regions of the brain (e.g., ARC, PVN) (Timper & Brüning, 2017). Cholecystokinin facilitates nutrient absorption, stimulates gall bladder contraction, enhances pancreatic enzyme secretion and delays gastric emptying (Alhabeeb et al., 2021; Lean & Malkova, 2016). It also has a stimulating effect on the vagus nerve (Alhabeeb et al., 2021). GLP1 acts as an incretin, stimulating INS release and at the same time inhibiting glucagon release. Further, GLP1 delays gastric emptying leading to enhanced satiety (Lean & Malkova, 2016). Peptide tyrosine tyrosine is co-secreted with GLP1 and exerts its anorexigenic functions through inhibiting NPY neurons and promoting POMC neurons. This leads to reduced gastric motility and delayed gastric emptying (Alhabeeb et al., 2021; Lean & Malkova, 2016).

INS, a peptide hormone produced by the pancreatic β -cells, has an important role in GLC metabolism and appetite. INS enters the brain by either penetrating the blood-brain barrier or crossing the vascular endothelium via transport proteins. In the brain, INS exerts its anorexigenic effect by altering the expression of NPY, AgRP, POMC and CART in the ARC (Agrawal et al., 2021).

Leptin is mainly produced in the white adipose cells and has a variety of functions (e.g., regulation of food intake, body mass, and reproductive function; role in foetal growth, proinflammatory immune responses, angiogenesis and lipolysis). In feeding regulation, leptin affects the transcription of POMC which can be converted to α -MSH; α -MSH is then released into the synapse to activate neurons via binding to the melanocortin receptors leading to a suppressed appetite. Further, in neurons, leptin inhibits NPY and AgRP synthesis (Obradovic et al., 2021). The molecular mechanisms involved in the regulation of appetite and energy homeostasis are complex and include different central and peripheral regulators. Therefore, the pathways to dysregulation of energy homeostasis, that may lead to overweight and obesity, are diverse.

2.6. The reward system and obesity

CNS has multiple roles in the development of obesity. A variety of factors related to cognitive control, regulation of motivation, and reward contribute to its development (Mansur et al., 2015). Individual variation in the functioning of the reward system has most influentially been conceptualised in Gray's Reinforcement Sensitivity Theory (RST) (Gray, 1994; Smillie et al., 2006). The original RST consisted of a reward system, a punishment system, and a threat-response system known as the Behavioural Approach System (BAS), the Behavioural Inhibition System (BIS), and the Fight/Flight System (FFS), where BIS was thought to generate responses to conditioned signals of punishment and non-reward, BAS responses to conditioned signals of reward and non-punishments and FFS responses to unconditioned aversive stimuli (Smillie et al., 2006). When testing the original RST, various issues emerged leading Gray and McNaughton (2000) to revise the RST (Gray & McNaughton, 2000). The BAS remained largely unaltered mediating reactions to all appetitive stimuli; BIS was now responsible for resolving goal conflict in general; FFS was renamed as the Fight Flight and Freeze System mediating reactions to all aversive stimuli (Corr, 2008; Gray & McNaughton, 2000; Smillie et al., 2006).

Reward sensitivity, a psychobiological trait to seek rewarding substances or enjoyment with high reward potential, has been associated with overeating (Davis, 2013; Loxton & Tipman, 2017; Volkow et al., 2011), preference for foods high in fat and sugar (Davis et al., 2007; De Decker et al., 2016), and use of addictive substances (Emery & Simons, 2017; Jonker et al., 2014; Tatnell et al., 2019). Several neurotransmitter systems, most overwhelmingly dopamine and serotonin, regulate the rewarding effects of food (Volkow et al., 2011). Both palatable foods and substance use activate the dopaminergic pathways in the brain, indicating a higher response to reward (Davis, 2013). In addition, low serotonin levels are a known inclination for the development of depression, anxiety disorders, and addiction (Fischer & Ullsperger, 2017). Therefore, it has been suggested that obese individuals may differ from people with normal weight regarding reward sensitivity.

A study among 346 Dutch children (aged 6–13 years) found that children with obesity had higher scores of reward responsiveness, compared to children with overweight, normal weight, or underweight. Further, obese children had greater impulsivity and fun seeking scores, compared to normal weight and underweight children (Berg et al., 2011). A study investigating food addiction, over-eating, and reward sensitivity in women ($n = 374$), demonstrated an association between higher reward sensitivity and symptoms of food addiction, mediated by binge-eating, emotional eating, and food availability (Loxton & Tipman, 2017). Merchán-Clavellino et al. (2020) observed a significant correlation between reward sensitivity and alcohol consumption among 384 Spanish university students (Merchán-Clavellino et al., 2020).

Despite growing evidence supporting the presence of a relationship between reward sensitivity and obesity, the inner structure of reward sensitivity has not

been sufficiently understood (Corr, 2008; Corr & Krupic, 2017), and the association between components of reward sensitivity and weight remains unexplored. Pulver et al. (2020) differentiated reward sensitivity into Openness to Rewards, the strive towards multiplicity of rewards, and Insatiability by Reward, a fixation to a particular reward (Pulver et al., 2020). These two aspects of reward sensitivity diverge in their relationship with basic personality dimensions and symptoms of attention deficit hyperactivity disorder, a condition that is often co-morbid with obesity (Chen et al., 2018).

2.7. Candidate genes of interest in overweight and obesity

Genetic reasons behind obesity can broadly be classified into monogenic reasons, caused by a single gene mutations primarily located in the leptin-melanocortin pathway, syndromic reasons, where severe obesity is associated with other phenotypes such as neurodevelopmental abnormalities, or organ/system malformations (e.g., Bardet-Biedel Syndrome, Prader Willi Syndrome), and polygenic reasons, caused by cumulative contribution of multiple genetic variants whose effect is usually amplified by the obesogenic environment (Thaker, 2017).

The application of GWAS approximately 20 years ago enabled to find associations between several genetic variants and different traits (Frayling et al., 2007; Visscher et al., 2017). More than 3000 height-associated and 900 BMI-associated single nucleotide polymorphisms (SNP) have been identified in GWAS (Yengo et al., 2018). However, it is difficult to estimate the contribution of genes to BMI variability as heritability estimates of BMI differ, and range from 0.24 to 0.81 in family studies and 0.47 to 0.90 in twin studies (Elks et al., 2012). There is also evidence of genotype-age, genotype-environment (Robinson et al., 2017), and genotype-birth cohort interactions (Rosenquist et al., 2015) contributing to BMI variation. It is likely that obesity occurs from interactions between a polygenic risk profile and external factors (e.g., intrauterine environment, medications, SES, physical activity, insufficient sleep, endocrine disruptions, and the microbiome) (Goodarzi, 2018). However, the pathways and molecular mechanisms through which obesity develops, are not fully understood and detailed mechanistic understanding of how genetic variations influence the phenotype is required (Goodarzi, 2018; Loos & Yeo, 2022). This has led to a need to again study candidate genes separately to reveal etiopathogenetic pathways; likely, there are many.

2.7.1. TFAP2B and implication of the *TFAP2B* gene

TFAP2B gene is located on chromosome 6p12 and is composed of 7 exons (Raap et al., 2021). *TFAP2B* encodes a transcription factor expressed in the neural crest, the nervous system, and surface epithelium (Eckert et al., 2005; Mitchell et al., 1991). *TFAP2B* regulates cell survival, promotes cell proliferation and suppresses differentiation and has a role in the development of different tissues and

organs of ectodermal, neuroectodermal and mesodermal origin such as the kidneys, the CNS, and peripheral nervous system (Eckert et al., 2005; Raap et al., 2021). Further, *TFAP2B* influences both the serotonin and dopamine systems (see Section 2.5.). Overexpression of *TFAP2B* in 3T3-L1 adipocytes decreased the expression and secretion of adiponectin, by directly inhibiting adiponectin gene expression (Ikeda et al., 2006). Moreover, overexpression of *TFAP2B* caused adipocyte cell enlargement, stimulation of GLC transport activity, triglyceride (TRG) accumulation and insulin resistance (Tao et al., 2006).

A meta-analysis of GWAS in individuals of European and non-European descent and Metabochip studies, with a total of 339,224 individuals, identified 97 loci, including the *TFAP2B* gene, associated with BMI (Locke et al., 2015). A meta-analysis of GWAS in children (aged 2–10 years) produced similar results: It included 20 studies ($n = 35,668$) in the discovery phase and 13 studies ($n = 11,873$) in the replication phase; 15 loci, including *TFAP2B*, reached genome-wide significance and were thus reliably associated with childhood BMI (Felix et al., 2016).

Earlier studies have shown that polymorphisms in the first intron of *TFAP2B* affect the transcriptional activity of the gene (Tsukada et al., 2006). Moreover, polymorphism in the second intron of the *TFAP2B* was associated with abdominal obesity and insulin resistance in male subjects at 15 years of age (Nordquist et al., 2009).

2.7.2. *FTO* and *FTO* rs1421085

The gene encoding the *FTO* was originally identified in 1999 in a fused-toe mouse model, and called *Fatso* because of its size (Peters et al., 1999). It is located on chromosome 16q12.2 and has a total length of 410.50 kb including 9 exons and 8 introns (Lan et al., 2020). *FTO* acts as an RNA demethylase (see Section 2.5.).

In year 2007, a GWAS by Frayling et al. (2007) first demonstrated the association between *FTO* rs9939609 and obesity (Frayling et al., 2007). In the same year, these findings were confirmed by two other research groups (Dina et al., 2007; Scuteri et al., 2007). Subsequently, several GWAS have affirmed the association between different *FTO* SNP-s and BMI in children and adults (Felix et al., 2016; Locke et al., 2015; Yengo et al., 2018). Some of the *FTO* variants, e.g., rs1421085, rs17817449 and rs9939609, are in strong linkage disequilibrium (pairwise r^2 0.85–97) (Price et al., 2008; Villalobos-Comparán et al., 2008).

The association between *FTO* variants and eating behaviour has been suggested. Stutzmann et al. (2009) did not find any association between *FTO* rs1421085 genotype and snacking or eating large amounts of food in adolescents and adults with European ancestry (Stutzmann et al., 2009), whereas Wardle et al. (2009) found that the *FTO* rs9939609 T-allele was protective of overeating among children aged 4–5 years (Wardle et al., 2009). *FTO* rs1421085 C allele has been associated with higher perceived hunger score (Harbron et al., 2014), but *FTO* rs9939609 was not associated with altered postprandial responses in hunger

hormones and metabolic flexibility (Danaher et al., 2019). Inversely, *FTO* rs9939609 risk allele has been associated with lower energy intake and lower fat and protein intake, when adjusted to weight (Livingstone et al., 2015).

Another mechanism was proposed by Claussnitzer et al. (2015), who demonstrated that *FTO* rs1421085 increased *IRX3* and *IRX5* expression in preadipocytes, promoting white adipocyte differentiation and resulting in reduced mitochondrial thermogenesis (Claussnitzer et al., 2015). There is also evidence of an effect modification by the environment. Foraita et al. (2015) observed an interaction between SES and *FTO* rs9939609 in childhood obesity (Foraita et al., 2015).

2.7.3. NPY and variants in the *NPY* gene

NPY is a 36 amino-acid neuropeptide first isolated from porcine brain in 1982 by Tatemoto and Mutt (Tatemoto et al., 1982). The gene encoding NPY is located on chromosome 7p15.3 and has 4 exons (Cattaneo et al., 2021). NPY is widely expressed throughout the central and peripheral nervous system with higher concentrations in the ARC, the PVN, the supraoptic nucleus, the superior nucleus, median eminence, dorsal medial hypothalamic nucleus, paraventricular thalamic nucleus, amygdala, and hippocampus. NPY biological actions are exerted via its G-protein coupled receptors. Four functional NPY receptors are expressed in humans: Y1, Y2, Y4, and Y5 (Cattaneo et al., 2021; Huang et al., 2021). NPY has a critical role in the feeding behaviour, with Y1 and Y5 most strongly implicated in mediating the hyperphagic effects (Nguyen et al., 2012). It was observed that overexpression of NPY in the brain led to overweight (Kaga et al., 2001) and central administration of NPY markedly increased food intake (Clark et al., 1984; Stanley et al., 1986).

Zhou et al. (2008) demonstrated that *NPY* rs16147, located in the promoter region of the gene, altered NPY expression in vitro and accounted for more than half of the variation in expression in vivo. *NPY* rs16147 C allele was associated with decreased expression of mRNA in post-mortem brain and lymphoblasts (Zhou et al., 2008), and lower levels of plasma NPY (Shah et al., 2009; Zhou et al., 2008). Kallio et al. (2001) was the first to report the functional consequences of the *NPY* rs16139 (T>C) substitution, demonstrating a higher overall plasma NPY concentration and faster heart rate in C allele carriers (Kallio et al., 2001). Mitchell et al. (2008) replicated the results, showing that *NPY* rs16139 (T>C) led to an increase in the levels of prohormone and elevated NPY secretion in C allele carriers (Mitchell et al., 2008).

However, the effect of *NPY* gene variations on overweight and obesity, GLC metabolism, and lipid metabolism is inconclusive. Zain et al. (2015) demonstrated that *NPY* rs16147 TT homozygotes had higher odds (OR 1.27; 95% CI 1.04, 1.55) for obesity, compared to CC homozygotes, and *NPY* rs5574 TT homozygotes had lower odds (OR 0.76; 95% CI 0.61, 0.96) for obesity, compared to CC homozygotes (Zain et al., 2015). Yeung et al. (2011) did not observe any

association between *NPY* rs16147 and obesity among 2,071 women from the Nurses' Health Study and 1,268 men from Health Professionals Follow-Up Study. However, they reported higher odds (OR 1.72; 95% CI 1.20, 2.47) for obesity in *NPY* rs17149106 heterozygotes compared to GG homozygotes. Further, carriers of the *NPY* rs16139 C allele had higher odds (OR 1.79; 95% CI 1.24, 2.60) for obesity, compared to TT homozygotes. Findings were similar when comparing the mean difference in BMI by *NPY* genotype over the follow-up period (years 1986–2006) (Yeung et al., 2011). *NPY* rs16139 (T>C) was associated with higher BMI values in both men (van Rossum et al., 2006) and women (Ding et al., 2005; van Rossum et al., 2006), while CHL, TRG and BP did not differ between genotype groups (Ding et al., 2005). Another study by Karvonen et al. (2006) did not find any association between *NPY* rs16139 and weight in children, but observed an association with TRG levels (Karvonen et al., 2006). GWAS has not revealed a role for *NPY* in obesity, that is surprising given its physiological function.

2.8. Summary of the literature review

Overweight and obesity are major public health concerns, increasing the risk for several NCDs e.g., cardiovascular disease, diabetes, chronic kidney disease, cancer, and musculoskeletal disorders, and have a wide array of causes. Even though GWAS have identified hundreds of genetic variants associated with overweight and obesity, the specific contributions of these genetic variants and the underlying mechanisms need to be investigated. Further, several other factors e.g., cognitive control, regulation of motivation, and sensitivity to reward, contribute to excess weight gain. In addition, as the effect of specific genetic variants may be influenced by sex, age, physical environment, birth cohort, and individual behaviours, more should be known about their potential interactions.

3. AIMS OF THE THESIS

The main aim of this research was to explore the longitudinal association between selected genetic, behavioural and environmental factors in the development of obesity and related conditions from adolescence to young adulthood in a sample representative of birth cohorts. The following specific aims were formulated:

1. To describe the longitudinal change in measures of obesity and dietary intake in the Estonian Children Personality Behaviour and Health Study (ECPBHS) subjects, considering possible differences between the birth cohorts (**Paper V**).
2. To investigate the effect of *TFAP2B* intron 2 genotype on measures of obesity and insulin resistance (**Paper I**).
3. To analyse the association between *FTO rs1421085* polymorphism and measures of obesity, dietary intake, CRF, physical activity, and SES (**Paper II**).
4. To analyse the association between *NPY* variants and measures of obesity, dietary intake, physical activity, BP, GLC, and lipid metabolism (**Paper IV**).
5. To evaluate the association between reward sensitivity and measures of obesity, paying attention to the inner structure of reward sensitivity (**Paper III**).

4. SUBJECTS AND METHODS

4.1. Subjects and study design

The study sample was originally formed for the European Youth Heart Study (EYHS) in 1998/99 and was later incorporated into the ECPBHS. The study procedure and the selection of the original sample has been described in detail elsewhere (Harro et al., 2026). In brief, ECPBHS is a longitudinal birth cohort study with a population representative sample of participants, all European descent, with school as the sampling unit. All schools of Tartu County, Estonia that agreed to participate (54 of the total of 56) were included into the sampling and 25 schools were selected using probability proportional to eligible sample size at school. All children from grades 3 (aged 9 years) and grades 9 (aged 15 years) were invited to participate and 79.1% of the invited subjects participated in the original study ($n = 583$ and 593 , respectively). The selected age groups reflected key stages of sexual maturation, with 9-year-olds typically corresponding to the prepubertal stage and 15-year-olds representing the late stages of pubertal development. Follow-up studies for the younger birth cohort took place in year 2004 at age 15 years ($n = 483$), in year 2007 at age 18 years ($n = 454$), in year 2014 at age 25 years ($n = 441$) and in year 2022 at age 33 years ($n = 428$) and for the older birth cohort in year 2001 at age 18 years ($n = 417$ + additional 62 subjects), in year 2008 at age 25 years ($n = 541$) and in year 2016 at 33 years ($n = 504$) (**Figure 3**).

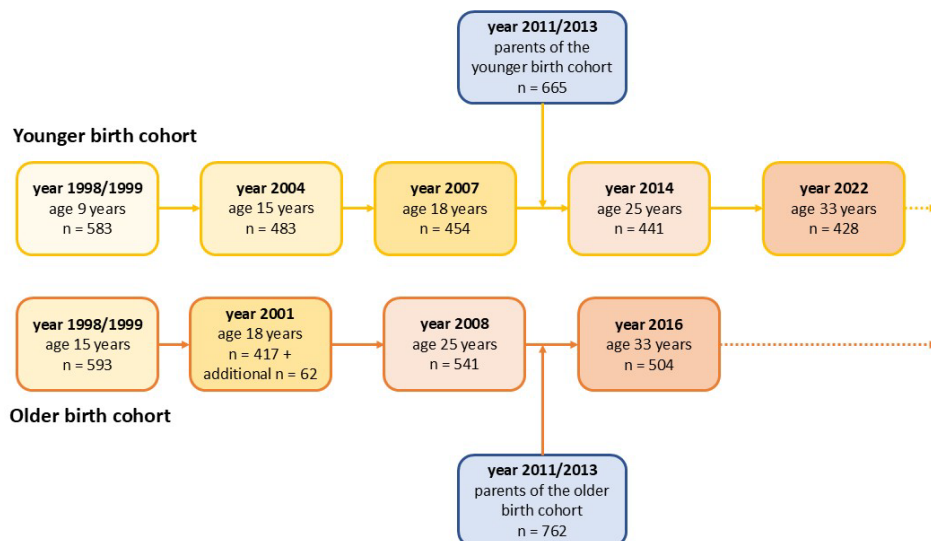


Figure 3. Timeline of the ECPBHS study waves.

4.2. Methods

4.2.1. Anthropometric measurements and blood pressure

Height was measured to the nearest 1 millimetre, and weight was measured to the nearest 0.1 kilogram. BMI was calculated as weight in kilograms / height in meters squared (kg/m^2). The WHO classification (**Table 1**) was used to define overweight and obesity in adults (World Health Organization, 2000) and the definition by Cole et al. (2000) (**Table 3**) was used to define overweight and obesity in children (Cole et al., 2000). A Harpenden calliper (Baty, West Sussex, England) was used to measure skinfold thickness from the left side of the body at the biceps, triceps, subscapular, suprailiac and medial calf areas. BF% was calculated based on values of skinfold thickness (biceps, triceps, subscapular, and suprailiac) using age-appropriate equations (Durnin and Womersley, 1974; Durnin and Rahaman, 1967). WC was measured to the nearest 1 millimetre between the lower rib margin and the iliac crest, at the end of gentle expiration. Hip circumference (HC) was measured to the nearest 1 millimetre over the buttocks, at the level of the great trochanter. WHR and WHtR were calculated. All anthropometrical measurements were taken twice, and a mean value was used in the analysis (**Papers I to V**).

Resting systolic BP and diastolic BP was measured in a laboratory setting from the left arm in a sitting position with an automatic oscillometric method. Five consecutive measurements were made at 2 min intervals, and the mean value was used in the analysis (**Papers I and IV**).

4.2.2. Biochemical measures

Venous blood samples were taken after an 8–12 h fast and analysed in a certified clinical laboratory. Insulin resistance was estimated, using the Homeostatic Model Assessment (HOMA) index, which was calculated as fasting GLC (mmol/l) $\times$ fasting INS (mU/l) / 22.5 (Matthews et al., 1985) (**Papers I, IV and V**).

4.2.3. Dietary intake

The subjects were asked to complete a 24-hour (year 1998), 48-hour (years 2001, 2004, and 2007), or 72-hour (years 2008 and 2014) diet record at home during the day(s) before the study day. On the study day, a face-to-face interview, using pictures of portion sizes (Haapa et al., 1985), was conducted to specify portion sizes that were not recorded in the food diary. For the 24-hour dietary record, subjects recorded their dietary intake on the day preceding the study day. For the 48-hour dietary record, subjects recorded intake on one weekday and one weekend day. For the 72-hour dietary record, subjects recorded intake on two weekdays and one weekend day. Where data on two or three days were available, the mean consumption was calculated.

To assess dietary intake the Finnish Micro-Nutrica Nutritional Analysis programme (Estonian version 2.0, Tallinn University of Technology, Food Pro-

cessing Institute, Estonia) and the Estonian NutriData food consumption database (versions 4.0–7.0, National Institute for Health Development, Estonia) were used. NutriData is an evidence-based food composition database, established by the National Institute for Health Development, and based on the Micro-Nutrica software. Over the years, the food list of Micro-Nutrica has been updated with local food data (**Papers I to V**).

4.2.4. Reward sensitivity

Reward sensitivity was assessed using the Reward Openness and Insatiability Scale (ROIS), which specifies the inner structure of reward sensitivity. The construction and description of ROIS has been described in detail elsewhere (Pulver et al., 2020). In brief, the ROIS was constructed post hoc making use of previously collected information on personality. Items thought to reflect reward sensitivity were extracted from the Estonian versions of International Personality Item Pool NEO, Barratt Impulsiveness Scale, the brief version of the Affective Neuroscience Personality Scale, Spielberger State-Trait Anxiety Inventory, and Adaptive and Maladaptive Impulsivity Scale. Out of the initial item pool, 28 items were selected based on factor loadings, communalities, and internal homogeneity. ROIS comprises of 28 items, divided equally between two higher-order factors – Openness to Rewards, a strive toward multiplicity of rewards and Insatiability by Reward, characterised by an excessive fixation to a particular reward (**Supplementary table 1**). Openness to Rewards (Cronbach $\alpha = 0.82$) includes Excitement and Novelty (Cronbach $\alpha = 0.79$), with items reflecting the search for new experiences and excitement and Social Experiences (Cronbach $\alpha = 0.75$), with items largely associated with sociability and social exchange. Insatiability by Reward (Cronbach $\alpha = 0.86$) comprises of Excessive Spending (Cronbach $\alpha = 0.85$), with items related to impulsive buying and excessive spending and Giving in to Cravings (Cronbach $\alpha = 0.77$), with items related to low self-control and trouble in resisting to temptations. Personality information for analysis by ROIS was collected at age 25 or 33 years. The mean item score was used in statistical analysis (**Paper III**).

4.2.5. Physical activity and cardiorespiratory fitness

Physical activity levels were evaluated using self-reported and parent-reported questionnaires. At 9 and 15 years, the questions included participation in training groups (e.g., Do you participate in organised sports?) and physical activity lessons (e.g., To what extent have you participated in physical education classes during this school year?) and self-evaluated physical activity patterns (e.g., I am not physically active and do not intend to become physically active in the near future / I am not physically active, but I intend to become physically active / I am physically active on a regular basis, but have only recently started / I have been physically active on a regular basis for more than 6 months / I was physically active on a regular basis for more than 6 months, but am no longer physically

active). Questions reflecting participation in training groups and parent-reported physical activity patterns (e.g., Much less physically active than their peers / Somewhat less physically active than their peers / About as physically active as their peers / Somewhat more physically active than their peers / Much more physically active than their peers) were included for subjects at 18 years. At 25 and 33 years, questions including the number of days during the previous week when participants were active for at least 30 minutes and number of days when participants were involved in work-related moderate to vigorous physical activity were used. For each answer option a numerical value was given, and individual physical activity scores were computed. The number of questions, and thus the maximum possible physical activity score, varied by age. To account for it, the physical activity scores were standardised, and z-scores were used in longitudinal analysis (**Papers II to IV**).

CRF was defined as the maximum power output (MPO) per kilogram of body weight (MPO/kg) and determined by a maximum cycle-ergometer test. The protocol for CRF originates from the EYHS and has been validated against the direct measurement of $\text{VO}_{2\text{max}}$. The correlation between $\text{VO}_{2\text{max}}$ measurements and the MPO was 0.96 (Klasson-Heggebø et al., 2006). The procedure of the cycle-ergometer test has been described in detail elsewhere (Lätt et al., 2018). In short, after a warming up period of 3 min, subjects pedalled at a self-selected rate between 60 and 80 rpm. The initial workload for male subjects was set at 50 W, increasing by 50 W every 3 min and the initial workload for female subjects was set at 40 W, increasing by 40 W every 3 min until exhaustion. Participants were encouraged by the researcher throughout the cycle-ergometer test and monitored by medical personnel to safely achieve their maximal performance. The following formula was used to calculate MPO: $W1 + (W2 \times t / 180)$, where W1 is the work rate at the last fully completed stage, W2 is the work rate increment at the final incomplete stage, and t is the time in seconds at the final incomplete stage (**Papers II, IV and V**).

4.2.6. Socioeconomic status

Self-reported and parent-reported questionnaires were used to assess SES at ages 15, 18, and 25 years. To calculate an SES score, at 15 years and 18 years questions about parental education level (e.g., Primary or basic education / Secondary education / Vocational education / Incomplete higher education / Higher education), total household income (divided into income groups) and self-assessed or parent-assessed SES (whichever was highest) compared to peers (e.g., We are poor / We are not poor, but we are on the verge of poverty / We are neither wealthy nor poor / We are not wealthy, but are financially secure / I believe we are among the most wealthiest families in Estonia) were used. At age 25 years, questions about the level of education of the subject, total household income, and self-reported SES assessment compared to peers was used. Individual SES scores were calculated by matching a numerical value for each answer option. SES scores were standardised (sSES) and z-scores were used in longitudinal analysis (**Paper II**).

4.2.7. Genotyping

4.2.7.1. Genotyping of *TFAP2B* variable number tandem repeat polymorphism

Genotyping of *TFAP2B* intron 2 variable number tandem repeat (VNTR) (a tetra-nucleotide repeat, 4–5 times) polymorphism (**Papers I and III**) was conducted at the Department of Neuroscience, Uppsala University. It yielded the following frequencies: 4/4=89, 4/5=407, 5/5=619). PCR amplification of the *TFAP2B* polymorphism was carried out using the oligonucleotides: intron 2-F cct acc acc aga gcc agg acc c; intron 2-R ccc ccc ctc cag aag cat tcc t. PCR reactions were set up and run accordingly: 1× Taq gold PCR buffer, 250 µmol/l deoxynucleotide triphosphates (Amersham Biosciences, Uppsala, Sweden), 2 mmol/l MgCl₂, 1 µmol/l of each primer, 1 U AmpliTaq Gold (Applied Biosystems, Foster City, CA), and 20 ng genomic DNA, in a 20 µl reaction volume, were amplified in an ABI 7900 genetic analyser (Applied Biosystems) with the temperature cycling program; 94 °C for 10 min, followed by 35 cycles of 94 °C for 45 s, 57 °C for 45 s, 72 °C for 90 s, ending with 72 °C for 10 min. Products were analysed on an ABI 730 sequence detector (Applied Biosystems) and genotypes assessed using GeneMarker (SoftGenetics, State College, PA) software. All genotypes were manually checked on chromatograms to detect inconsistencies, and where needed, amplified and scored a second time. Genotype frequencies were in Hardy–Weinberg equilibrium.

4.2.7.2. Genotyping of *FTO* rs1421085

Genotyping of the *FTO* rs1421085 was conducted at the Chair of Neuropsychopharmacology, University of Tartu. Genomic DNA was extracted from venous blood samples using Qiagen QIAamp® DNA Blood Midi Kit. The real-time polymerase chain reaction (RT-PCR) for genotyping the *FTO* rs1421085 polymorphism (**Paper II**) was performed using a TaqMan Pre-Designed SNP Genotyping Assay (Applied Biosystems; Foster City, CA, USA) C__8917103_10 containing primers and fluorescent probes. Genotyping reactions were performed in a total volume of 10 µl with ~25 ng of template DNA. RT-PCR reaction components and final concentrations were as follows: 1:5 5 x HOT FIREPol® Probe qPCR Mix Plus (ROX) (Solis BioDyne) and 1:20 80 x TaqMan Primers Probe. Context sequence [VIC/FAM] was as follows: TAGCAGTTCAGGTCCTAAG GCATGA[C/T]ATTGATTAAGTGTCTGATGAGAATT. Reactions were performed on the Applied Biosystems ViiA™ 7 Real-Time PCR System. The amplification procedure consisted of an initial denaturation step at 95 °C for 12 min and 40 cycles of 95 °C for 15 s and 60 °C for 1 min. Positive and negative controls were added to each reaction plate. No inconsistencies occurred. Genotyping was performed blind to all phenotypic data. Genotype frequencies were in Hardy–Weinberg equilibrium.

4.2.7.3. Genotyping of *NPY* rs5574, rs16147, rs16139 and rs17149106

NPY rs5574, rs16147, rs16139, and rs17149106 were genotyped at the Chair of Neuropsychopharmacology, University of Tartu. Genomic DNA was extracted from venous blood samples using Qiagen QIAamp® DNA Blood Midi Kit. The real-time polymerase chain reaction (RT-PCR) for genotyping the *NPY* rs5574, rs16147, rs16139 and rs17149106 polymorphisms (**Paper IV**) was performed using a TaqMan Pre- Designed SNP Genotyping Assay (Applied Biosystems; Foster City, CA, USA) containing primers and fluorescent probes. Context sequence [VIC/FAM] for rs5574 was as follows: TTTTTCAGATATGGAA AACGATC[C/T]AGCCCAGAGACACTGATTTTCAGACC; for rs16147: GCTTCCTACTCCGGCACCCAGTGGG[C/T]TGGTAGTCCTGTTGGCAGG AGACAA; for rs16139: CTGCAGATGCTAGGTAACAAGCGAC[C/T]GGG GCTGTCCGGACTGACCTCGCC; for rs17149106: CCCCTGAAACCACG GGCGGGGGTGG[G/T]GTGGGGAGCGCAGCTTTGGGACCCT. Genotyping reactions were performed in a total volume of 10 µL with ~25 ng of template DNA. RT-PCR reaction components and final concentrations were as follows: 1:5 5 x HOT FIREPol® Probe qPCR Mix Plus (ROX) (Solis BioDyne) and 1:20 80 x TaqMan Primers Probe. Reactions were performed on the Applied Biosystems ViiA™ 7 Real-Time PCR System. The amplification procedure consisted of an initial denaturation step at 95 °C for 12 min and 40 cycles of 95 °C for 15 s and 60 °C for 1 min. Positive and negative controls were added to each reaction plate. No inconsistencies occurred. Genotyping was performed blind to all phenotypic data. Allele frequencies agreed with National Centre for Biotechnology Information database and published reports. Genotype frequencies were in Hardy–Weinberg equilibrium.

4.2.8. Statistical analysis

All statistical analysis was performed with Stata software, versions 13 and 14 (StataCorp LP, College Station, Texas, USA). Significance level was set at 0.05.

Linear mixed-effects regression models with random intercept and random slope were used for longitudinal analysis. Linear mixed-effects regression models consider the correlations between repeated measurements within each subject and use all available observations and assume that the missingness is independent of unobserved measurements, but dependent on the observed measurements, and thus random (Detry and Ma, 2016). Models with random intercept and slope allow individual variation not only in baseline values, but also in terms of mean response over time, giving the model more flexibility to fit the data (Harrison et al., 2018). Time was treated as a continuous variable. The likelihood-ratio test was used to assess the goodness of fit of the statistical models. Where interaction with time was not significant and the likelihood-ratio test did not show superiority of the more complicated model, interaction with time was not included in the final models. Unstructured covariance structure and restricted maximum likelihood method was used. Heteroscedasticity was not detected based on the graphical examination of standardised residual versus fitted values plot (**Papers I to V**).

Continuous variables are presented as means and SDs. Differences in anthropometric measurements, biochemical measures, dietary intake, CRF and physical activity at ages 9, 15, 18, 25 and 33 years were assessed by one-way ANOVA. The p values obtained from the pairwise comparisons were corrected by the Bonferroni method (**Papers II and IV**) or the Sidak method using the following equation $p^* = 1 - (1 - p)^3$ where p^* is compared with significance level 0.05 (**Papers I and III**). Independent group t-test was used to test differences by sex (**Paper III**) and birth cohort (**Paper V**).

4.2.9. Ethical considerations

Before participation, written informed consent was obtained from the subjects and, in case of minors (aged < 18 years), also from their parent. The study was approved by the Ethics Review Committee on Human Research of the University of Tartu and conducted in accordance with the Declaration of Helsinki. Ethics approvals relevant to this thesis include: EYHS protocol number (pr. no) 49/30, date 25.08.1997; ECPBHS pr. no 151/11, date 21.08.2006; ECPBHS phase II pr. no 197T-14, date 03.11.2010; neurobiological and environmental factors in ADHD pr. no 197T-13, date 03.11.2010; ECPBHS II pr. no 235/M-20, 17.03.2014; AGGRESSOTYPE (University of Tartu) pr. no 236/T-21, date 21.04.2014; Horizon 2020 CoCA (University of Tartu) pr. no 262/T-19, 19.09.2016; Horizon 2020 Eat2beNICE (University of Tartu) pr. no 280/T-4, date 04.04.2018; ECPBHS study wave for younger cohort at 33 years pr. no 365/T-7, date 13.06.2022, and pr. no 377/M-2, date 15.05.2023, and pr. no 394/M-8, date 21.10.2024.

The central database for ECPBHS is located at the National Institute for Health Development, Tallinn, Estonia. Pseudonymised data were used in the analysis.

5. RESULTS

5.1. Anthropometric measurements, metabolic biomarkers, dietary intake and cardiorespiratory fitness of the Estonian Children Personality Behaviour and Health Study sample from childhood to adulthood (Paper V)

Weight, BMI, WC, and HC increased from age 9–33 years. In addition, prevalence of overweight and obesity (combined), assessed by BMI, increased over time across both birth cohorts and sexes (**Figure 4** and **Table 6**).

CHL, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), TRG, and GLC showed no significant change between ages 9–33 years. INS levels doubled between age 9–15 years. From age 15 years INS started to decrease and plateaued between ages 18–33 years (**Table 6**).

DEI increased from age 9–15 years, peaking at age 15 years. DEI did not change significantly between ages 15–18 years. From age 18 years DEI started to decrease and plateaued between ages 25–33 years (**Table 6**).

CRF, as assessed by MPO/kg, peaked at age 15 years in males and age 9 years in females, after which began to decline (**Table 6**).

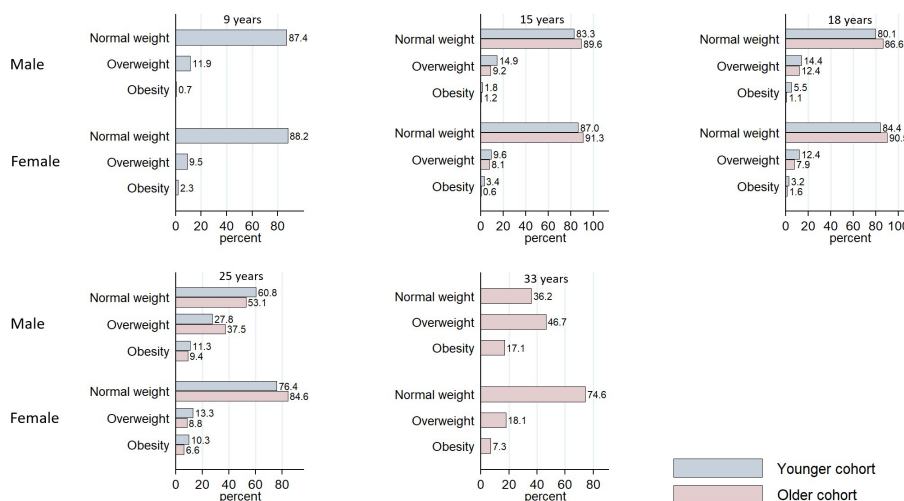


Figure 4. Distribution of individuals in the normal weight, overweight and obesity category in the birth cohorts of the ECPBHS at age 9, 15, 18, 25 and 33 years by birth cohort and sex using the BMI.

Table 6. Anthropometric measurements, metabolic biomarkers, and dietary intake (mean and SD) of the ECPBHS sample at age 9, 15, 18, 25 and 33 years by sex.

	9 years old ¹		15 years old ²		18 years old ³		25 years old ⁴		33 years old ⁵	
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
Age (years)	9.6 ± 0.5	9.4 ± 0.5	14.9 ± 0.6	14.9 ± 0.6	17.9 ± 0.9	17.8 ± 0.6	24.8 ± 0.7	24.7 ± 0.6	33.1 ± 1.0	33.0 ± 0.7
Height (cm)	137.5 ± 6.4	137.0 ± 6.7	174.1 ± 7.8	165.5 ± 6.0	180.5 ± 6.5	167.7 ± 6.2	181.3 ± 6.8	168.1 ± 6.1	181.5 ± 6.3	167.7 ± 6.2
Weight (kg)	31.7 ± 5.4	31.1 ± 6.3	62.0 ± 10.5	56.6 ± 9.7	73.3 ± 11.1	61.2 ± 10.5	82.1 ± 13.2	64.7 ± 13.3	87.8 ± 13.9	66.1 ± 12.8
BMI (kg/m ²)	16.7 ± 1.9	16.5 ± 2.3	20.4 ± 2.7	20.6 ± 3.0	22.5 ± 3.2	21.7 ± 3.3	25.0 ± 3.7	22.8 ± 4.4	26.6 ± 3.9	23.5 ± 4.4
WC (cm)	58.1 ± 4.3	55.5 ± 5.5	71.3 ± 5.8	66.5 ± 6.1	77.8 ± 7.3	70.3 ± 7.7	85.9 ± 9.5	74.4 ± 10.4	90.5 ± 10.2	76.8 ± 10.3
HC (cm)	69.2 ± 5.3	70.4 ± 6.2	89.3 ± 6.6	91.7 ± 6.7	94.4 ± 6.7	94.6 ± 7.4	100.8 ± 7.7	98.1 ± 9.3	102.6 ± 7.1	98.8 ± 8.6
WHR (units)	0.84 ± 0.04	0.79 ± 0.04	0.80 ± 0.04	0.73 ± 0.04	0.82 ± 0.04	0.74 ± 0.04	0.85 ± 0.05	0.76 ± 0.06	0.88 ± 0.06	0.78 ± 0.06
WHR (units)	0.42 ± 0.03	0.40 ± 0.03	0.41 ± 0.03	0.40 ± 0.04	0.43 ± 0.04	0.42 ± 0.05	0.47 ± 0.05	0.44 ± 0.06	0.50 ± 0.06	0.46 ± 0.06
Sum of 5 sf (mm)	34.2 ± 12.6	42.2 ± 17.2	40.7 ± 19.1	65.7 ± 25.1	50.7 ± 28.9	83.0 ± 30.0	64.0 ± 32.7	86.4 ± 37.5	69.6 ± 30.6	85.3 ± 38.8
CHL (mmol/L)	4.4 ± 0.7	4.5 ± 0.8	3.8 ± 0.7	4.3 ± 0.7	4.0 ± 0.7	4.4 ± 0.8	4.4 ± 0.8	4.5 ± 0.8	5.0 ± 0.9	4.6 ± 0.7
HDL-C (mmol/L)	1.5 ± 0.3	1.4 ± 0.3	1.4 ± 0.3	1.5 ± 0.3	1.4 ± 0.3	1.6 ± 0.4	1.3 ± 0.3	1.7 ± 0.4	1.3 ± 0.3	1.7 ± 0.4
LDL-C (mmol/L)	–	–	2.1 ± 0.6	2.4 ± 0.6	2.3 ± 0.6	2.5 ± 0.7	2.8 ± 0.8	2.6 ± 0.7	3.3 ± 0.8	2.7 ± 0.7
TRG (mmol/L)	0.7 ± 0.3	0.8 ± 0.3	0.8 ± 0.5	0.8 ± 0.4	0.9 ± 0.5	0.8 ± 0.4	1.1 ± 0.7	0.9 ± 0.4	1.4 ± 0.9	0.9 ± 0.5
GLC (mmol/L)	5.1 ± 0.4	4.9 ± 0.4	5.2 ± 0.4	4.9 ± 0.4	5.0 ± 0.5	4.7 ± 0.5	5.1 ± 0.5	4.8 ± 0.4	5.4 ± 0.5	5.1 ± 0.6
INS (mU/L)	5.8 ± 3.2	6.7 ± 3.8	11.4 ± 7.0	12.1 ± 6.3	8.0 ± 6.3	8.2 ± 4.9	7.9 ± 5.3	7.5 ± 4.7	9.8 ± 7.2	7.6 ± 4.4
DEI (kcal)	1940.7 ± 777.4	1795.4 ± 611.0	2636.6 ± 977.1	1884.6 ± 693.3	2700.4 ± 920.6	1804.5 ± 628.5	2402.2 ± 767.5	1670.5 ± 485.8	2324.6 ± 700.3	1672.8 ± 528.6
Protein (g)	58.7 ± 24.8	54.0 ± 19.9	83.4 ± 35.1	59.5 ± 25.2	92.6 ± 34.9	58.5 ± 21.7	97.3 ± 37.2	65.6 ± 21.5	101.7 ± 36.7	68.8 ± 23.0
Lipids (g)	76.7 ± 40.6	68.4 ± 31.2	104.8 ± 48.1	73.0 ± 35.3	110.5 ± 44.7	72.0 ± 32.6	99.2 ± 37.1	67.7 ± 24.9	100.7 ± 37.8	72.9 ± 27.7
Carb (g)	247.5 ± 99.4	235.1 ± 83.9	330.4 ± 137.2	240.8 ± 94.4	312.1 ± 121.3	221.1 ± 80.0	264.8 ± 94.1	199.6 ± 65.1	241.1 ± 83.0	188.3 ± 69.9
Protein E%	12.6 ± 3.1	12.4 ± 2.8	13.0 ± 3.0	13.0 ± 3.3	14.1 ± 3.1	13.4 ± 2.8	16.4 ± 4.4	15.8 ± 3.7	17.9 ± 4.2	17.0 ± 3.7
Lipids E%	34.9 ± 8.6	33.9 ± 8.2	35.9 ± 8.1	34.5 ± 8.1	37.0 ± 7.6	35.5 ± 7.6	36.2 ± 6.3	35.3 ± 6.4	38.4 ± 7.3	38.9 ± 6.6
Carb E%	52.5 ± 9.5	53.6 ± 8.8	51.1 ± 9.1	52.4 ± 8.9	47.2 ± 8.3	50.4 ± 8.4	44.2 ± 8.2	47.6 ± 7.8	40.5 ± 8.1	42.9 ± 8.1
MPO/kg (W/kg)	3.1 ± 0.5	2.7 ± 0.5	3.4 ± 0.6	2.5 ± 0.4	3.0 ± 0.7	2.1 ± 0.5	3.1 ± 0.7	2.3 ± 0.6	3.0 ± 0.5	2.2 ± 0.2

BMI, body mass index; Carb, carbohydrates; CHL, cholesterol; DEI, daily energy intake; GLC, glucose; HC, hip circumference; HDL-C, high density lipoprotein cholesterol; INS, insulin; LDL-C, low density lipoprotein cholesterol; MPO/kg, maximum power output per kilogram of body mass; sum of 5 sf, sum of five skinfolds; TRG, triglycerides; WC, waist circumference; WHR, waist-to-hip ratio; WHtR, waist-to-height ratio.

¹ Sample size at age 9 years by sex (males/females) anthropometric measures n = 278/305, biochemical measures n = 270/297, dietary intake n = 278/305, CRF n = 276/303.

² Sample size at age 15 years by sex (males/females) anthropometric measures n = 482/594, biochemical measures n = 479/587, dietary intake n = 477/594, CRF n = 478/593.

³ Sample size at age 18 years by sex (males/females) anthropometric measures n = 381/491, biochemical measures n = 381/491, dietary intake n = 375/504, CRF n = 356/475.

⁴ Sample size at age 25 years by sex (males/females) anthropometric measures n = 418/507, biochemical measures n = 406/503, dietary intake n = 403/510, CRF n = 406/477.

⁵ Sample size at age 33 years by sex (males/females) anthropometric measures n = 210/260, biochemical measures n = 208/255, dietary intake n = 209/254, CRF n = 199/247.

5.2. Genetic factors associated with the development of overweight, obesity and insulin resistance

5.2.1. *TFAP2B* intron 2 variable number tandem repeat genotype and measures of obesity, insulin resistance, and dietary intake (Paper I)

5.2.1.1. Association between measures of obesity and *TFAP2B* genotype

According to the linear mixed-effects regression models, male *TFAP2B* 5-repeat homozygotes had significantly greater ($p < 0.05$) weight, BMI, sum of 5 skinfolds, and BF%, compared to heterozygotes, at each time-point from 15–25 years. In female subjects *TFAP2B* $\times$ time interaction was observed, where the rate of change per year in weight, and BMI was significantly larger ($p < 0.05$ for interaction) in 5-repeat homozygotes compared to heterozygotes (**Figure 5**).

According to one-way ANOVA test, at 33 years, male 5-repeat homozygotes had greater weight compared to heterozygotes and 4-repeat homozygotes ($p < 0.05$). BMI was higher in male 5-repeat homozygotes at 15 years and 18 years, compared to heterozygotes and at 33 years compared to heterozygotes and 4-repeat homozygotes ($p < 0.05$). Sum of 5 skinfolds was greater in male 5-repeat homozygotes at 18 years, compared to heterozygotes and at 33 years compared to heterozygotes and 4-repeat homozygotes ($p < 0.05$). Male 5-repeat homozygotes had higher BF% at 15 years and 18 years, compared to heterozygotes and at 33 years compared to heterozygotes and 4-repeat homozygotes ($p < 0.05$). In female subjects, no significant associations between weight, BMI, sum of 5 skinfolds, BF%, and *TFAP2B* genotype were identified at 15, 18, 25 and 33 years.

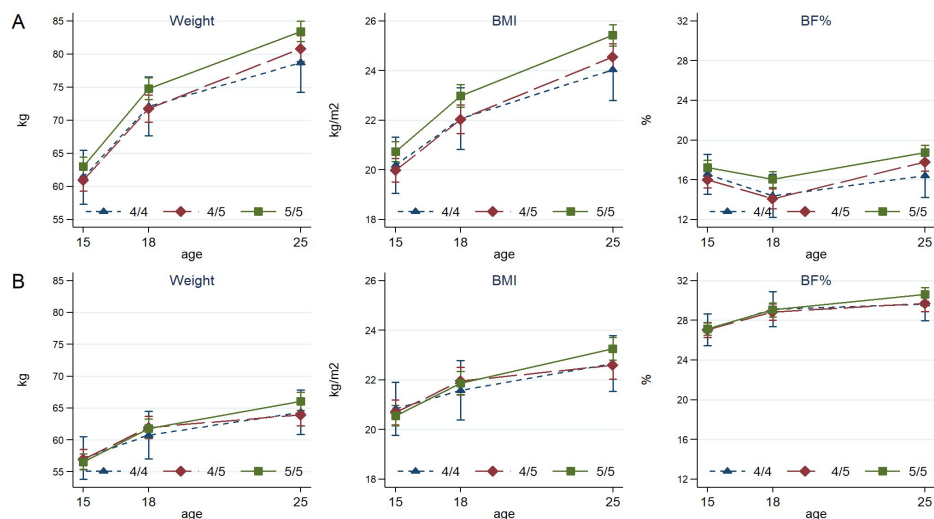


Figure 5. Association between *TFAP2B* intron 2 VNTR genotype and weight, BMI, and BF% from 15–25 years in male (panel A) and female (panel B) subjects of the ECPBHS sample. BF%, body fat percentage; BMI, body mass index.

5.2.1.2. Association between measures of abdominal obesity and *TFAP2B* genotype

According to the linear mixed-effects regression models, male *TFAP2B* 5-repeat homozygotes had greater ($p < 0.05$) WC, HC, subscapular skinfold thickness, WHR, and WHtR, compared to heterozygotes, at each time-point from age 15–25 years. In female subjects *TFAP2B* $\times$ time interaction was observed, where the rate of change per year in HC was significantly larger in 5-repeat homozygotes compared to heterozygotes ($p < 0.05$ for interaction) (**Figure 6**).

According to one-way ANOVA test, male 5-repeat homozygotes had higher WC at 15 years, and 18 years compared to heterozygotes and at 33 years compared to heterozygotes and 4-repeat homozygotes ($p < 0.05$). HC was higher in male 5-repeat homozygotes at 18 years and 33 years, compared to heterozygotes ($p < 0.05$). Subscapular skinfold thickness was greater at 15 years and 18 years in male 5-repeat homozygotes compared to heterozygotes and at 33 years compared to heterozygotes and 4-repeat homozygotes ($p < 0.05$). Male 5-repeat homozygotes had higher WHR at 18 years and 33 years, compared to heterozygotes ($p < 0.05$). 5-repeat homozygotes had higher WHtR at 15 years, 18 years, and 33 years, compared to heterozygotes ($p < 0.05$). Female 5-repeat homozygotes had lower WHR at age 18 years compared to 4-repeat homozygotes ($p < 0.05$).

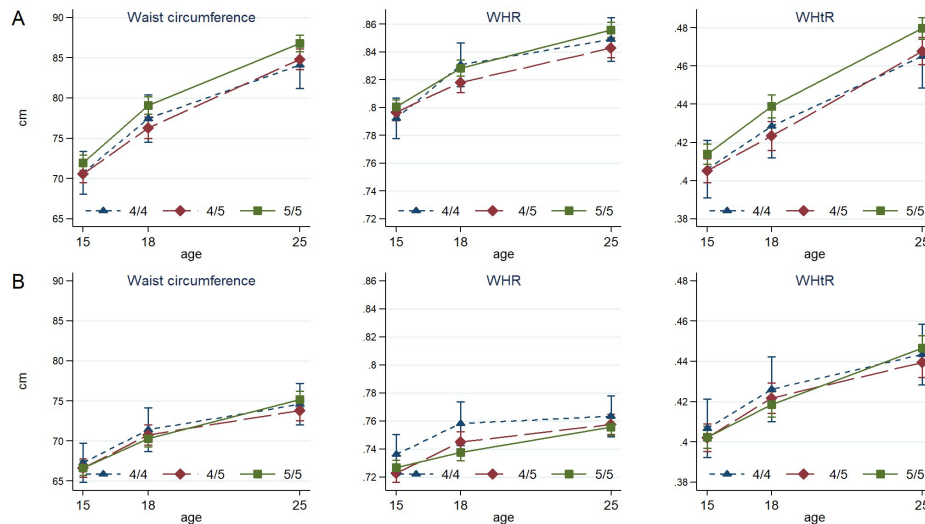


Figure 6. Association between *TFAP2B* intron 2 VNTR genotype and waist circumference, WHR, and WHtR from 15–25 years in male (panel A) and female (panel B) subjects of the ECPBHS sample. WHR, waist-to-hip ratio; WHtR, waist-to-height ratio.

5.2.1.3. Association between insulin resistance and *TFAP2B* genotype

According to the linear mixed-effects regression models, male *TFAP2B* 5-repeat homozygotes had greater ($p < 0.05$) fasting INS and HOMA index, compared to heterozygotes, at each time-point from 15–25 years. In female subjects, fasting INS, fasting GLC, and HOMA index did not differ between *TFAP2B* genotype from 15–25 years (**Figure 7**).

According to one-way ANOVA test, at 15 years, male 5-repeat homozygotes had higher fasting INS and HOMA, compared to heterozygotes. In female subjects, significant associations between GLC, INS, HOMA, and *TFAP2B* genotype were not identified at any age.

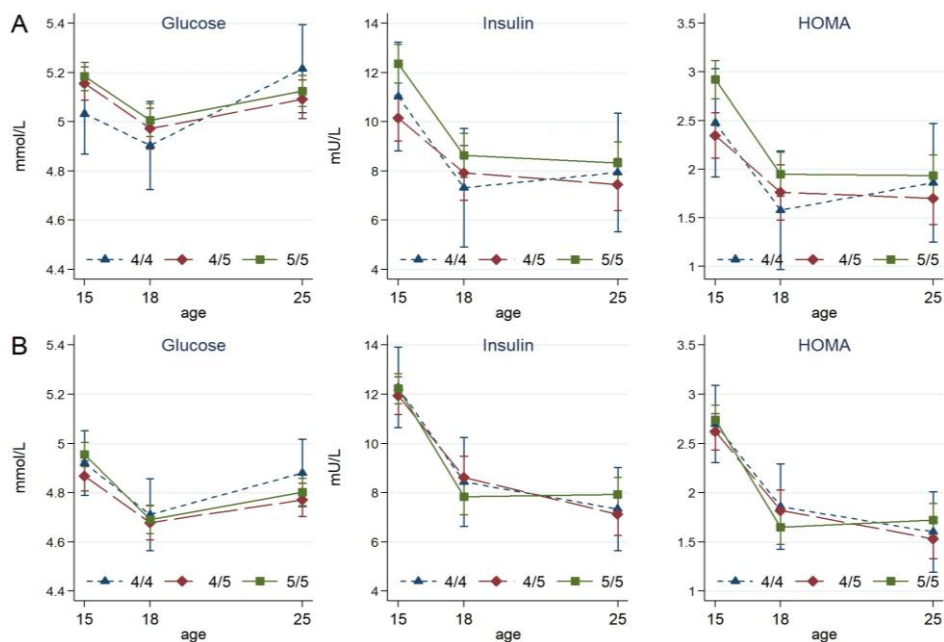


Figure 7. Association between *TFAP2B* intron 2 VNTR genotype and fasting glucose, fasting insulin, and HOMA index, from 15–25 years in male (panel A) and female (panel B) subjects of the ECPBHS sample. HOMA, Homeostatic Model Assessment.

5.2.1.4. Association between dietary intake and *TFAP2B* genotype

In male subjects *TFAP2B* $\times$ time interaction was observed, where the rate of change per year in DEI was significantly larger in 5-repeat homozygotes compared to heterozygotes ($p = 0.023$ for interaction) the former having a larger decrease in the rate of change per year in DEI from 15–25 years. In female subjects, DEI did not differ between *TFAP2B* genotypes from 15–25 years. A difference in protein, lipid and carbohydrate intake in grams per kilogram of body weight (g/kg) or protein, lipid and carbohydrate intake as a percentage from DEI

(E%) was not observed between *TFAP2B* genotype in male or female subjects from 15–25 years (**Figure 8**).

According to one-way ANOVA test, at 25 years, male heterozygotes had higher DEI compared to 5-repeat homozygotes and 4-repeat homozygotes ($p < 0.05$). Lipid intake (g/kg) was greater in male heterozygote at age 25 years and 33 years compared to 5-repeat homozygotes ($p < 0.05$). At age 25 years and 33 years, male heterozygotes had higher carbohydrate intake (g/kg) compared to 5-repeat homozygotes ($p < 0.05$). In female 4-repeat homozygotes, protein intake (E%) was greater at age 33 years compared to heterozygotes and 5-repeat homozygotes ($p < 0.05$).

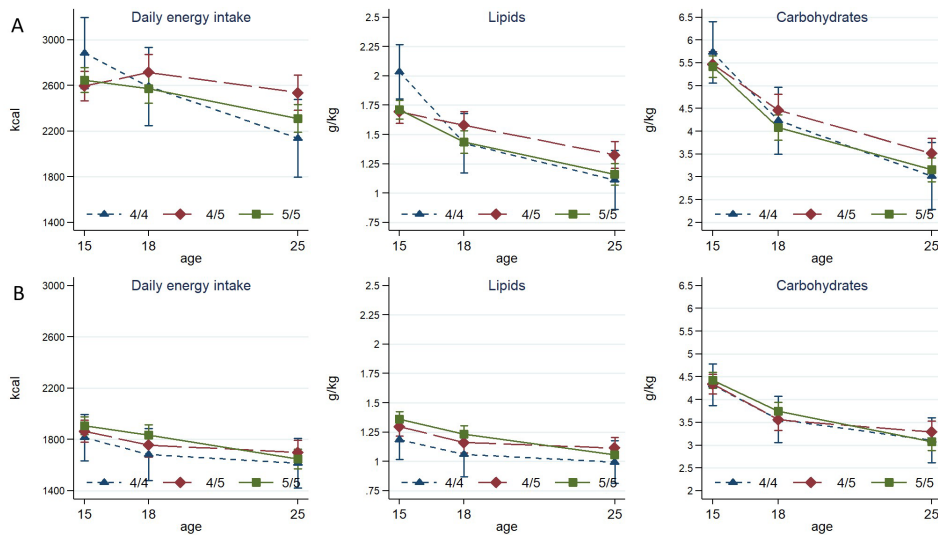


Figure 8. Association between *TFAP2B* intron 2 VNTR genotype and daily energy intake, lipid intake per body weight and carbohydrate intake per body weight, from 15–25 years of age in male (panel A) and female (panel B) subjects of the ECPBHS sample.

5.2.2. Association of *FTO* rs1421085 with measures of obesity, dietary intake, physical activity, and socioeconomic status

5.2.2.1. Association between measures of obesity, abdominal obesity, and *FTO* rs1421085 genotype

According to the linear mixed-effects regression models, male *FTO* rs1421085 TC heterozygotes had significantly higher weight, and TC heterozygotes and CC homozygotes had higher BMI, sum of 5 skinfolds, BF%, and HC, compared to TT homozygotes, at each time-point from 15–25 years. Similar effect was observed in models adjusted for DEI, standardised physical activity score and *FTO* × sSES interaction. In female subjects, WHR was significantly greater in CC

homozygotes, compared to TT homozygotes. In the adjusted model, the rate of change in weight, sum of 5 skinfolds, WC, HC, and WHtR per one unit rise in the sSES score differed significantly between TT homozygotes and CC homozygotes in the adjusted model (**Table 7** and **Table 8**).

Interaction terms for sex $\times$ *FTO* were significant for sum of 5 skinfolds, BF%, HC, WHR. The interaction terms for sex $\times$ time were significant for weight, BMI, sum of 5 skinfolds, BF%, WC, HC, WHR, and WHtR.

According to one-way ANOVA test, at 9 years, male CC homozygotes had significantly higher BMI and HC, compared to TT homozygotes, and greater sum of 5 skinfolds, compared to TC heterozygotes and TT homozygotes ($p < 0.05$). At age 15 years, male TC heterozygotes had higher sum of 5 skinfolds and BF%, compared to TT homozygotes ($p < 0.05$). At age 18 years, CC homozygotes and TC heterozygotes had higher sum of 5 skinfolds and BF % and TC heterozygotes had larger HC, compared to TT homozygotes ($p < 0.05$). No statistically significant associations were observed by one-way ANOVA between *FTO* rs1421085 genotype and measures of obesity or abdominal obesity in female subjects.

5.2.2.2. Association between dietary intake and *FTO* rs1421085 genotype

According to the linear mixed-effects regression models, male *FTO* rs1421085 TC heterozygotes had significantly lower protein and lipid intake (g/kg), and lower lipid intake (E%), compared to TT homozygotes. In female subjects, a significant difference in the rate of change per year in DEI (kcal) and lipid intake (g/kg) was observed, between female CC homozygotes and TT homozygotes, the former having a larger decrease in the rate of change per year in both DEI (kcal) and lipid intake (g/kg) (**Table 9** and **Table 10**).

According to one-way ANOVA test, at age 25 years, female CC homozygotes had significantly higher protein intake (E%) compared to TT homozygotes ($p < 0.05$). One-way ANOVA did not identify statistically significant associations between *FTO* rs1421085 genotype in male subjects.

Table 7. Estimated main effects (mean and 95% CI) in male and female subjects of the ECPBHS sample in anthropometric measurements from 15–25 years between *FTO* rs1421085 genotype according to the linear mixed effects regression model.

	MALE ³			FEMALE ³			MALE ³			FEMALE ³		
	Coeff. ¹	95% CI	p value	Coeff. ¹	95% CI	p value	Adjusted Coeff. ²	95% CI	p value	Adjusted Coeff. ²	95% CI	p value
Weight (kg)												
TC genotype	2.199	0.160; 4.238	0.035	0.039	-1.699; 1.777	0.965	1.721	-0.459; 3.901	0.122	-0.309	-2.200; 1.582	0.749
CC genotype	2.137	-0.413; 4.687	0.100	1.623	-0.524; 3.771	0.139	1.687	-1.042; 4.415	0.226	1.560	-0.781; 3.901	0.191
CT genotype × sSES score							0.573	-0.844; 1.990	0.428	0.064	-1.006; 1.135	0.906
CC genotype × sSES score							-0.266	-2.093; 1.561	0.775	-1.400	-2.753; -0.046	0.043
BMI (kg/m²)												
TC genotype	0.740	0.200; 1.280	0.007	0.083	-0.467; 0.633	0.767	0.619	0.040; 1.197	0.036	-0.011	-0.618; 0.596	0.973
CC genotype	0.836	0.160; 1.512	0.015	0.449	-0.231; 1.129	0.196	0.671	-0.053; 1.396	0.069	0.434	-0.318; 1.186	0.258
CT genotype × sSES score							0.054	-0.314; 0.422	0.773	-0.078	-0.436; 0.280	0.670
CC genotype × sSES score							-0.121	-0.593; 0.352	0.616	-0.392	-0.843; 0.060	0.089
Sum of 5 sf (mm)												
TC genotype	8.046	3.957; 12.135	< 0.001	0.126	-4.461; 4.713	0.957	7.233	2.743; 11.722	0.002	-1.051	-6.037; 3.934	0.679
CC genotype	6.837	1.717; 11.956	0.009	2.965	-2.699; 8.630	0.305	5.911	0.284; 11.538	0.039	2.471	-3.705; 8.647	0.433
CT genotype × sSES score							1.031	-2.534; 4.596	0.571	-1.452	-5.050; 2.146	0.429
CC genotype × sSES score							1.304	-3.271; 5.879	0.576	-5.284	-9.776; -0.792	0.021
BF (%)												
TC genotype	1.682	0.751; 2.613	< 0.001	-0.004	-0.790; 0.782	0.992	1.492	0.472; 2.512	0.004	-0.241	-1.096; 0.613	0.580
CC genotype	1.590	0.426; 2.755	0.007	0.272	-0.699; 1.243	0.583	1.484	0.207; 2.761	0.023	0.098	-0.961; 1.157	0.857
CT genotype × sSES score							0.192	-0.604; 0.988	0.636	-0.179	-0.795; 0.437	0.568
CC genotype × sSES score							0.054	-0.963; 1.071	0.918	-0.712	-1.479; 0.055	0.069
WC (cm)												
TC genotype	0.986	-0.189; 2.161	0.100	0.482	-0.689; 1.653	0.420	0.782	-0.502; 2.066	0.232	0.298	-1.008; 1.605	0.654
CC genotype	1.173	-0.297; 2.642	0.118	1.157	-0.289; 2.603	0.117	0.715	-0.893; 2.323	0.383	1.248	-0.372; 2.868	0.131
CT genotype × sSES score							0.228	-0.720; 1.175	0.638	-0.223	-1.106; 0.661	0.621
CC genotype × sSES score							0.298	-0.915; 1.510	0.630	-1.473	-2.577; -0.370	0.009
HC (cm)												
TC genotype	1.860	0.649; 3.071	0.003	0.074	-1.108; 1.256	0.902	1.482	0.207; 2.756	0.023	0.052	-1.237; 1.341	0.937
CC genotype	1.524	0.009; 3.039	0.049	0.362	-1.098; 1.821	0.627	1.270	-0.326; 2.866	0.119	0.388	-1.206; 1.982	0.633
CT genotype × sSES score							0.329	-0.578; 1.236	0.477	0.153	-0.698; 1.004	0.724
CC genotype × sSES score							-0.207	-1.368; 0.953	0.726	-1.073	-2.138; -0.007	0.048

	MALE ³			FEMALE ³			MALE ³			FEMALE ³		
	Coeff. ¹	95% CI	p value	Coeff. ¹	95% CI	p value	Adjusted Coeff. ²	95% CI	p value	Adjusted Coeff. ²	95% CI	p value
WHR (units)												
TC genotype	-0.0060	-0.0123; 0.0002	0.056	0.0046	-0.0021; 0.0113	0.181	-0.0051	-0.0118; 0.0016	0.133	0.0034	-0.0038; 0.0107	0.350
CC genotype	-0.0013	-0.0091; 0.0065	0.751	0.0088	0.0005; 0.0171	0.037	-0.0049	-0.0133; 0.0035	0.255	0.0095	0.0005; 0.0184	0.038
CT genotype × sSES score							0.0025	-0.0032; 0.0082	0.394	-0.0046	-0.0102; 0.0010	0.110
CC genotype × sSES score							0.0050	-0.0022; 0.0123	0.173	-0.0069	-0.0138; 0.0001	0.052
WHR (units)												
TC genotype	0.0057	-0.0008; 0.0123	0.084	0.0032	-0.0036; 0.0100	0.360	0.0049	-0.0021; 0.0119	0.173	0.0026	-0.0051; 0.0103	0.515
CC genotype	0.0081	-0.0001; 0.0162	0.052	0.0056	-0.0029; 0.0140	0.196	0.0047	-0.0041; 0.0136	0.294	0.0061	-0.0034; 0.0157	0.210
CT genotype × sSES score							0.0001	-0.0050; 0.0052	0.967	-0.0021	-0.0073; 0.0030	0.419
CC genotype × sSES score							0.0014	-0.0051; 0.0079	0.677	-0.0072	-0.0137; -0.0008	0.028

BMI, body mass index; BF%, body fat percentage; HC, hip circumference, sSES, standardised socioeconomic status; Sum of 5 sf, sum of 5 skinfolds; WC, waist circumference; WHR, waist-to-hip ratio; WHtR, waist-to-height ratio.

¹ Coefficient (Coeff.) can be interpreted as the mean difference in anthropometrical measurements between *FTO* rs1421085 TC and TT genotype or between CC and TT genotype at each timepoint.

² Coefficient (Coeff.) can be interpreted as the mean difference, adjusted to daily energy intake, standardised physical activity score and *FTO* × sSES interaction, in anthropometrical measurements between *FTO* rs1421085 TC and TT genotype or between CC and TT genotype at each timepoint.

³ Sample size by sex and *FTO* rs1421085 genotype at age 15, 18, and 25 years: male subjects TT = 153/119/128, CT = 231/200/204, CC= 97/81/86; female subjects TT = 182/154/155, CT = 288/256/244, CC = 123/103/109, respectively.

Table 8. The rate of change per sSES score unit in anthropometric measurements (mean and 95% CI) in the female subjects of the ECPBHS sample according to the linear mixed effects regression model with *FTO* rs1421085 genotype $\times$ sSES interaction.

	TT genotype	TC genotype	CC genotype
Weight (kg)	0.176 (−0.646; 0.998) ^a	0.240 (−0.445; 0.925)	−1.224 (−2.299; −0.149) ^a
BMI (kg/m ²)	0.052 (−0.223; 0.328) ^b	−0.025 (−0.255; 0.204)	−0.339 (−0.697; 0.018) ^b
Sum of 5 skinfolds (mm)	2.510 (−0.270; 5.290) ^a	1.058 (−1.227; 3.344)	−2.774 (−6.303; 0.754) ^a
BF (%)	0.429 (−0.047; 0.905) ^b	0.250 (−0.141; 0.641)	−0.283 (−0.884; 0.318) ^b
WC (cm)	0.505 (−0.177; 1.187) ^a	0.282 (−0.280; 0.844)	−0.968 (−1.836; −0.101) ^a
HC (cm)	0.266 (−0.392; 0.923) ^a	0.419 (−0.122; 0.959)	−0.807 (−1.645; 0.031) ^a
WHR (units)	0.0018 (−0.0026; 0.0061) ^b	−0.0028 (−0.0063; 0.0008)	−0.0051 (−0.0105; 0.0003) ^b
WHR (units)	0.0028 (−0.0012; 0.0067) ^a	0.0006 (−0.0027; 0.0039)	−0.0045 (−0.0095; 0.0006) ^a

BMI, body mass index; BF%, body fat percentage; HC, hip circumference, sSES, standardised socioeconomic status; WC, waist circumference; WHR, waist-to-hip ratio; WHtR, waist-to-height ratio.

^a $p < 0.05$ significant difference in the rate of change between *FTO* rs1421085 genotypes TT and CC.

^b $0.05 \leq p < 0.10$ trend in the rate of change between *FTO* rs1421085 genotypes TT and CC.

Table 9. Estimated main effects in male subjects and estimated main and interaction effects in female subjects of the ECPBHS sample in DEI (kcal), nutrient intake (g/kg, E%) (mean and 95% CI) from 15–25 years between *FTO* rs1421085 genotype according to the linear mixed effects regression model.

	MALE ³			FEMALE ³		
	Coefficient ¹	95% CI	p value	Coefficient ²	95% CI	p value
DEI (kcal)						
TC genotype	−103.172	−231.644; 25.301	0.115	234.711	−74.469; 543.892	0.137
CC genotype	−43.858	−203.413; 115.697	0.590	402.881	23.857; 781.904	0.037
TC genotype $\times$ time				−12.441	−28.445; 3.563	0.128
CC genotype $\times$ time				−20.426	−39.967; −0.885	0.040
Protein (g/kg)						
TC genotype	−0.089	−0.166; −0.013	0.022	0.194	−0.019; 0.407	0.075
CC genotype	−0.081	−0.176; 0.015	0.097	0.164	−0.098; 0.425	0.221
TC genotype $\times$ time				−0.010	−0.020; 0.001	0.063
CC genotype $\times$ time				−0.008	−0.020; 0.005	0.219
Lipids (g/kg)						
TC genotype	−0.137	−0.224; −0.051	0.002	0.136	−0.156; 0.427	0.361
CC genotype	−0.055	−0.163; 0.052	0.313	0.367	0.010; 0.724	0.044
TC genotype $\times$ time				−0.007	−0.022; 0.008	0.338
CC genotype $\times$ time				−0.020	−0.038; −0.001	0.035
Carbohydrates (g/kg)						
TC genotype	−0.214	−0.475; 0.047	0.108	0.576	−0.213; 1.364	0.153
CC genotype	−0.219	−0.544; 0.106	0.187	0.798	−0.171; 1.767	0.106
TC genotype $\times$ time				−0.030	−0.067; 0.006	0.102
CC genotype $\times$ time				−0.044	−0.089; 0.001	0.053
Protein E%						
TC genotype	−0.152	−0.616; 0.311	0.520	0.568	−1.196; 2.333	0.528
CC genotype	−0.286	−0.863; 0.291	0.332	−0.793	−2.954; 1.367	0.472
TC genotype $\times$ time				−0.015	−0.109; 0.078	0.746
CC genotype $\times$ time				0.076	−0.038; 0.190	0.189
Lipids E%						
TC genotype	−1.018	−1.990; −0.046	0.040	−0.178	−4.137; 3.782	0.930
CC genotype	−0.102	−1.309; 1.105	0.869	3.044	−1.815; 7.904	0.219
TC genotype $\times$ time				0.008	−0.189; 0.204	0.939
CC genotype $\times$ time				−0.154	−0.394; 0.087	0.210

	MALE ³			FEMALE ³		
	Coefficient ¹	95% CI	p value	Coefficient ²	95% CI	p value
Carbohydrates E%						
TC genotype	0.839	-0.342; 2.020	0.164	-0.079	-4.460; 4.302	0.972
CC genotype	0.424	-1.043; 1.892	0.571	-1.506	-6.877; 3.865	0.583
TC genotype × time				-0.014	-0.239; 0.212	0.906
CC genotype × time				0.043	-0.233; 0.318	0.762

¹ Coefficient can be interpreted as the mean difference in daily energy intake (DEI) (kcal), nutrient intake (g/kg) and nutrient intake as a percentage from daily energy intake (E%) between *FTO* rs1421085 TC and TT genotype or between CC and TT genotype at each timepoint.

² Difference in the rate of change in DEI (kcal), nutrient intake (g/kg) and nutrient intake as a percentage from DEI (E%) between *FTO* rs1421085 TC and TT genotype or between CC and TT genotype can be calculated as the sum of main effect coefficient and time × interaction coefficient at given timepoint.

³ Sample size by sex and *FTO* rs1421085 genotype at age 15, 18, and 25 years: male subjects TT = 153/119/128, CT = 231/200/204, CC = 97/81/86; female subjects TT = 182/154/155, CT = 288/256/244, CC = 123/103/109, respectively.

Table 10. The rate of change per year in DEI (kcal), nutrient intake (g/kg, E%) (mean and 95% CI) in the female subjects of the ECPBHS sample according to the linear mixed effects regression model with *FTO* rs1421085 genotype × time interaction.

	TT genotype	TC genotype	CC genotype
DEI (kcal/kg)	-11.362 (-23.903; 1.179) ^a	-23.803 (-33.746; -13.861)	-31.788 (-46.774; -16.802) ^a
Protein (g/kg)	0.004 (-0.004; 0.012) ^b	-0.006 (-0.012; 0.001) ^b	-0.004 (-0.013; 0.006)
Lipids (g/kg)	-0.017 (-0.029; -0.005) ^a	-0.024 (-0.034; -0.015)	-0.037 (-0.051; -0.022) ^a
Carbohydrates (g/kg)	-0.089 (-0.118; 0.061)	-0.120 (-0.142; -0.097) ^b	-0.133 (-0.168; -0.099) ^b
Protein E%	0.274 (0.201; 347)	0.259 (0.201; 0.316)	0.350 (0.263; 0.437)
Lipids E%	0.088 (-0.066; 0.243)	0.096 (-0.026; 0.218)	-0.065 (-0.250; 0.119)
Carbohydrates E%	-0.048 (-0.657; -0.304)	-0.494 (-0.634; -0.354)	-0.438 (-0.649; -0.226)

DEI, daily energy intake; E%, nutrient intake as a percentage from DEI.

^a $p < 0.05$ significant difference in the rate of change between *FTO* rs1421085 genotype TT and CC.

^b $0.05 \leq p < 0.10$ trend in the rate of change between *FTO* rs1421085 genotype TT and TC or TT and CC.

5.2.2.3. Association between cardiorespiratory fitness, physical activity, and *FTO* rs1421085 genotype

According to the linear mixed-effects regression model with quadratic trends, a trend in MPO/kg between *FTO* rs1421085 TC heterozygotes and TT homozygotes was observed, but with opposite direction in male and female subjects. Physical activity score was 0.162 units (95% CI 0.003, 0.321) greater in female CC homozygotes compared to TT homozygotes in every fixed timepoint (**Table 11**).

One-way ANOVA test at ages 9, 15, 18 and 25 years did not demonstrate a statistically significant difference in CRF or physical activity score between *FTO* rs1421085 genotypes in male or female subjects.

Table 11. Estimated main effects (mean and 95% CI) of the ECPBHS sample in MPO per kg and standardised physical activity score from 15–25 years between *FTO* rs1421085 genotype according to the non-linear mixed effects regression model.

	MALE ²			FEMALE ²		
	Coefficient ¹	95% CI	p value	Coefficient ¹	95% CI	p value
MPO per kg						
TC genotype	-0.095	-0.201; 0.011	0.080	0.058	-0.010; 0.126	0.092
CC genotype	-0.088	-0.220; 0.044	0.192	-0.001	-0.085; 0.082	0.975
Standardised physical activity score						
TC genotype	-0.040	-0.178; 0.097	0.563	0.103	-0.025; 0.232	0.116
CC genotype	0.099	-0.072; 0.270	0.255	0.162	0.003; 0.321	0.046

¹ Coefficient can be interpreted as the mean difference in maximum power output per kilogram body mass (MPO per kg) and standardised physical activity score between *FTO* rs1421085 TC and TT genotype or between CC and TT genotype at every fixed timepoint.

² Sample size by sex and *FTO* rs1421085 genotype at age 15, 18, and 25 years: male subjects TT = 153/119/128, CT = 231/200/204, CC = 97/81/86; female subjects TT = 182/154/155, CT = 288/256/244, CC = 123/103/109, respectively.

5.2.2.4. Association between socioeconomic status and *FTO* rs1421085 genotype

According to the linear mixed-effects regression models, male *FTO* rs1421085 TC heterozygotes and CC homozygotes had higher sSES score at each time point. No difference was found among female subjects (**Table 12**).

According to one-way ANOVA test, at age 25 years, male CC homozygotes had significantly higher sSES score, compared to TT homozygotes ($p < 0.05$). No statistically significant associations between *FTO* rs1421085 genotypes were identified in female subjects by one-way ANOVA.

Table 12. Estimated main effects (mean and 95% CI) in male and female subjects of the ECPBHS sample in sSES score from 15–25 years between *FTO* rs1421085 genotype according to the linear mixed effects regression model.

	MALE ²			FEMALE ²		
	Coefficient ¹	95% CI	p value	Coefficient ¹	95% CI	p value
Standardised SES score						
TC genotype	0.198	0.038; 0.358	0.015	-0.032	-0.196	0.132
CC genotype	0.240	0.038; 0.441	0.020	0.075	-0.127	0.277

¹ Coefficient (Coeff.) can be interpreted as the mean difference in standardised socioeconomic status (sSES) score between *FTO* rs1421085 TC and TT genotype or between CC and TT genotype at each timepoint.

² Sample size by sex and *FTO* rs1421085 genotype at age 15, 18, and 25 years: male subjects TT = 153/119/128, CT = 231/200/204, CC = 97/81/86; female subjects TT = 182/154/155, CT = 288/256/244, CC = 123/103/109, respectively.

5.2.3. Neuropeptide Y gene variants and measures of obesity, dietary intake, blood pressure, lipid and glucose metabolism

5.2.3.1. Association between measures of obesity, abdominal obesity and *NPY* gene variants

In linear mixed-effects regression models with time $\times$ *NPY* rs5574 interaction a smaller increase per year in WHR was observed in TT homozygotes compared to CC homozygotes from 15–25 years. Rs16147 CC homozygotes compared to TT homozygotes had lower weight. A smaller increase in sum of 5 skinfolds, WHR, and WHtR per year was observed in heterozygotes and CC homozygotes, compared to TT homozygotes in models with time $\times$ *NPY* rs16147 interaction. Heterozygotes compared to TT homozygotes had a smaller increase per year in WC. No longitudinal association between measures of obesity or abdominal obesity and rs16139 or rs17149106 was observed (**Figure 9**).

According to one-way ANOVA test, rs16147 CC homozygotes had lower weight at 15, 18, and 25 years, compared to TT homozygotes. At 25 years CC homozygotes had lower BMI and WC, and both heterozygotes and CC homozygotes had smaller WHR compared to TT homozygotes, respectively ($p < 0.05$). An association between obesity, abdominal obesity and rs5574, rs16139 or rs17149106 was not observed by one-way ANOVA at 15, 18, and 25 years.

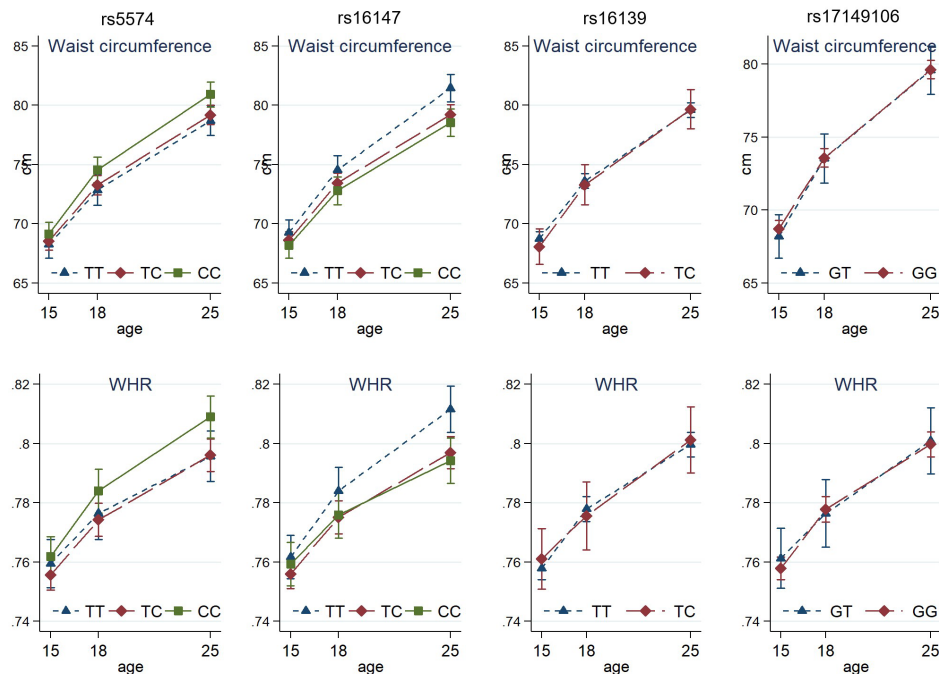


Figure 9. Association between *NPY* gene variants and measures of abdominal obesity in subjects of the ECPBHS sample from 15–25 years of age.

5.2.3.2. Association between blood pressure, metabolic biomarkers and *NPY* gene variants

In models with time $\times$ *NPY* rs5574 and time $\times$ *NPY* rs16147 interaction a smaller increase per year in diastolic BP was observed in rs5574 TT homozygotes, compared to CC homozygotes and rs16147 CC homozygotes, compared to TT homozygotes. Rs5574 heterozygotes compared to CC homozygotes had lower GLC. Both rs16147 heterozygotes and CC homozygotes had lower GLC compared to TT homozygotes, at each time-point from 15–25 years. CHL and HDL-C levels were higher in rs5574 heterozygotes compared to CC homozygotes and in rs16147 heterozygotes, compared to TT homozygotes ($p < 0.05$). Both rs16139 and rs17149106 heterozygotes had lower systolic and diastolic BP at each time-point from 15–25 years, compared to TT homozygotes and GG homozygotes. Rs17149106 heterozygotes had higher CHL, compared to GG homozygotes. Models with time $\times$ *NPY* rs16139 and time $\times$ *NPY* rs17149106 interaction observed a greater increase per year in TRG among heterozygotes (**Figure 10**).

According to one-way ANOVA, at 18 years, rs16139 heterozygotes had significantly lower diastolic BP. Rs5574 heterozygotes had higher CHL compared to CC homozygotes, and rs16139 heterozygotes had higher CHL and LDL-C, compared to TT homozygotes. Rs17149106 heterozygotes had higher CHL and LDL-C, compared to GG homozygote ($p < 0.05$).

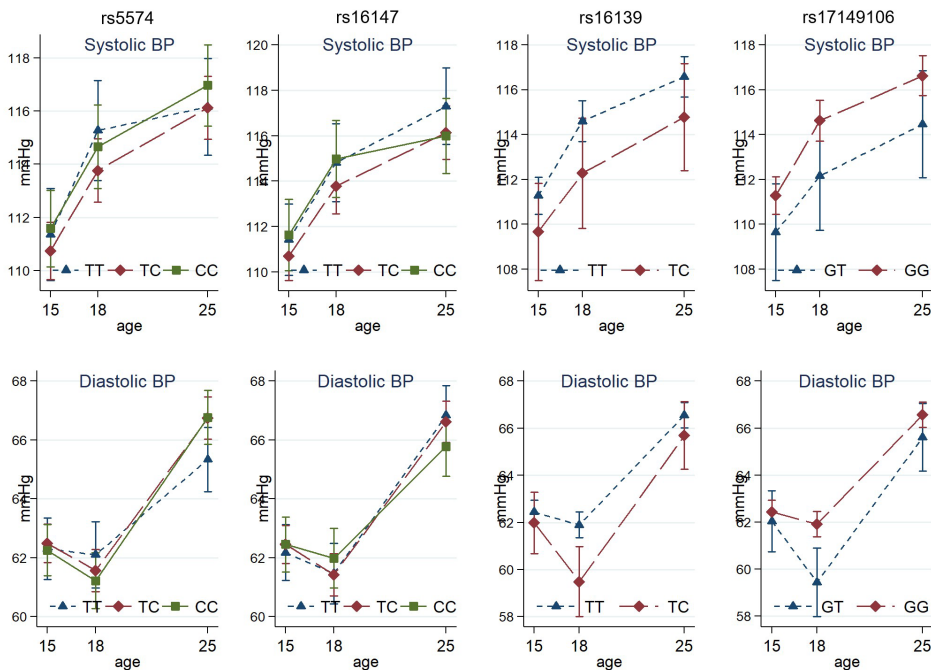


Figure 10. Association between *NPY* gene variants and blood pressure in subjects of the ECPBHS sample from 15–25 years of age.

5.2.3.3. Association between dietary intake, CRF, physical activity and *NPY* gene variants

Models with time $\times$ rs5574 interaction showed a difference in the rate of change per year in DEI (kcal) and carbohydrate intake (g) between CC and TT homozygotes. Models with time $\times$ rs16139 and time $\times$ rs17149106 showed a smaller increase in protein (E%) intake in heterozygotes compared to TT and GG homozygotes. Rs5574 heterozygotes had lower protein intake (E%), compared to CC homozygotes at each time-point from 15–25 years. Rs16147 CC homozygotes had greater carbohydrate intake (g), compared to TT homozygotes, and both rs16147 heterozygotes and CC homozygotes had greater carbohydrate intake (E%), compared to TT homozygotes. Rs16147 heterozygotes had lower protein (E%) intake, versus TT homozygotes. Rs16139 and rs17149106 heterozygotes had lower protein intake compared to TT and GG homozygotes. No associations between MPO, physical activity and rs5574, rs16147, rs16139, and rs17149106 were identified (**Figure 11**).

According to one-way ANOVA, at 15 years, rs5574 CC homozygotes had lower DEI (kcal) and carbohydrate intake (g), compared to TT homozygotes. At 18 years, rs5574 heterozygotes, had lower protein intake (E%), compared to CC homozygotes. Rs16147 heterozygotes had lower protein intake (E%), compared to TT homozygotes. Both heterozygotes and CC homozygotes had larger carbohydrate intake (E%), compared to TT homozygotes. Rs16139 heterozygotes had lower protein intake (g), compared to TT homozygotes at 15 years and 25 years. At 25 years, rs17149106 heterozygotes had lower protein intake (g and E%) compared to GG homozygotes. Rs16139 heterozygotes had lower MPO (per kg) compared to GG homozygotes, at 25 years.

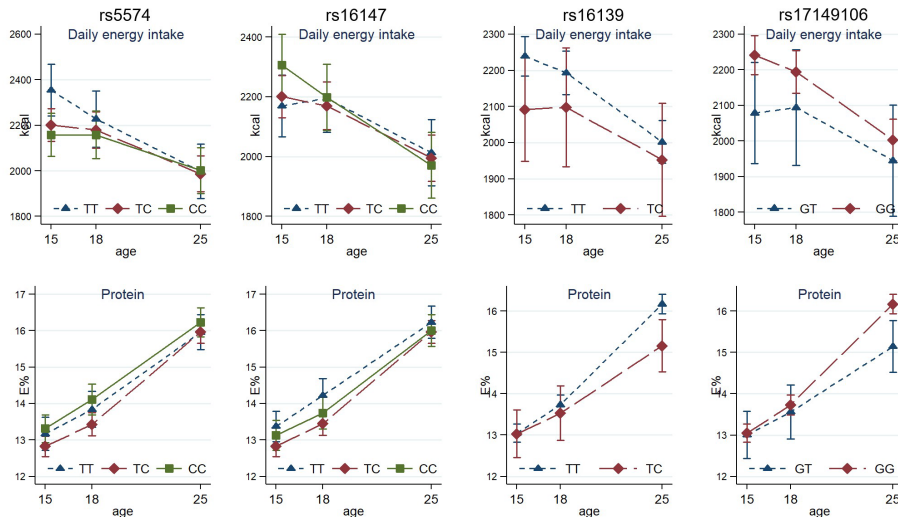


Figure 11. Association between *NPY* gene variants and daily energy intake, protein intake (E%), and carbohydrates intake (E%) in subjects of the ECPBHS sample from 15–25 years of age.

5.3. The role of reward sensitivity in obesity

Linear mixed effects regression models adjusted for physical activity and DEI (kcal) demonstrated a significant relationship between Insatiability by Reward and its subscales and weight, BMI, sum of 5 skinfolds, WC, HC, and WHtR (**Table 13**).

According to one-way ANOVA test, at 9 years, a significant difference between weight categories, in Giving in to Cravings score, was observed ($p = 0.011$). At 15 years, overweight subjects had higher Giving in to Cravings score, compared to normal weight subjects ($p = 0.015$). At 18 years, overweight subjects had greater Excitement and Novelty score ($p = 0.020$), and obese subjects had higher Insatiability by Reward ($p = 0.017$), especially Excessive Spending score ($p = 0.035$), compared to normal weight individuals. At 25 years, both overweight and obese subjects had greater Insatiability by Reward scores, compared to normal weight subjects ($p < 0.001$). Further, obese subjects compared to normal weight subjects had also higher Excessive Spending ($p = 0.002$) and overweight subjects compared to normal weight subjects had higher Giving in to Cravings scores ($p = 0.001$), compared to normal weight individuals. At 33 years, overweight and obese subjects, compared to normal weight individuals had higher Insatiability by reward ($p = 0.002$), especially Giving in to Cravings score ($p = 0.001$), respectively (**Table 14**).

Table 13. Estimated main effects (mean and 95% CI) of the ECPBHS sample in anthropometric measurements from 15–25 years of age by reward sensitivity according to the linear mixed effects regression model adjusted for physical activity ¹ and DEI ².

	Coefficient ³	95% CI	p value	Weight (kg)	Coefficient ³	95% CI	p value
Weight (kg)							
Openness to Rewards	0.36	-0.94; 1.66	0.588	Insatiability by Reward	2.27	1.16; 3.38	< 0.001
Excitement and Novelty	0.85	-0.29; 1.99	0.145	Excessive Spending	1.36	0.48; 2.24	0.002
Social Experiences	-0.25	-1.33; 0.83	0.648	Giving in to Cravings	2.13	1.09; 3.18	< 0.001
BMI (kg/m²)							
Openness to Rewards	0.13	-0.23; 0.50	0.471	BMI (kg/m²)			
Excitement and Novelty	0.16	-0.16; 0.48	0.321	Insatiability by Reward	0.75	0.44; 1.06	< 0.001
Social Experiences	0.04	-0.26; 0.34	0.784	Excessive Spending	0.47	0.22; 0.71	< 0.001
Sum of 5 skinfolds (mm)				Giving in to Cravings	0.68	0.39; 0.98	< 0.001
Openness to Rewards	1.80	-1.45; 5.06	0.278	Sum of 5 skinfolds (mm)			
Excitement and Novelty	-0.09	-2.94; 2.77	0.953	Insatiability by Reward	7.56	4.79; 10.33	< 0.001
Social Experiences	2.53	-0.15; 5.21	0.064	Excessive Spending	5.09	2.88; 7.30	< 0.001
Waist circumference (cm)				Giving in to Cravings	6.28	3.65; 8.91	< 0.001
Openness to Rewards	0.34	-0.51; 1.19	0.437	Waist circumference (cm)			
Excitement and Novelty	0.62	-0.12; 1.37	0.101	Insatiability by Reward	1.38	0.66; 2.11	< 0.001
Social Experiences	-0.08	-0.79; 0.62	0.816	Excessive Spending	0.94	0.36; 1.51	0.001
Hip circumference (cm)				Giving in to Cravings	1.14	0.45; 1.83	0.001
Openness to Rewards	0.24	-0.56; 1.05	0.553	Hip circumference (cm)			
Excitement and Novelty	0.24	-0.47; 0.94	0.508	Insatiability by Reward	1.60	0.92; 2.29	< 0.001
Social Experiences	0.13	-0.54; 0.79	0.704	Excessive Spending	0.98	0.43; 1.52	< 0.001
WHR (units)				Giving in to Cravings	1.48	0.83; 2.13	< 0.001
Openness to Rewards	0.0006	-0.0056; 0.0067	0.854	WHR (units)			
Excitement and Novelty	0.0040	-0.0013; 0.0094	0.138	Insatiability by Reward	0.0020	-0.0033; 0.0073	0.465
Social Experiences	-0.0028	-0.0078; 0.0023	0.285	Excessive Spending	0.0016	-0.0026; 0.0058	0.447
WHtR (units)				Giving in to Cravings	0.0013	-0.0038; 0.0063	0.624
Openness to Rewards	0.0020	-0.0026; 0.0065	0.390	WHtR (units)			
Excitement and Novelty	0.0023	-0.0017; 0.0062	0.268	Insatiability by Reward	0.0079	0.0040; 0.0118	< 0.001
Social Experiences	0.0008	-0.0030	0.691	Excessive Spending	0.0056	0.0025; 0.0086	< 0.001
				Giving in to Cravings	0.0063	0.0026; 0.0100	0.001

DEI, daily energy intake; WHR, waist-to-hip ratio; WHtR, waist-to-height ratio.

¹ Physical activity was assessed using self- and parent-reported questionnaires. Individual physical activity scores were calculated and standardised physical activity scores were used.

² During the day(s) before the study day, the subjects were asked to complete a 24h (year 1998), 48h (years 2001, 2004, 2007) or 72h (years 2008, 2014) diet record at home. On the study day, a face-to-face interview, to specify portion sizes, was conducted. Where data on two or three days was available the mean consumption was calculated.

³ Coefficient can be interpreted as the mean change in anthropometric measurements at each time point if reward sensitivity score increases by one unit, adjusted for physical activity and DEI.

Table 14. Reward sensitivity (mean and SD) of the younger cohort at age 9, both cohorts from 15–25 years and older cohort at 33 years of the ECPBHS sample by weight category.

	Openness to Rewards	Excitement and Novelty	Social Experiences	Insatiability by Reward	Excessive Spending	Giving in to Cravings
Age 9 years						
Individuals with normal weight ^{1a}	3.78 ± 0.52 (322)	3.87 ± 0.59 (322)	3.69 ± 0.66 (322)	2.57 ± 0.68 (322)	2.49 ± 0.86 (322)	2.64 ± 0.72 (322)
Individuals with overweight ^b	3.65 ± 0.56 (36)	3.72 ± 0.68 (36)	3.58 ± 0.69 (36)	2.83 ± 0.69 (36)	2.72 ± 0.92 (36)	2.93 ± 0.64 (36)
Individuals with obesity ^c	3.79 ± 0.48 (7)	3.86 ± 0.53 (7)	3.71 ± 0.57 (7)	2.88 ± 0.44 (7)	2.57 ± 0.76 (7)	3.18 ± 0.80 (7) ⁱ
Age 15 years						
Individuals with normal weight ^{1d}	3.65 ± 0.58 (661)	3.71 ± 0.65 (661)	3.58 ± 0.70 (661)	2.54 ± 0.66 (657)	2.45 ± 0.83 (657)	2.63 ± 0.69 (567) ^h
Individuals with overweight ^{1e}	3.65 ± 0.54 (69)	3.70 ± 0.66 (69)	3.59 ± 0.65 (69)	2.72 ± 0.64 (68)	2.55 ± 0.83 (68)	2.88 ± 0.71 (68) ^h
Individuals with obesity ^{1f}	3.84 ± 0.59 (11)	3.87 ± 0.53 (11)	3.82 ± 0.75 (11)	2.72 ± 0.80 (10)	2.78 ± 0.93 (10)	2.67 ± 0.83 (10)
Age 18 years						
Individuals with normal weight ^{2g}	3.64 ± 0.57 (566)	3.70 ± 0.65 (566) ^h	3.58 ± 0.68 (566)	2.51 ± 0.66 (561) ⁱ	2.41 ± 0.82 (561) ⁱ	2.60 ± 0.70 (561)
Individuals with overweight ^{2h}	3.81 ± 0.54 (74)	3.92 ± 0.55 (74) ^h	3.69 ± 0.72 (74)	2.62 ± 0.65 (72)	2.48 ± 0.86 (72)	2.76 ± 0.69 (72)
Individuals with obesity ²ⁱ	3.60 ± 0.68 (18)	3.68 ± 0.67 (18)	3.52 ± 0.82 (18)	2.91 ± 0.50 (18) [#]	2.91 ± 0.67 (18) ⁱ	2.91 ± 0.62 (18)
Age 25 years						
Individuals with normal weight ^{2g}	3.68 ± 0.58 (540)	3.75 ± 0.65 (540)	3.61 ± 0.70 (540)	2.49 ± 0.66 (537) ^{h,i}	2.39 ± 0.83 (537) ⁱ	2.59 ± 0.70 (537) ^h
Individuals with overweight ^{2h}	3.60 ± 0.55 (142)	3.64 ± 0.63 (142)	3.55 ± 0.66 (142)	2.69 ± 0.61 (141) ^h	2.57 ± 0.81 (141)	2.81 ± 0.62 (141) ^h
Individuals with obesity ²ⁱ	3.69 ± 0.50 (70)	3.77 ± 0.55 (70)	3.61 ± 0.67 (70)	2.74 ± 0.65 (68) ⁱ	2.71 ± 0.82 (68) ⁱ	2.78 ± 0.67 (68)
Age 33 years						
Individuals with normal weight ^{2g}	3.54 ± 0.62 (251)	3.59 ± 0.70 (251)	3.49 ± 0.72 (251)	2.42 ± 0.66 (249) ^{h,i}	2.34 ± 0.85 (249)	2.50 ± 0.67 (249) ^{h,i}
Individuals with overweight ^{2h}	3.52 ± 0.53 (128)	3.56 ± 0.60 (128)	3.48 ± 0.69 (128)	2.62 ± 0.54 (127) ^h	2.52 ± 0.66 (127)	2.73 ± 0.63 (127) ^h
Individuals with obesity ²ⁱ	3.67 ± 0.54 (48)	3.71 ± 0.61 (48)	3.64 ± 0.66 (48)	2.68 ± 0.58 (45) ⁱ	2.53 ± 0.65 (45)	2.83 ± 0.64 (45) ⁱ

¹ definition by Cole TJ, Bellizzi MC, Flegal KM, Dietz WH. Establishing a standard definition for child overweight and obesity worldwide: international survey. *BMJ*. 2000; 320(7244):1–6.

² definition by World Health Organization. Obesity: preventing and managing the global epidemic. Report of a WHO consultation. World Health Organ Tech Rep Ser 2000;894:1–253.

^a Individuals with normal weight (BMI < 19.10 kg/m² in males and < 19.07 kg/m² in females).

^b Individuals with overweight (BMI ≥ 19.10 kg/m² and < 22.77 kg/m² in males and ≥ 19.07 kg/m² and < 22.81 kg/m² in females).

^c Individuals with obesity (BMI ≥ 22.77 kg/m² in males and ≥ 22.81 kg/m² in females).

^d Individuals with normal weight (BMI < 23.29 kg/m² in males and < 23.94 kg/m² in females).

^e Individuals with overweight (BMI ≥ 23.29 kg/m² and < 28.30 kg/m² in males and ≥ 23.94 kg/m² and < 29.11 kg/m² in females).

^f Individuals with obesity (BMI ≥ 28.30 kg/m² in males and ≥ 29.11 kg/m² in females).

^g Individuals with normal weight (BMI < 25.00 kg/m²); ^h individuals with overweight (BMI ≥ 25.00 and < 30.00 kg/m²); ⁱ individuals with obesity (BMI ≥ 30.00 kg/m²).

^h P < 0.05 significant difference in the mean values of reward sensitivity between individuals with normal weight and individuals with overweight corrected by the Sidak method.

ⁱ P < 0.05 significant difference in the mean values of reward sensitivity between individuals with normal weight and individuals with obesity corrected by the Sidak method.

^j P > 0.05 significant differences were not found between weight groups after correcting by the Sidak method.

5.4. The effect of the birth cohort

5.4.1. Birth cohort effects on measures of obesity, glucose metabolism, dietary intake, and cardiorespiratory fitness (Paper V)

5.4.1.1. Association between measures of obesity and the birth cohort

In a linear mixed-effects regression models with a time $\times$ cohort interaction, males from the older cohort showed a significantly greater increase per year in weight, BMI, WC, HC, WHR, and WHtR from 15–25 years, compared to those from the younger cohort. Similarly, females from the older cohort showed a significantly greater annual increase in WC, WHR, and WHtR compared to those from the younger cohort (**Table 15** and **Table 16**).

According to an independent t-test, at 15 years, females in the younger cohort had significantly higher weight, BMI, WC, WHR, and WHtR, compared to those in the older cohort ($p < 0.05$). No significant differences were observed between the birth cohorts among male subjects at the same age. At 18 years, males in the younger cohort had higher WC, HC, and WHtR compared to the older cohort. Additionally, females in the younger cohort showed higher weight, BMI, WC, HC, WHR, and WHtR than those in the older cohort ($p < 0.05$). In contrast, at 25 years, males in the younger cohort had lower WHR, compared to the older cohort, while females had higher weight, BMI, and HC, but lower WHR ($p < 0.05$).

5.4.1.2. Association between dietary intake and the birth cohort

Linear mixed-effects regression models with quadratic trends showed significant between-cohort differences in the slopes and rates of change in DEI (kcal) and lipid intake (g) in male participants from 15–25 years. Among females, a significant difference between cohorts was found in the slopes and rate of change in protein intake (g) (**Table 15** and **Figure 12**).

According to the models with a time $\times$ cohort interaction, males in the younger cohort demonstrated a greater increase per year in protein (g and E%) and lipid intake (E%) but a greater decrease in carbohydrate intake (E%) from 15–25 years, compared to the older cohort. Similarly, females in the younger cohort demonstrated a greater increase in lipid intake (g and E%) and protein intake (E%), but a greater decrease in carbohydrate intake (E%) compared to the older cohort (**Table 15** and **Table 16**).

At 15 years, males of the younger cohort had significantly lower DEI (kcal), protein (g), lipid (g and E%), and carbohydrate (g) intake, but higher protein (E%) intake, compared to those in the older cohort. Similarly, at 15 years, females of the younger cohort had lower DEI (kcal), protein intake (g) and lipid (g and E%) intake, but higher carbohydrate (E%) intake ($p < 0.05$). At 18 years, both males and females of the younger cohort had higher protein (E%) intake, and lower carbohydrate (g and E%) intake at age 18 years, compared to the older cohort ($p < 0.05$). At 25 years, males of the younger cohort had lower DEI (kcal) and carbohydrate (g and E%) intake, but higher lipid (E%) intake, compared to the

older cohort. Females of the younger cohort had lower DEI (kcal) and carbohydrate (g and E%) intake, but higher protein (E%) and lipid (E%) intake ($p < 0.05$).

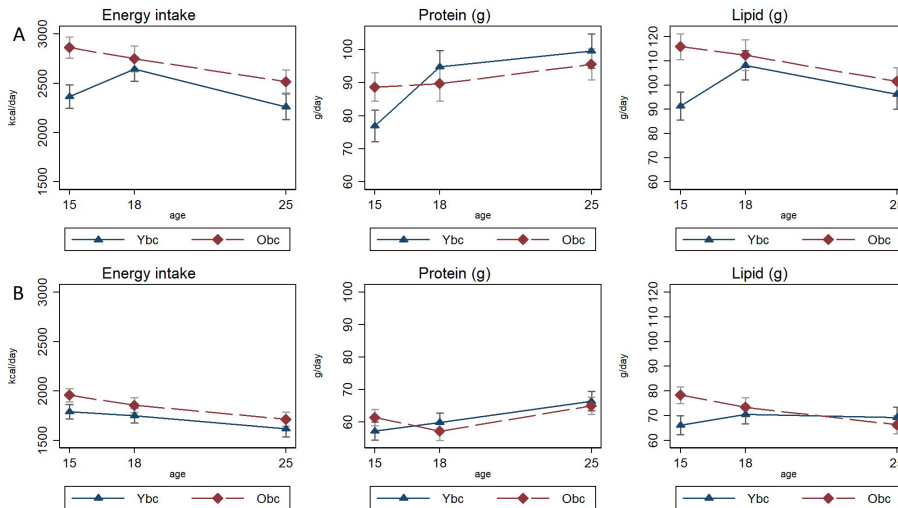


Figure 12. Association between birth cohort and dietary intake, in male (panel A) and female (panel B) subjects of the ECPBHS sample from 15–25 years. Ybc, younger birth cohort; Obc, older birth cohort

5.4.1.3. Association between glucose metabolism and the birth cohort

Linear mixed-effects regression models with quadratic trends showed significant between-cohort differences in the slopes and rates of change in GLC and INS levels in both males and females (**Table 15** and **Figure 13**).

At 15 years, both males and females of the younger cohort had significantly lower GLC levels, compared to the older cohort. INS levels did not differ between the birth cohorts at that age ($p < 0.05$). In contrast, at 18 years, both males and females of the younger cohort had significantly higher GLC levels, compared to the older cohort. Females of the younger cohort had lower INS levels, compared to the older cohort ($p < 0.05$). At 25 years, males of the younger cohort had significantly lower GLC but higher INS levels, compared to the older cohort. Similarly, females of the younger cohort had higher INS levels, compared to the older cohort ($p < 0.05$).

5.4.1.4. Association between cardiorespiratory fitness and the birth cohort

Linear mixed-effects regression models with quadratic trends showed significant between-cohort differences or trends toward significance in the slopes and rates of change in MPO/kg in both males and females (**Table 15** and **Figure 13**).

At 15 years, both males and females of the younger cohort had significantly lower MPO/kg, compared to the older cohort ($p < 0.05$). At 18 years, males of the younger cohort had significantly lower MPO/kg, compared to the older cohort ($p < 0.05$). No significant differences were observed between the birth cohorts among female subjects at age 18. No differences in MPO/kg were observed between the birth cohorts at age 25.

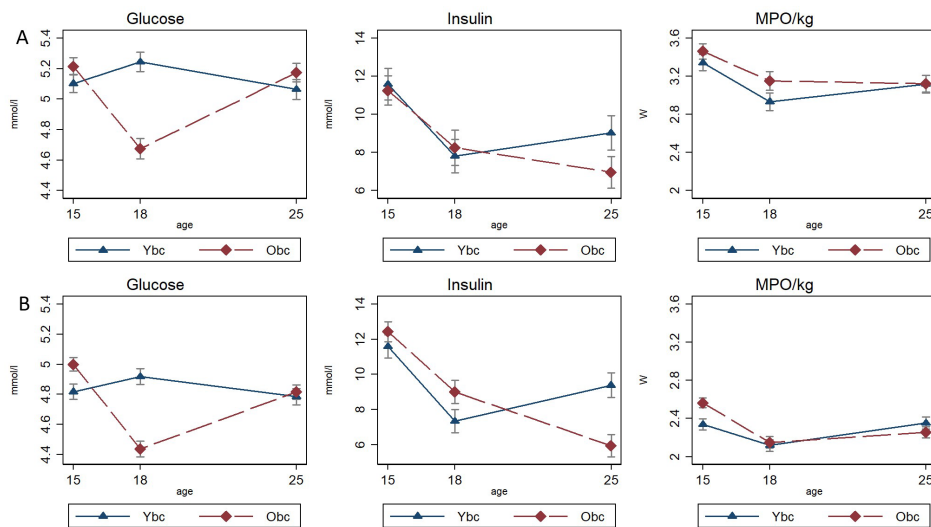


Figure 13. Association between birth cohort and glucose metabolism and CRF, in male (panel A) and female (panel B) subjects of the ECPBHS sample from 15–25 years. CRF, cardiorespiratory fitness; Obc, older birth cohort; Ybc, younger birth cohort.

Table 15. Estimated main effects (mean and 95% CI) and estimated main and interaction effects (mean and 95% CI) in anthropometric measurements, metabolic biomarkers, dietary intake, and CRF in male and female subjects of the ECPBHS sample from 15–25 years between the younger and older birth cohort according to the linear mixed-effects regression models.

	Male			Female		
	Coefficient	95% CI	P value	Coefficient	95% CI	P value
Weight (kg)						
Older birth cohort	-5.899	-9.284; -2.515	0.001	-2.793	-5.719; 0.133	0.073
Older birth cohort × time	0.286	0.108; 0.463	0.002	-0.013	-0.173; 0.148	0.832
BMI (kg/m²)						
Older birth cohort	-1.440	-2.348; -0.532	0.002	-0.349	-1.349; 0.651	0.494
Older birth cohort × time	0.071	0.021; 0.120	0.005	-0.024	-0.080; 0.033	0.414
WC (cm)						
Older birth cohort	-6.666	-9.110; -4.221	<0.001	-6.102	-8.667; -3.537	<0.001
Older birth cohort × time	0.325	0.181; 0.469	<0.001	0.199	0.048; 0.350	0.011
HC (cm)						
Older birth cohort	-3.922	-6.222; -1.621	0.001	-0.761	-3.131; 1.608	0.529
Older birth cohort × time	0.168	0.051; 0.285	0.005	-0.073	-0.203; 0.057	0.269
WHR (units)						
Older birth cohort	-0.0324	-0.0500; -0.0147	<0.001	-0.0569	-0.0727; -0.0412	<0.001
Older birth cohort × time	0.0018	0.0008; 0.0027	<0.001	0.0027	0.0018; 0.0036	<0.001
WHR (units)						
Older birth cohort	-0.0330	-0.0468; -0.0193	<0.001	-0.0301	-0.0452; -0.0150	<0.001
Older birth cohort × time	0.0016	0.0008; 0.0024	<0.001	0.0010	0.0001; 0.0019	0.030
Glucose (mmol/L)						
Older birth cohort	12.224	10.558; 13.889	<0.001	11.229	9.931; 12.526	<0.001
Older birth cohort × time	-1.292	-1.464; -1.120	<0.001	-1.169	-1.303; -1.035	<0.001
Time × time	-0.007	-0.010; -0.004	<0.001	-0.005	-0.008; -0.003	<0.001
Older birth cohort × time × time	0.032	0.028; 0.037	<0.001	0.029	0.026; 0.032	<0.001
Insulin (mU/L)						
Older birth cohort	-24.214	-49.077; 0.650	0.056	-31.999	-49.973; -14.025	<0.001
Older birth cohort × time	2.638	0.071; 5.205	0.044	3.745	1.893; 5.596	<0.001
Time × time	0.145	0.101; 0.189	<0.001	0.172	0.140; 0.205	<0.001
Older birth cohort × time × time	-0.070	-0.133; -0.007	0.031	-0.104	-0.150; -0.058	<0.001

	Male			Female		
	Coefficient	95% CI	P value	Coefficient	95% CI	P value
Daily energy intake (kcal)						
Older birth cohort	7091.006	3490.685; 10691.330	<0.001	250.648	-25.298; 526.595	0.075
Older birth cohort × time	-685.702	-1057.385; -314.020	<0.001	-6.433	-19.547; 6.682	0.336
Time × time	-14.664	-21.081; -8.247	<0.001			
Older birth cohort × time × time	16.482	7.300; 25.664	<0.001			
Protein (g)						
Older birth cohort	27.700	9.634; 45.767	0.003	108.041	24.078; 192.004	0.012
Older birth cohort × time	-1.371	-2.303; -0.440	0.004	-10.705	-19.366; -2.044	0.015
Time × time				-0.001	-0.154; 0.153	0.994
Older birth cohort × time × time				0.253	0.039; 0.467	0.020
Lipids (g)						
Older birth cohort	342.109	160.268; 523.949	<0.001	31.840	17.556; 46.123	<0.001
Older birth cohort × time	-32.634	-51.406; -13.862	<0.001	-1.428	-2.116; -0.740	<0.001
Time × time	-0.726	-1.051; -0.402	<0.001			
Older birth cohort × time × time	0.766	0.303; 1.230	<0.001			
Carbohydrates (g)						
Older birth cohort	54.570	-5.205; 114.346	0.074	-11.041	-46.562; 24.479	0.542
Older birth cohort × time	-0.634	-3.424; 2.157	0.656	1.516	-0.311; 3.343	0.104
Protein E%						
Older birth cohort	2.045	0.267; 3.824	0.024	1.122	-0.388; 2.633	0.145
Older birth cohort × time	-0.181	-0.273; -0.084	<0.001	-0.110	-0.189; -0.031	0.006
Lipids E%						
Older birth cohort	6.202	2.438; 9.966	0.001	10.173	6.800; 13.547	<0.001
Older birth cohort × time	-0.318	-0.503; -0.133	0.001	-0.556	-0.723; -0.390	<0.001
Carbohydrates E%						
Older birth cohort	-6.479	-10.728; -2.229	0.003	-10.902	-14.651; -7.154	<0.001
Older birth cohort × time	0.407	0.188; 0.626	<0.001	0.634	0.446; 0.821	<0.001
MPO/kg (W/kg)						
Older birth cohort	-1.932	-4.225; 0.361	0.099	2.339	0.868; 3.811	0.002
Older birth cohort × time	-0.228	-0.009; 0.466	0.060	-0.204	-0.356; -0.051	0.009
Time × time	0.017	0.013; 0.021	<0.001	0.011	0.009; 0.014	<0.001
Older birth cohort × time × time	-0.006	-0.012; -0.0002	0.044	0.004	0.0005; 0.008	0.027

BMI, body mass index; CRF, cardiorespiratory fitness; HC, hip circumference; MPO, maximum power output WC, waist circumference; WHR, waist-to-hip ratio; WHtR, waist-to-height ratio.
Significance levels were set at 0.05 and significant differences between the birth cohorts are highlighted in bold.

Table 16. The rate of change per year in anthropometric measurements, metabolic biomarkers, dietary intake (mean and 95% CI) in male and female subjects of the ECPBHS sample according to the linear mixed effects regression models with birth cohort $\times$ time interaction.

	Male		Female	
	Younger birth cohort	Older birth cohort	Younger birth cohort	Older birth cohort
Weight (kg)	1.775 (1.775; 1.905) ^a	2.061 (1.940; 2.182) ^a	NA	NA
BMI (kg/m ²)	0.418 (0.382; 0.455) ^a	0.489 (0.455; 0.523) ^a	NA	NA
WC (cm)	1.264 (1.158; 1.369) ^a	1.588 (1.490; 1.686) ^a	0.670 (0.559; 0.781) ^b	0.867 (0.764; 0.969) ^b
HC (cm)	1.036 (0.950; 1.122) ^a	1.205 (1.125; 1.284) ^a	NA	NA
WHR (units)	0.0042 (0.0035; 0.0049) ^a	0.0060 (0.0053; 0.0067) ^a	0.0016 (0.0009; 0.0022) ^b	0.0042 (0.0036; 0.0048) ^b
WHR (units)	0.0057 (0.0051; 0.0063) ^a	0.0073 (0.0067; 0.0078) ^a	0.0035 (0.0029; 0.0028) ^b	0.0045 (0.0039; 0.0052) ^b
Protein (g)	2.007 (1.318; 2.696) ^a	0.635 (0.008; 1.263) ^a	NA	NA
Lipids (g)	NA	NA	0.242 (-0.272; 0.756) ^b	-1.186 (-1.643; -0.729) ^b
Protein E%	0.434 (0.362; 0.506) ^a	0.253 (0.187; 0.318) ^a	0.345 (0.286; 0.404) ^b	0.235 (0.182; 0.288) ^b
Lipids E%	0.183 (0.047; 0.320) ^a	-0.135 (-0.259; -0.010) ^a	0.368 (0.244; 0.493) ^b	-0.188 (-0.298; -0.077) ^b
Carbohydrates E%	-0.877 (-1.039; -0.716) ^a	-0.470 (-0.617; -0.323) ^a	-0.829 (-0.969; -0.689) ^b	-0.195 (-0.319; -0.071) ^b

BMI, body mass index; HC, hip circumference; WC, waist circumference; WHR, waist-to-hip ratio; WHtR, waist-to-height ratio.

^a $p < 0.05$ significant difference in the rate of change between male subjects of the younger birth cohort and older birth cohort.

^b $p < 0.05$ significant difference in the rate of change between female subjects of the younger birth cohort and older birth cohort.

6. DISCUSSION

This dissertation explored the effects of selected genetic (i.e., *TFAP2B*, *FTO*, *NPY*), and psychobiological factors (i.e., reward sensitivity) with measures of overweight, obesity, and its related conditions (i.e., insulin resistance) while considering interactions with age, sex, diet, physical activity, SES, and the birth cohort. Data from the longitudinal ECPBHS cohort study was utilised to assess changes over time. Effects were explored during a critical time of growth and maturation from childhood to early adulthood (9–33 years of age).

Associations between *TFAP2B* intron 2 VNTR genotype and measures of obesity and insulin resistance were observed independently of dietary intake (**Paper I**). *FTO* rs1421085 was linked with measures of obesity with evidence of *FTO* × SES interaction, but not with diet or physical activity (**Paper II**). *NPY* polymorphisms (rs16139, rs5574, rs16147 and rs17149106) were associated with measures of obesity in an age-dependent manner (**Paper IV**). Reward sensitivity and measures of obesity were associated through its reward fixation component (**Paper III**). Notably, an association between birth cohort, measures of obesity, and metabolism which was at least partly driven by higher DEI, particularly from carbohydrates, was detected (**Paper V**).

6.1. *TFAP2B* intron 2 variable number tandem repeat genotype was associated with measures of obesity and insulin resistance, but not with dietary intake (Paper I)

TFAP2B is a susceptibility locus for obesity-related phenotypes. GWAS have repeatedly identified *TFAP2B* as being associated with BMI, WC, and WHR (Felix et al., 2016; Locke et al., 2015; Yengo et al., 2018).

We demonstrated that the *TFAP2B* intron 2 VNTR polymorphism was associated with measures of obesity, abdominal obesity, and insulin resistance in male and female subjects of the ECPBHS from 15–25 years. Male 5-repeat homozygotes had significantly higher body weight, BMI, sum of 5 skinfolds, BF%, WC, HC, WHR, WHtR, fasting INS and HOMA index. Female 5-repeat homozygotes had significantly larger increase in the rate of change per year in body weight, BMI and HC from 15–25 years.

Interestingly, the effect of *TFAP2B* intron 2 VNTR polymorphism on measures of obesity and insulin resistance differed between sexes. In males, the association was present throughout adolescence to young adulthood, however, in females, it appeared later, in young adulthood. The difference in the effect of *TFAP2B* on body weight between sexes has been further explored by Kulberg (2024) in the Estonian Biobank cohort, where *TFAP2B* rs2207139 was associated with body weight only in females aged < 30 years. Homozygotes for the G allele weighed on average 2.81 kg more than non-carriers after adjustment for lifestyle and demographic covariates. No association between *TFAP2B* rs2207139 geno-

type and body weight was identified in male subjects at any age (i.e., < 30 years, 30–45 years, 46–65 years, 66 + years) (Kulberg, 2024).

The pathways through which *TFAP2B* influences the development of obesity and insulin resistance remain unclear. We hypothesised that the association may be mediated by dietary intake. However, we found that male 5-repeat homozygotes had a larger decrease in the rate of change per year in DEI in MJ (1 kcal = 0.0042 MJ) compared to heterozygotes. Thus, our results indicated that the effect of *TFAP2B* on obesity was not mediated by dietary intake and other biological mechanisms should be considered.

6.2. *FTO* rs1421085 was associated with measures of obesity, with evidence of *FTO* × SES interaction, but not with diet or physical activity (Paper II)

Frayling et al. (2007) was the first to link *FTO* variants to obesity (Frayling et al., 2007). Subsequently, several GWAS have affirmed the association between different *FTO* SNPs and BMI in children and adults (Felix et al., 2016; Locke et al., 2015; Yengo et al., 2018).

We demonstrated that *FTO* rs1421085 was associated with measures of obesity and abdominal obesity in male and female subjects of the ECPBHS from 15–25 years. We found that male *FTO* rs1421085 C allele carriers had significantly higher BMI, sum of 5 skinfolds, BF%, and HC from 15–25 years. Findings were similar at 9 years. Female *FTO* rs1421085 CC homozygotes had significantly greater WHR from 15–25 years.

We explored whether the obesity-promoting effect of *FTO* may be explained through differences in lifestyle factors e.g., dietary intake and physical activity, as indicated by several studies (Al-Jawadi et al., 2021; Harbron et al., 2014; Kilpeläinen et al., 2011; Poosri et al., 2024). However, we observed a greater decrease in the rate of change in DEI (kcal) and lipid intake (g/kg) per year in female *FTO* rs1421085 CC homozygotes, compared to TT homozygotes and a lower protein (g/kg) and lipid (g/kg; E%) intake in male heterozygotes compared to TT homozygotes from 15–25 years. Female *FTO* rs1421085 CC homozygotes also had greater physical activity scores compared to TT homozygotes from 15–25 years in every fixed time point.

Notably, we observed an interaction between *FTO* rs1421085 genotype and sSES score in female subjects, where increasing SES led to an increase in measurements of obesity in TT homozygotes, but to a decrease in CC homozygotes. A study by Foraita et al (2015) has previously shown an interaction between SES and *FTO* with respect to childhood obesity (Foraita et al., 2015), however, the evidence on *FTO* × SES interaction is relatively limited and needs further research.

Claussnitzer et al. (2015) showed that the *FTO* rs1421085 risk allele causes dysregulation of *IRX3* and *IRX5* expression, resulting in increased lipid storage, reduced adipocyte browning, and impaired mitochondrial thermogenesis (Clauss-

nitzer et al., 2015). Our findings are consistent with the aforementioned hypothesis, as being the main mechanism behind increased risk of obesity.

6.3. *NPY* gene variants were associated with measures of obesity in an age-dependent manner (Paper IV)

NPY has an extensive physiological and homeostatic role in the mammalian organism including, but not limited to, feeding behaviour (Nguyen et al., 2012), immune homeostasis (Farzi et al., 2015), mood disorders (Mickey et al., 2011), vasomotion, angiogenesis and cardiac remodeling (Tan et al., 2018). However, studies describing the association between *NPY* genetic variants and weight gain or obesity have been inconclusive. We assessed the association between four *NPY* polymorphisms rs16139, rs5574, rs16147 and rs17149106 (of which two pairs rs16147 with rs5574 and rs17149106 with rs16139 are in strong linkage disequilibrium) and measures of obesity, dietary intake, physical activity, BP and GLC and lipid metabolism.

We demonstrated that *NPY* rs5574 and rs16147 were associated with measures of obesity and abdominal obesity in subjects of the ECPBHS from 15–25 years. We found that *NPY* rs5574 CC homozygotes had significantly higher measure of abdominal obesity i.e., a greater increase per year in WHR from 15–25 years. *NPY* rs16147 TT homozygotes had significantly higher measure of both obesity and abdominal obesity i.e., higher body weight throughout the study period and a greater increase in sum of 5 skinfolds, WC, WHR and WHtR from 15–25 years. No association between *NPY* rs16139 or *NPY* rs17149106 and measures of obesity and abdominal obesity were detected. These findings align with previous studies where *NPY* rs16147 and rs5574 have been associated with measures of obesity in children and adolescence (Olza et al., 2013; Zain et al., 2015) and *NPY* rs16139 or *NPY* rs17149106 in adults and middle-age populations (Ding et al., 2005; van Rossum et al., 2006; Zain et al., 2015) suggesting the effect of *NPY* variants on measures of obesity may be age-related.

However, our findings did not reveal a clear mechanism in terms of increased weight gain through lifestyle factors e.g., dietary intake or physical activity. We observed a smaller decrease in DEI (kcal/day) and carbohydrate intake (g) per year in *NPY* rs5574 CC homozygotes from 15–25 years. Inversely, a lower carbohydrate intake at every timepoint in *NPY* rs16147 TT homozygotes from 15–25 years; however, the overall DEI was not different between genotypes. Furthermore, we did not identify any association between *NPY* SNP-s and physical activity. However, *NPY* rs16139 heterozygotes compared to GG homozygotes had a lower MPO, at 25 years, indicating a poorer CRF.

All four *NPY* SNP-s were associated with BP. *NPY* rs5574 CC homozygotes, and rs16147 TT homozygotes had a higher increase in diastolic BP from 15–25 years, and *NPY* rs16139 heterozygotes and rs17149106 heterozygotes had lower systolic and diastolic BP as compared to the TT and GG homozygotes. In contrast, Sianturi et al. (2022) observed a higher average systolic BP in *NPY*

rs16147 C allele carriers among adults with a median age 51,5 years (22–83 years). Although evidence on the relationship between NPY and BP is limited, this may indicate another age-dependent effect (Sianturi, et al., 2022).

6.4. Reward sensitivity and measures of obesity are associated through its reward fixation component (Paper III)

Sensitivity to reward is a psychobiological trait to seek rewarding substances or enjoyment with high reward potential (Loxton & Tipman, 2017). Findings on the association between reward sensitivity and obesity have been inconsistent, with some studies reporting a positive association (De Decker et al., 2016) and others reporting no association (Jonker et al., 2019, 2016). However, most studies have not considered the inner structure of reward sensitivity.

We demonstrated that reward sensitivity was associated with measures of obesity and abdominal obesity through its reward fixation component among ECPBHS subjects from 15–25 years. We observed that higher Insatiability by Reward and its subscale scores, which consist of items reflecting trouble resisting temptations and cravings, overindulging, excessive spending and impulsivity, were associated with higher measures of overall and abdominal obesity from 15–25 years. Moreover, at 9 years, a trend in Giving in to Cravings score, between normal weight and overweight subjects, and at 33 years, a dose-response relationship for Insatiability by Reward, particularly the Giving in to Cravings score (reward sensitivity score increased together with BMI category) was observed. In contrast, no longitudinal association between obesity and Openness to Rewards, including items such as openness to new things and experiences, adventures and social situations, were detected.

Furthermore, we later demonstrated that Openness to Rewards was associated with higher physical activity and lower BP and serum GLC, INS, and CHL, whereas Insatiability by Reward was associated with higher serum TRG levels and DEI and CRF (Kiive et al., 2025).

Our findings highlight how the two facets of reward sensitivity relate to measures of obesity and energy expenditure and may explain the variable findings in literature.

6.5. Birth cohort was associated with measures of obesity through dietary intake (Paper V)

A birth cohort refers to a group of individuals born at a specific time point or within a similar time period who are exposed to shared socioeconomic and environmental factors (Canizares et al., 2018). Separate birth cohorts experience different social and environmental factors, which may lead to differences in psychological and social development, and health-related behaviour (Yoo, 2023).

We observed an overall increase in the prevalence of overweight and obesity over time across both birth cohorts and sexes of the ECPBHS. Prevalence of overweight and obesity was higher in male subjects. Our results align with national (National Institute for Health Development, 2025) and regional data, which has demonstrated that the prevalence of overweight and obesity in Central and Eastern Europe is higher in males than in females before age 40 years, however the prevalence in females surpasses that of males thereafter (GBD 2021 Adult BMI Collaborators, 2025).

Notably, subjects from the older cohort had lower weight during childhood but experienced more rapid increases in obesity-related measures from 15–25 years. Moreover, both male and female subjects from the older cohort had higher DEI (kcal) at ages 15 and 25 compared to the younger cohort. Additionally, subjects from the younger cohort had a significantly higher protein intake (E%) and a lower carbohydrate intake (E%).

Our findings suggest a clear association between birth cohort, measures of obesity, and metabolism that emerged during a period of socioeconomic transition at a critical stage of development. This relationship may be partly driven by higher energy intake, particularly from carbohydrates.

6.6. Strengths and limitations of the study (Papers I–V)

Results reported in this dissertation are based on the ECPBHS sample. The ECPBHS is a longitudinal birth cohort study with a population representative sample, with schools serving as the sampling unit. The original sample (1998/99) had a high participation rate, with 79.1% of the individuals invited to participate enrolling in the study. Moreover, subsequent attrition at follow-up waves has been relatively low, and it is estimated that population representativeness has been maintained. The methodology of the study has been consistent throughout the study waves (some measurements even taken by the very same investigator). Due to its school-based recruitment strategy, the ECPBHS has a unique birth cohort representative and homogenous study sample. Subjects from the younger and older birth cohorts lived in the same area and attended the same schools. This allows for a clearer observation and analysis of the independent effect of birth cohort.

However, there are some limitations to our study. The ECPBHS comprises a homogeneous sample of individuals of European ancestry, therefore, it is not known whether the results can be extrapolated to other ethnicities. ECPBHS sample is, for the time being, limited with the age 33 being the last point of observation. Because of the size of the sample, the ECPBHS study has limited statistical power. Adiposity and central adiposity were assessed using indirect measures such as BMI, WC, WHR, and WHtR as data from dual-energy X-ray absorptiometry, computed tomography, or magnetic resonance imaging were not available. The ROIS instrument (Pulver et al., 2020), used for the assessment of reward sensitivity, was developed post hoc, applied in a Finnic language, and

requires further development and characterisation together with related instruments. Dietary intake was assessed using self-reported data, which are susceptible to measurement error and systematic underreporting of food and energy intake. To reduce these limitations, on the study day, subjects completed a face-to-face interview, using portion size photographs, to specify portion sizes that were not recorded in the food diary.

7. CONCLUSIONS

1. The *TFAP2B* intron 2 VNTR polymorphism was associated with measures of obesity, abdominal obesity, and insulin resistance. In males, the association was present throughout adolescence to young adulthood, however, in females, it appeared later, in young adulthood. This effect was not mediated by dietary intake, and other biological mechanisms should be considered.
2. *FTO* rs1421085 was associated with measures of obesity, however, this was not mediated by dietary intake and/or physical activity. An interaction between *FTO* rs1421085 genotype and SES was identified in female subjects, where increasing SES was associated with higher measures of obesity in TT homozygotes, but lower measures of obesity in CC homozygotes.
3. *NPY* gene variants were associated with measures of obesity in an age-dependent manner. Notably, all four *NPY* SNP-s were associated with BP. However, a clear mechanism in terms of increased weight gain through dietary intake and/or physical activity was not identified.
4. The inner structure of reward sensitivity should be considered when studying the relationship between reward sensitivity and measures of obesity. We demonstrated that measures of obesity were associated with reward sensitivity only through its reward fixation component.
5. A clear association was observed between birth cohort and measures of obesity and metabolism during a period of socioeconomic transition at a critical stage of development. This relationship was at least partly driven by higher DEI, particularly from carbohydrates.

REFERENCES

- Agrawal, R., Reno, C.M., Sharma, S., Christensen, C., Huang, Y., Fisher, S.J. Insulin action in the brain regulates both central and peripheral functions. *Am J Physiol Endocrinol Metab.* 2021;321(1):E156–E163. <https://doi.org/10.1152/ajpendo.00642.2020>
- Alhabeeb, H., AlFaiz, A., Kutbi, E., AlShahrani, D., Alsuhail, A., AlRajhi, S., et al. Gut Hormones in Health and Obesity: The Upcoming Role of Short Chain Fatty Acids. *Nutrients.* 2021;13(2):481. <https://doi.org/10.3390/nu13020481>
- Al-Jawadi, A.A., Priliani, L., Oktavianthi, S., Febinia, C.A., Daya, M., Artika, I.M., et al. Association of FTO rs1421085 single nucleotide polymorphism with fat and fatty acid intake in Indonesian adults. *BMC Res Notes.* 2021;14(1):411. <https://doi.org/10.1186/s13104-021-05823-1>
- Allman-Farinelli, M.A., Chey, T., Bauman, A.E., Gill, T., James, W.P.T. Age, period and birth cohort effects on prevalence of overweight and obesity in Australian adults from 1990 to 2000. *Eur J Clin Nutr.* 2008;62(7):898–907. <https://doi.org/10.1038/sj.ejcn.1602769>
- An, S.J., Jung, M.-H., Ihm, S.-H., Yang, Y., Youn, H.-J. Effect of physical activity on the cardiometabolic profiles of non-obese and obese subjects: Results from the Korea National Health and Nutritional Examination Survey. *PLoS One.* 2019;14(3):e0208189. <https://doi.org/10.1371/journal.pone.0208189>
- Anderson, B., Lyon-Callo, S., Fussman, C., Imes, G., Rafferty, A.P. Fast-Food Consumption and Obesity Among Michigan Adults. *Prev Chronic Dis.* 2011;8(4):A71. https://www.cdc.gov/pcd/issues/2011/jul/10_0186.htm
- Ashwell, M., Gibson, S. Waist-to-height ratio as an indicator of “early health risk”: simpler and more predictive than using a “matrix” based on BMI and waist circumference. *BMJ Open.* 2016;6:e010159. <https://doi.org/10.1136/bmjopen-2015-010159>
- Ashwell, M., Gunn, P., Gibson, S. Waist-to-height ratio is a better screening tool than waist circumference and BMI for adult cardiometabolic risk factors: systematic review and meta-analysis. *Obes Rev.* 2012;13(3):275–286. <https://doi.org/10.1111/j.1467-789X.2011.00952.x>
- Austin, J., Marks, D. Hormonal Regulators of Appetite. *Int J Pediatr Endocrinol.* 2009;2009:141753. <https://doi.org/10.1155/2009/141753>
- Azzam, S.K., Alsafar, H., Sajini, A.A. FTO m6A Demethylase in Obesity and Cancer: Implications and Underlying Molecular Mechanisms. *Int J Mol Sci.* 2022;23(7):3800. <https://doi.org/10.3390/ijms23073800>
- Berg, L. van den, Pieterse, K., Malik, J.A., Luman, M., Dijk, K.W. van, Oosterlaan, J., et al. Association between impulsivity, reward responsiveness and body mass index in children. *Int J Obes.* 2011;35(10):1301–1307. <https://doi.org/10.1038/ijo.2011.116>
- Blomhoff, R., Andersen, R., Arnesen, E., Christensen, J., Eneroth, H., Erkkola, M., et al. Nordic Nutrition Recommendations 2023. Copenhagen: Nordic Council of Ministers; 2023.
- Blüher, M. Obesity: global epidemiology and pathogenesis. *Nat Rev Endocrinol.* 2019;15(5):288–298. <https://doi.org/10.1038/s41574-019-0176-8>
- Bray, G.A., Frühbeck, G., Ryan, D.H., Wilding, J.P.H. Management of obesity. *Lancet.* 2016;387(10031):1947–1956. [https://doi.org/10.1016/S0140-6736\(16\)00271-3](https://doi.org/10.1016/S0140-6736(16)00271-3)
- Canizares, M., Hogg-Johnson, S., Gignac, M.A.M., Glazier, R.H., Badley, E.M. Increasing Trajectories of Multimorbidity Over Time: Birth Cohort Differences and the

- Role of Changes in Obesity and Income. *J Gerontol B Psychol Sci Soc Sci*. 2018;73(7):1303–1314. <https://doi.org/10.1093/geronb/gbx004>
- Cattaneo, S., Verlengia, G., Marino, P., Simonato, M., Bettegazzi, B. NPY and Gene Therapy for Epilepsy: How, When,... and Y. *Front Mol Neurosci*. 2021;13:608001. <https://doi.org/10.3389/fnmol.2020.608001>
- Chen, Q., Hartman, C.A., Haavik, J., Harro, J., Klungsøyr, K., Hegvik, T.-A., et al. Common psychiatric and metabolic comorbidity of adult attention-deficit/hyperactivity disorder: A population-based cross-sectional study. *PLoS One*. 2018;13(9):e0204516. <https://doi.org/10.1371/journal.pone.0204516>
- Chin, S.-H., Kahathuduwa, C.N., Binks, M. Physical activity and obesity: what we know and what we need to know. *Obes Rev*. 2016;17(12):1226–1244. <https://doi.org/10.1111/obr.12460>
- Chung, A., Backholer, K., Wong, E., Palermo, C., Keating, C., Peeters, A. Trends in child and adolescent obesity prevalence in economically advanced countries according to socioeconomic position: a systematic review. *Obes Rev*. 2016;17(3):276–295. <https://doi.org/10.1111/obr.12360>
- Clark, J.T., Kalra, P.S., Crowley, W.R., Kalra, S.P. Neuropeptide Y and human pancreatic polypeptide stimulate feeding behavior in rats. *Endocrinology*. 1984;115(1):427–429. <https://doi.org/10.1210/endo-115-1-427>
- Claussnitzer, M., Dankel, S.N., 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. <https://doi.org/10.1056/NEJMoa1502214>
- Cloetens, L., Ellegård, L. Energy – a scoping review for the Nordic Nutrition Recommendations 2023 project. *Food Nutr Res*. 2023;67. <https://doi.org/10.29219/fnr.v67.10233>
- Cole, T.J., Bellizzi, M.C., Flegal, K.M., Dietz, W.H. Establishing a standard definition for child overweight and obesity worldwide: international survey. *BMJ*. 2000;320(7244):1240–1243. <https://doi.org/10.1136/bmj.320.7244.1240>
- Corr, P. The reinforcement sensitivity theory of personality. In: *Reinforcement Sensitivity Theory (RST): Introduction*. New York: Cambridge University Press; 2008. p. 1–43.
- Corr, P., Krupić, D. Motivating personality: Approach, avoidance, and their conflict. In: *Advances in Motivation Science*. Elsevier Academic Press; 2017.
- Corsi, D.J., Marschner, S., Lear, S., Hystad, P., Rosengren, A., Ismail, R., et al. Assessing the built environment through photographs and its association with obesity in 21 countries: the PURE Study. *Lancet Glob Health*. 2024;12(11):e1794–e1806. [https://doi.org/10.1016/s2214-109x\(24\)00287-0](https://doi.org/10.1016/s2214-109x(24)00287-0)
- Damberg, M., Berggård, C., Farde, L., Sedvall, G.C., Jönsson, E.G. Transcription factor AP-2 β genotype, striatal dopamine D2 receptor density and cerebrospinal fluid monoamine metabolite concentrations in humans. *J Neural Transm*. 2004;111(5): 537–545. <https://doi.org/10.1007/s00702-003-0097-4>
- Damberg, M., Eller, M., Tönissaar, M., Orelund, L., Harro, J. Levels of transcription factors AP-2 α and AP-2 β in the brainstem are correlated to monoamine turnover in the rat forebrain. *Neurosci Lett*. 2001;313(1–2):102–104. [https://doi.org/10.1016/S0304-3940\(01\)02243-1](https://doi.org/10.1016/S0304-3940(01)02243-1)
- Danaher, J., Stathis, C.G., Cooke, M.B. Similarities in Metabolic Flexibility and Hunger Hormone Ghrelin Exist between FTO Gene Variants in Response to an Acute Dietary Challenge. *Nutrients*. 2019;11(4):701. <https://doi.org/10.3390/nu11102518>
- Davis, C. Compulsive Overeating as an Addictive Behavior: Overlap Between Food Addiction and Binge Eating Disorder. *Curr Obes Rep*. 2013;2(2):171–178.

- <https://doi.org/10.1007/s13679-013-0049-8>
- Davis, C., Patte, K., Levitan, R., Reid, C., Tweed, S., Curtis, C. From motivation to behaviour: a model of reward sensitivity, overeating, and food preferences in the risk profile for obesity. *Appetite*. 2007;48(1):12–19.
<https://doi.org/10.1016/j.appet.2006.05.016>
- De Decker, A., Sioen, I., Verbeken, S., Braet, C., Michels, N., De Henauw, S. Associations of reward sensitivity with food consumption, activity pattern, and BMI in children. *Appetite*. 2016;100:189–196. <https://doi.org/10.1016/j.appet.2016.02.028>
- de Onis, M., Garza, C., Victora, C.G., Onyango, A.W., Frongillo, E.A., Martines, J. The WHO Multicentre Growth Reference Study: planning, study design, and methodology. *Food Nutr Bull*. 2004;25(Suppl 1):S15–S26.
<https://doi.org/10.1177/15648265040251S103>
- Detry, M.A., Ma, Y. Analyzing Repeated Measurements Using Mixed Models. *JAMA*. 2016;315(4):407–408. <https://doi.org/10.1001/jama.2015.19394>
- Devaux, M., Sassi, F. Social inequalities in obesity and overweight in 11 OECD countries. *Eur J Public Health*. 2013;23(3):464–469. <https://doi.org/10.1093/eurpub/ckr058>
- Dina, C., Meyre, D., Gallina, S., Durand, E., Körner, A., Jacobson, P., et al. Variation in FTO contributes to childhood obesity and severe adult obesity. *Nat Genet*. 2007;39(6):724–726. <https://doi.org/10.1038/ng2048>
- Ding, B., Kull, B., Liu, Z., Mottagui-Tabar, S., Thonberg, H., Gu, H.F., et al. Human neuropeptide Y signal peptide gain-of-function polymorphism is associated with increased body mass index: possible mode of function. *Regul Pept*. 2005;127(1–3):45–53. <https://doi.org/10.1016/j.regpep.2004.10.011>
- Dixon, B.N., Ugwoaba, U.A., Brockmann, A.N., Ross, K.M. Associations between the built environment and dietary intake, physical activity, and obesity: A scoping review of reviews. *Obes Rev*. 2021;22(4):e13171. <https://doi.org/10.1111/obr.13171>
- Durnin, J.V., Womersley, J. Body fat assessed from total body density and its estimation from skinfold thickness: measurements on 481 men and women aged from 16 to 72 years. *Br J Nutr*. 1974;32(1):77–97. <https://doi.org/10.1079/BJN19740060>
- Durnin, J.V.G.A., Rahaman, M.M. The assessment of the amount of fat in the human body from measurements of skinfold thickness. *Br J Nutr*. 1967;21(3):681–689.
<https://doi.org/10.1079/BJN19670070>
- Eckert, D., Buhl, S., Weber, S., Jäger, R., Schorle, H. The AP-2 family of transcription factors. *Genome Biol*. 2005;6(13):246. <https://doi.org/10.1186/gb-2005-6-13-246>
- Elks, C.E., den Hoed, M., Zhao, J.H., Sharp, S.J., Wareham, N.J., Loos, R.J.F. Variability in the Heritability of Body Mass Index: A Systematic Review and Meta-Regression. *Front Endocrinol*. 2012;3:29. <https://doi.org/10.3389/fendo.2012.00029>
- Emery, N.N., Simons, J.S. A reinforcement sensitivity model of affective and behavioral dysregulation in marijuana use and associated problems. *Exp Clin Psychopharmacol*. 2017;25(4):281–294. <https://doi.org/10.1037/pha0000131>
- Farr, O.M., Li, C.-R., Mantzoros, C.S. Central Nervous System Regulation of Eating: Insights from Human Brain Imaging. *Metabolism*. 2016;65(5):699–713.
<https://doi.org/10.1016/j.metabol.2016.02.002>
- Farzi, A., Reichmann, F., Holzer, P. The homeostatic role of neuropeptide Y in immune function and its impact on mood and behaviour. *Acta Physiol*. 2015;213(3):603–627. <https://doi.org/10.1111/apha.12445>
- Felix, J.F., Bradfield, J.P., Monnereau, C., van der Valk, R.J.P., Stergiakouli, E., Chesi, A., et al. Genome-wide association analysis identifies three new susceptibility loci for childhood body mass index. *Hum Mol Genet*. 2016;25(2):389–403.

- <https://doi.org/10.1093/hmg/ddv472>
- Fischer, A.G., Ullsperger, M. An Update on the Role of Serotonin and its Interplay with Dopamine for Reward. *Front Hum Neurosci.* 2017;11:484.
<https://doi.org/10.3389/fnhum.2017.00484>
- Food and Agriculture Organization of the United Nations, World Health Organization, United Nations University. Human Energy Requirements: Report of a Joint FAO/WHO/UNU Expert Consultation. Rome: Food and Agriculture Organization of the United Nations; 2004.
- Foraita, R., Günther, F., Gwozdz, W., Reisch, L.A., Russo, P., Lauria, F., et al. Does the FTO gene interact with the socioeconomic status on the obesity development among young European children? Results from the IDEFICS study. *Int J Obes.* 2015;39(1):1–6. <https://doi.org/10.1038/ijo.2014.156>
- Frayling, T.M., Timpson, N.J., Weedon, M.N., Zeggini, E., Freathy, R.M., Lindgren, C.M., et al. A Common Variant in the FTO Gene Is Associated with Body Mass Index and Predisposes to Childhood and Adult Obesity. *Science.* 2007;316(5826):889–894. <https://doi.org/10.1126/science.1141634>
- Fung, T.T., Pan, A., Hou, T., Chiuve, S.E., Tobias, D.K., Mozaffarian, D., et al. Long-Term Change in Diet Quality Is Associated with Body Weight Change in Men and Women. *J Nutr.* 2015;145(8):1850–1856. <https://doi.org/10.3945/jn.114.208785>
- GBD 2021 Adolescent BMI Collaborators. Global, regional, and national prevalence of child and adolescent overweight and obesity, 1990–2021, with forecasts to 2050: a forecasting study for the Global Burden of Disease Study 2021. *Lancet.* 2025;405(10482):785–812. [https://doi.org/10.1016/s0140-6736\(25\)00397-6](https://doi.org/10.1016/s0140-6736(25)00397-6)
- GBD 2021 Adult BMI Collaborators. Global, regional, and national prevalence of adult overweight and obesity, 1990–2021, with forecasts to 2050: a forecasting study for the Global Burden of Disease Study 2021. *Lancet.* 2025;405(10482):813–838. [https://doi.org/10.1016/s0140-6736\(25\)00355-1](https://doi.org/10.1016/s0140-6736(25)00355-1)
- GBD 2023 Disease and Injury and Risk Factor Collaborators. Burden of 375 diseases and injuries, risk-attributable burden of 88 risk factors, and healthy life expectancy in 204 countries and territories, including 660 subnational locations, 1990–2023: a systematic analysis for the Global Burden of Disease Study 2023. *Lancet.* 2025;406(10513):1873–1922. [https://doi.org/10.1016/s0140-6736\(25\)01637-x](https://doi.org/10.1016/s0140-6736(25)01637-x)
- Gerken, T., Girard, C.A., Tung, Y.-C.L., Webby, C.J., Saudek, V., Hewitson, K.S., et al. The obesity-associated FTO gene encodes a 2-oxoglutarate-dependent nucleic acid demethylase. *Science.* 2007;318(5855):1469–1472.
<https://doi.org/10.1126/science.1151710>
- Goodarzi, M.O. Genetics of obesity: what genetic association studies have taught us about the biology of obesity and its complications. *Lancet Diabetes Endocrinol.* 2018;6(3):223–236. [https://doi.org/10.1016/s2213-8587\(17\)30200-0](https://doi.org/10.1016/s2213-8587(17)30200-0)
- Gray, J. Three fundamental emotion systems. In: *The Nature of Emotion: Fundamental Questions.* New York: Oxford University Press; 1994.
- Gray, J., McNaughton, N. *The Neuropsychology of Anxiety.* 2nd ed. Oxford: Oxford University Press; 2000.
- Gruszfeld, D., Weber, M., Gradowska, K., Socha, P., Grote, V., Xhonneux, A., et al. Association of early protein intake and pre-peritoneal fat at five years of age: Follow-up of a randomized clinical trial. *Nutr Metab Cardiovasc Dis.* 2016;26(9):824–832. <https://doi.org/10.1016/j.numecd.2016.04.005>
- Grünberg, H., Adojaan, B., Thetloff, M.. Kasvamine ja kasvuhäired: metoodiline juhend laste füüsilise arengu hindamiseks. Tartu: Tartu Ülikool; 1998.

- Haapa, E., Toponen, T., Pietinen, P., Räsänen, L. Annoskuvakirja. Helsinki: Kansanterveyslaitos; 1985.
- Hales, C.M., Fryar, C.D., Carroll, M.D., Freedman, D.S., Ogden, C.L. Trends in Obesity and Severe Obesity Prevalence in US Youth and Adults by Sex and Age, 2007–2008 to 2015–2016. *JAMA*. 2018;319(16):1723–1725.
<https://doi.org/10.1001/jama.2018.3060>
- Hall, K.D., Farooqi, I.S., Friedman, J.M., Klein, S., Loos, R.J.F., Mangelsdorf, D.J., et al. The energy balance model of obesity: beyond calories in, calories out. *Am J Clin Nutr*. 2022;115(5):1243–1254. <https://doi.org/10.1093/ajcn/nqac031>
- Harbron, J., van der Merwe, L., Zaahl, M.G., Kotze, M.J., Senekal, M. Fat mass and obesity-associated (FTO) gene polymorphisms are associated with physical activity, food intake, eating behaviors, psychological health, and modeled change in body mass index in overweight/obese Caucasian adults. *Nutrients*. 2014;6(8):3130–3152.
<https://doi.org/10.3390/nu6083130>
- Harrison, X.A., Donaldson, L., Correa-Cano, M.E., Evans, J., Fisher, D.N., Goodwin, C.E.D., et al. A brief introduction to mixed effects modelling and multi-model inference in ecology. *PeerJ*. 2018;6:e4794. <https://doi.org/10.7717/peerj.4794>
- Harro, J., Eensoo, D., Kiive, E., Villa, I., Kurrikoff, T., Mäestu, J., et al. Insights into neuroscience from the representative birth cohort samples of a multidisciplinary longitudinal study. *Acta Neuropsychiatr*. 2026;38:e33.
<https://doi.org/10.1017/neu.2026.10072>
- Hermosillo-Gallardo, M.E., Sebire, S.J., Jago, R. Perception of Safety and Its Association With Physical Activity in Adolescents in Mexico. *Am J Prev Med*. 2020;58(5):748–755. <https://doi.org/10.1016/j.amepre.2019.12.007>
- Hirschberg, P.R., Sarkar, P., Teegala, S.B., Routh, V.H. Ventromedial hypothalamus glucose-inhibited neurones: A role in glucose and energy homeostasis? *J Neuroendocrinol*. 2020;32(1):e12773. <https://doi.org/10.1111/jne.12773>
- Holder, J.L., Butte, N.F., Zinn, A.R. Profound obesity associated with a balanced translocation that disrupts the SIM1 gene. *Hum Mol Genet*. 2000;9(1):101–108.
<https://doi.org/10.1093/hmg/9.1.101>
- Hooper, L., Abdelhamid, A.S., Jimoh, O.F., Bunn, D., Skeaff, C.M. Effects of total fat intake on body fatness in adults. *Cochrane Database Syst Rev*. 2020;2020(6):CD013636. <https://doi.org/10.1002/14651858.CD013636>
- Hruby, A., Hu, F.B. The Epidemiology of Obesity: A Big Picture. *Pharmacoeconomics*. 2015;33(7):673–689. <https://doi.org/10.1007/s40273-014-0243-x>
- Huang, Y., Lin, X., Lin, S. Neuropeptide Y and Metabolism Syndrome: An Update on Perspectives of Clinical Therapeutic Intervention Strategies. *Front Cell Dev Biol*. 2021;9:695623. <https://doi.org/10.3389/fcell.2021.695623>
- Ikeda, K., Maegawa, H., Ugi, S., Tao, Y., Nishio, Y., Tsukada, S., et al. Transcription factor activating enhancer-binding protein-2 β : A negative regulator of adiponectin gene expression. *J Biol Chem*. 2006;281(42):31245–31253.
<https://doi.org/10.1074/jbc.m605132200>
- Institute for Health Metrics and Evaluation. Global Burden of Disease 2023: GBD Results Tool. Seattle: Institute for Health Metrics and Evaluation; 2025.
<https://vizhub.healthdata.org/gbd-results/>
- Jackson, S.E., Llewellyn, C.H., Smith, L. The obesity epidemic – Nature via nurture: A narrative review of high-income countries. *SAGE Open Med*. 2020;8:2050312120918265. <https://doi.org/10.1177/2050312120918265>

- James, D.E., Stöckli, J., Birnbaum, M.J. The aetiology and molecular landscape of insulin resistance. *Nat Rev Mol Cell Biol.* 2021;22(11):751–771.
<https://doi.org/10.1038/s41580-021-00390-6>
- Jia, G., Fu, Y., Zhao, X., Dai, Q., Zheng, G., Yang, Y., et al. N⁶-methyladenosine in nuclear RNA is a major substrate of the obesity-associated FTO. *Nat Chem Biol.* 2011;7(12):885–887. <https://doi.org/10.1038/nchembio.687>
- Jia, G., Yang, C.-G., Yang, S., Jian, X., Yi, C., Zhou, Z., et al. Oxidative demethylation of 3-methylthymine and 3-methyluracil in single-stranded DNA and RNA by mouse and human FTO. *FEBS Lett.* 2008;582(23–24):3313–3319.
<https://doi.org/10.1016/j.febslet.2008.08.019>
- Jonker, N.C., Glashouwer, K.A., Ostafin, B.D., van Hemel-Ruiter, M.E., Smink, F.R.E., Hoek, H.W., et al. Attentional Bias for Reward and Punishment in Overweight and Obesity: The TRAILS Study. *PLoS One.* 2016;11(7):e0157573.
<https://doi.org/10.1371/journal.pone.0157573>
- Jonker, N.C., Ostafin, B.D., Glashouwer, K.A., van Hemel-Ruiter, M.E., de Jong, P.J. Reward and punishment sensitivity and alcohol use: The moderating role of executive control. *Addict Behav.* 2014;39(5):945–948.
<https://doi.org/10.1016/j.addbeh.2013.12.011>
- Jonker, N.C., van Malderen, E., Glashouwer, K.A., Vervoort, L., Braet, C., Goossens, L., et al. No Differential Reward Responsivity and Drive, Punishment Sensitivity or Attention for Cues Signaling Reward or Punishment in Adolescents With Obesity. *Front Psychol.* 2019;10:2353. <https://doi.org/10.3389/fpsyg.2019.02363>
- Kaga, T., Inui, A., Okita, M., Asakawa, A., Ueno, N., Kasuga, M., et al. Modest Overexpression of Neuropeptide Y in the Brain Leads to Obesity After High-Sucrose Feeding. *Diabetes.* 2001;50(6):1206–1210.
<https://doi.org/10.2337/diabetes.50.5.1206>
- Kahn, S.E., Hull, R.L., Utzschneider, K.M. Mechanisms linking obesity to insulin resistance and type 2 diabetes. *Nature.* 2006;444(7121):840–846.
<https://doi.org/10.1038/nature05482>
- Kallio, J., Pesonen, U., Kaipio, K., Karvonen, M.K., Jaakkola, U., Heinonen, O.J., et al. Altered intracellular processing and release of neuropeptide Y due to leucine 7 to proline 7 polymorphism in the signal peptide of preproneuropeptide Y in humans. *FASEB J.* 2001;15(7):1242–1244. <https://doi.org/10.1096/fj.00-0436fje>
- Karra, E., O'Daly, O.G., Choudhury, A.I., Yousseif, A., Millership, S., Neary, M.T., et al. A link between FTO, ghrelin, and impaired brain food-cue responsivity. *J Clin Invest.* 2013;123(8):3539–3551. <https://doi.org/10.1172/JCI44403>
- Karvonen, M.K., Ruottinen, S., Koulu, M., Pesonen, U., Niinikoski, H., Rask-Nissilä, L., et al. Nutrient intake, weight, and Leu7Pro polymorphism in prepro-neuropeptide Y in children. *J Clin Endocrinol Metab.* 2006;91(11):4664–4668.
<https://doi.org/10.1210/jc.2005-2083>
- Keyes, K.M., Nicholson, R., Kinley, J., Raposo, S., Stein, M.B., Goldner, E.M., et al. Age, Period, and Cohort Effects in Psychological Distress in the United States and Canada. *Am J Epidemiol.* 2014;179(10):1216–1227.
<https://doi.org/10.1093/aje/kwu029>
- Keyes, K.M., Utz, R.L., Robinson, W., Li, G. What is a cohort effect? Comparison of three statistical methods for modeling cohort effects in obesity prevalence in the United States, 1971–2006. *Soc Sci Med.* 2010;70(7):1100–1108.
<https://doi.org/10.1016/j.socscimed.2009.12.018>

- Kiive, E., Kanarik, M., Veidebaum, T., Harro, J. Neuropeptide Y gene variants and Agreeableness: interaction effect with the birth cohort and the serotonin transporter promoter polymorphism. *Acta Neuropsychiatr.* 2023;35(3):155–162. <https://doi.org/10.1017/neu.2023.23>
- Kiive, E., Katus, U., Eensoo, D., Villa, I., Mäestu, J., Veidebaum, T., et al. Parsing reward sensitivity reveals distinct relationships with energy intake, metabolic markers, physical activity and fitness. *Acta Neuropsychiatr.* 2025;37:e8. <https://doi.org/10.1017/neu.2024.63>
- Kilpeläinen, T.O., Qi, L., Brage, S., Sharp, S.J., Sonestedt, E., Demerath, E. Physical activity attenuates the influence of FTO variants on obesity risk: a meta-analysis of 218,166 adults and 19,268 children. *PLoS Med.* 2011;8(11):e1001116. <https://doi.org/10.1371/journal.pmed.1001116>
- Klasson-Heggebø, L., Andersen, L.B., Wennlöf, A.H., Sardinha, L.B., Harro, M., Froberg, K., et al. Graded associations between cardiorespiratory fitness, fatness, and blood pressure in children and adolescents. *Br J Sports Med.* 2006;40(1):25–29. <https://doi.org/10.1136/bjsm.2004.016113>
- Kuivjõgi, K., Liebert, T., Mitt, K., Saava, M., Teesalu, S. Eesti toitumissoovitusud. Tallinn: Sotsiaallabi Arenduskeskus; 1995.
- Kulberg, K. Relationships Between Genetic and Lifestyle Factors and Weight in the Estonian Biobank [Bachelor's thesis]. 2024.
- Lan, N., Lu, Y., Zhang, Y., Pu, S., Xi, H., Nie, X., et al. FTO—A Common Genetic Basis for Obesity and Cancer. *Front Genet.* 2020;11:559138. <https://doi.org/10.3389/fgene.2020.559138>
- Lean, M.E.J., Malkova, D. Altered gut and adipose tissue hormones in overweight and obese individuals: cause or consequence? *Int J Obes.* 2016;40(4):622–632. <https://doi.org/10.1038/ijo.2015.220>
- Lee, B.Y., Bartsch, S.M., Mui, Y., Haidari, L.A., Spiker, M.L., Gittelsohn, J. A systems approach to obesity. *Nutr Rev.* 2017;75(Suppl 1):94–106. <https://doi.org/10.1093/nutrit/nuw049>
- Leibowitz, S.F., Hammer, N.J., Chang, K. Hypothalamic paraventricular nucleus lesions produce overeating and obesity in the rat. *Physiol Behav.* 1981;27(6):1031–1040. [https://doi.org/10.1016/0031-9384\(81\)90366-8](https://doi.org/10.1016/0031-9384(81)90366-8)
- Li, M.M., Madara, J.C., Steger, J.S., Krashes, M.J., Balthasar, N., Campbell, J.N., et al. The Paraventricular Hypothalamus Regulates Satiety and Prevents Obesity via Two Genetically Distinct Circuits. *Neuron.* 2019;102(3):653–667.e6. <https://doi.org/10.1016/j.neuron.2019.02.028>
- Li, T., Yu, L., Yang, Z., Shen, P., Lin, H., Shui, L., et al. Associations of Diet Quality and Heavy Metals with Obesity in Adults: A Cross-Sectional Study from National Health and Nutrition Examination Survey (NHANES). *Nutrients.* 2022;14(19):4038. <https://doi.org/10.3390/nu14194038>
- Livingstone, K.M., Celis-Morales, C., Lara, J., Ashor, A.W., Lovegrove, J.A., Martinez, J.A., et al. Associations between FTO genotype and total energy and macronutrient intake in adults: a systematic review and meta-analysis. *Obes Rev.* 2015;16(8):666–678. <https://doi.org/10.1111/obr.12290>
- Locke, A.E., Kahali, B., Berndt, S.I., Justice, A.E., Pers, T.H., Day, F.R., et al. Genetic studies of body mass index yield new insights for obesity biology. *Nature.* 2015;518(7538):197–206. <https://doi.org/10.1038/nature14177>
- Loos, R.J.F., Yeo, G.S.H. The genetics of obesity: from discovery to biology. *Nat Rev Genet.* 2022;23(2):120–133. <https://doi.org/10.1038/s41576-021-00414-z>

- Lovasi, G.S., Schwartz-Soicher, O., Quinn, J.W., Berger, D.K., Neckerman, K.M., Jaslow, R., et al. Neighborhood safety and green space as predictors of obesity among preschool children from low-income families in New York City. *Prev Med.* 2013;57(3):189–193. <https://doi.org/10.1016/j.ypmed.2013.05.012>
- Loxton, N.J., Tipman, R.J. Reward sensitivity and food addiction in women. *Appetite.* 2017;115:28–35. <https://doi.org/10.1016/j.appet.2016.10.022>
- Lv, P., Feng, S., Xing, S. Efficacy of four exercise modalities on body composition in overweight and obese university students: a network meta-analysis of randomized controlled trials. *PeerJ.* 2026;14:e21418. <https://doi.org/10.7717/peerj.21418>
- Lätt, E., Jürimäe, J., Harro, J., Loit, H.-M., Mäestu, J. Low fitness is associated with metabolic risk independently of central adiposity in a cohort of 18-year-olds. *Scand J Med Sci Sports.* 2018;28(3):1084–1091. <https://doi.org/10.1111/sms.13002>
- Mansur, R.B., Brietzke, E., McIntyre, R.S. Is there a “metabolic-mood syndrome”? A review of the relationship between obesity and mood disorders. *Neurosci Biobehav Rev.* 2015;52:89–104. <https://doi.org/10.1016/j.neubiorev.2014.12.017>
- Matthews, D.R., Hosker, J.P., Rudenski, A.S., Naylor, B.A., Treacher, D.F., Turner, R.C. Homeostasis model assessment: insulin resistance and β -cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia.* 1985;28(7):412–419. <https://doi.org/10.1007/BF00280883>
- McLaren, L. Socioeconomic status and obesity. *Epidemiol Rev.* 2007;29:29–48. <https://doi.org/10.1093/epirev/mxm001>
- Merchán-Clavellino, A., Salguero-Alcañiz, M.P., Guil, R., Alameda-Bailén, J.R. Impulsivity, Emotional Intelligence, and Alcohol Consumption in Young People: A Mediation Analysis. *Foods.* 2020;9(1):71. <https://doi.org/10.3390/foods9010071>
- Michaud, J.L., Boucher, F., Melnyk, A., Gauthier, F., Goshu, E., Lévy, E., et al. Sim1 haploinsufficiency causes hyperphagia, obesity and reduction of the paraventricular nucleus of the hypothalamus. *Hum Mol Genet.* 2001;10(14):1465–1473. <https://doi.org/10.1093/hmg/10.14.1465>
- Mickey, B.J., Zhou, Z., Heitzeg, M.M., Heinz, E., Hodgkinson, C.A., Hsu, D.T., et al. Emotion processing, major depression, and functional genetic variation of neuropeptide Y. *Arch Gen Psychiatry.* 2011;68(2):158–166. <https://doi.org/10.1001/archgenpsychiatry.2010.197>
- Mitchell, G.C., Wang, Q., Ramamoorthy, P., Whim, M.D. A common single nucleotide polymorphism alters the synthesis and secretion of neuropeptide Y. *J Neurosci.* 2008;28(53):14428–14434. <https://doi.org/10.1523/jneurosci.0343-08.2008>
- Mitchell, P.J., Timmons, P.M., Hébert, J.M., Rigby, P.W.J., Tjian, R. Transcription factor AP-2 is expressed in neural crest cell lineages during mouse embryogenesis. *Genes Dev.* 1991;5(1):105–119. <https://doi.org/10.1101/gad.5.1.105>
- Mohammed, S.H., Habtewold, T.D., Birhanu, M.M., Sissay, T.A., Tegegne, B.S., Abuzerr, S., et al. Neighbourhood socioeconomic status and overweight/obesity: a systematic review and meta-analysis of epidemiological studies. *BMJ Open.* 2019;9(11):e028238. <https://doi.org/10.1136/bmjopen-2018-028238>
- Moon, K., Krems, C., Heuer, T., Hoffmann, I. Association between body mass index and macronutrients differs along the body mass index range of German adults: results from the German National Nutrition Survey II. *J Nutr Sci.* 2021;10:e8. <https://doi.org/10.1017/jns.2020.60>
- National Institute for Health Development. WHO Childhood Obesity Surveillance Initiative (COSI). Estonian Study Report for the Academic Year 2021/2022. Tallinn: National Institute for Health Development; 2023.

- National Institute for Health Development. Population Health Yearbook 2025. Estonian Population Health and Its Determinants. Tallinn: National Institute for Health Development.
- Naudé, C.E., Brand, A., Schoonees, A., Nguyen, K.A., Chaplin, M., Volmink, J. Low-carbohydrate versus balanced-carbohydrate diets for reducing weight and cardiovascular risk. *Cochrane Database Syst Rev.* 2022;1:CD013334.
<https://doi.org/10.1002/14651858.CD013334.pub2>
- Nelson, M.C., Gordon-Larsen, P., North, K.E., Adair, L.S. Body mass index gain, fast food, and physical activity: effects of shared environments over time. *Obesity.* 2006; 14(4):701–709. <https://doi.org/10.1038/oby.2006.80>
- Nguyen, A.D., Mitchell, N.F., Lin, S., Macia, L., Yulyaningsih, E., Baldock, P.A., et al. Y1 and Y5 receptors are both required for the regulation of food intake and energy homeostasis in mice. *PLoS One.* 2012;7(6):e40191.
<https://doi.org/10.1371/journal.pone.0040191>
- Nordquist, N., Göktürk, C., Comasco, E., Eensoo, D., Merenäkk, L., Veidebaum, T., et al. The transcription factor TFAP2B is associated with insulin resistance and adiposity in healthy adolescents. *Obesity.* 2009;17(9):1762–1767.
<https://doi.org/10.1038/oby.2009.83>
- Obradovic, M., Sudar-Milovanovic, E., Soskic, S., Essack, M., Arya, S., Stewart, A.J., et al. Leptin and Obesity: Role and Clinical Implication. *Front Endocrinol.* 2021;12: 585887. <https://doi.org/10.3389/fendo.2021.585887>
- Olza, J., Gil-Campos, M., Leis, R., Rupérez, A.I., Tojo, R., Cañete, R., et al. Influence of variants in the NPY gene on obesity and metabolic syndrome features in Spanish children. *Peptides.* 2013;45:22–27. <https://doi.org/10.1016/j.peptides.2013.04.007>
- Pabst, A., Kraus, L., Piontek, D., Mueller, S. Age, Period, and Cohort Effects on Time Trends in Alcohol Consumption in the German Adult Population. *Sucht.* 2010;56(5): 349–359. <https://doi.org/10.1024/0939-5911/a000046>
- Pan, X., Zhao, L., Luo, J., Li, Y., Zhang, L., Wu, T., et al. Access to bike lanes and childhood obesity: A systematic review and meta-analysis. *Obes Rev.* 2021;22(Suppl 1):e13042. <https://doi.org/10.1111/obr.13042>
- Peters, T., Ausmeier, K., Rüther, U. Cloning of Fatso (Fto), a novel gene deleted by the Fused toes (Ft) mouse mutation. *Mamm Genome.* 1999;10(10):983–986.
<https://doi.org/10.1007/s003359901144>
- Piksööt, J., Oja, L. Health Behaviour in School-aged Children (HBSC). Estonian Results for the Academic Year 2021/2022. Tallinn: National Institute for Health Development; 2023.
- Pimpin, L., Jebb, S., Johnson, L., Wardle, J., Ambrosini, G.L. Dietary protein intake is associated with body mass index and weight up to 5 y of age in a prospective cohort of twins. *Am J Clin Nutr.* 2016;103(2):389–397.
<https://doi.org/10.3945/ajcn.115.118612>
- Pimpin, L., Jebb, S.A., Johnson, L., Llewellyn, C., Ambrosini, G.L. Sources and pattern of protein intake and risk of overweight or obesity in young UK twins. *Br J Nutr.* 2018;120(7):820–829. <https://doi.org/10.1017/s0007114518002052>
- Pitsi, T., Lauk, J., Nurk, E., Priinits, M., Zilmer, M., Ehala-Aleksejev, K., et al. Eesti riiklikud toitumise, liikumise ja uneaja soovitused. Tabelraamat. Tallinn: Tervise Arengu Instituut; 2025.
- Pitsi, T., Zilmer, M., Vaask, S., Ehala-Aleksejev, K., Kuu, S., Lõhmus, K., et al. Eesti toitumis- ja liikumissoovitused 2015. Tallinn: Tervise Arengu Instituut; 2017.

- Pojednic, R., D'Arpino, E., Halliday, I., Bantham, A. The Benefits of Physical Activity for People with Obesity, Independent of Weight Loss: A Systematic Review. *Int J Environ Res Public Health*. 2022;19(9):4981. <https://doi.org/10.3390/ijerph19094981>
- Poosri, S., Boonyuen, U., Chupeerach, C., Soonthornworasiri, N., Kwanbunjan, K., Prangthip, P. Association of FTO variants rs9939609 and rs1421085 with elevated sugar and fat consumption in adult obesity. *Sci Rep*. 2024;14(1):25618. <https://doi.org/10.1038/s41598-024-77004-6>
- Poulain, T., Sobek, C., Ludwig, J., Igel, U., Grande, G., Ott, V., et al. Associations of Green Spaces and Streets in the Living Environment with Outdoor Activity, Media Use, Overweight/Obesity and Emotional Wellbeing in Children and Adolescents. *Int J Environ Res Public Health*. 2020;17(14):5136. <https://doi.org/10.3390/ijerph17176321>
- Price, R.A., Li, W.-D., Zhao, H. FTO gene SNPs associated with extreme obesity in cases, controls and extremely discordant sister pairs. *BMC Med Genet*. 2008;9:4. <https://doi.org/10.1186/1471-2350-9-4>
- Pulver, A., Kiive, E., Harro, J. Reward sensitivity, affective neuroscience personality, symptoms of attention-deficit/hyperactivity disorder, and TPH2-703G/T (rs4570625) genotype. *Acta Neuropsychiatr*. 2020;32(5):247–256. <https://doi.org/10.1017/neu.2020.18>
- Raap, M., Gierendt, L., Kreipe, H.H., Christgen, M. Transcription factor AP-2 β in development, differentiation and tumorigenesis. *Int J Cancer*. 2021;149(6):1221–1237. <https://doi.org/10.1002/ijc.33558>
- Raatz, S.K., Conrad, Z., Johnson, L.K., Picklo, M.J., Jahns, L. Relationship of the Reported Intakes of Fat and Fatty Acids to Body Weight in US Adults. *Nutrients*. 2017;9(5):438. <https://doi.org/10.3390/nu9050438>
- Raghuveer, G., Hartz, J., Lubans, D.R., Takken, T., Wiltz, J.L., Mietus-Snyder, M., et al. Cardiorespiratory Fitness in Youth: An Important Marker of Health: A Scientific Statement From the American Heart Association. *Circulation*. 2020;142(7):e101–e118. <https://doi.org/10.1161/cir.0000000000000866>
- Reile, R., Põlajev, A., Saavaste, J. Estonia Health Behavior Among the Adult Population Survey 2024. Tallinn: National Institute for Health Development; 2025.
- Rimfeld, K., Krapohl, E., Trzaskowski, M., Coleman, J.R.I., Selzam, S., Dale, P.S., et al. Genetic influence on social outcomes during and after the Soviet era in Estonia. *Nat Hum Behav*. 2018;2(4):269–275. <https://doi.org/10.1038/s41562-018-0332-5>
- Robinson, M.R., English, G., Moser, G., Lloyd-Jones, L.R., Triplett, M.A., Zhu, Z., et al. Genotype-covariate interaction effects and the heritability of adult body mass index. *Nat Genet*. 2017;49(8):1174–1181. <https://doi.org/10.1038/ng.3912>
- Robinson, W.R., Utz, R.L., Keyes, K.M., Martin, C.L., Yang, Y. Birth cohort effects on abdominal obesity in the United States: the Silent Generation, Baby Boomers and Generation X. *Int J Obes*. 2013;37(8):1129–1134. <https://doi.org/10.1038/ijo.2012.198>
- Romieu, I., Dossus, L., Barquera, S., Blotti re, H.M., Franks, P.W., Gunter, M., et al. Energy balance and obesity: what are the main drivers? *Cancer Causes Control*. 2017;28(3):247–258. <https://doi.org/10.1007/s10552-017-0869-z>
- Rosenquist, J.N., Lehrer, S.F., O'Malley, A.J., Zaslavsky, A.M., Smoller, J.W., Christakis, N.A. Cohort of birth modifies the association between FTO genotype and BMI. *Proc Natl Acad Sci U S A*. 2015;112(2):354–359. <https://doi.org/10.1073/pnas.1411893111>

- Rubino, F., Cummings, D.E., Eckel, R.H., Cohen, R.V., Wilding, J.P.H., Brown, W.A., et al. Definition and diagnostic criteria of clinical obesity. *Lancet Diabetes Endocrinol.* 2025;13(3):221–262. [https://doi.org/10.1016/s2213-8587\(24\)00316-4](https://doi.org/10.1016/s2213-8587(24)00316-4)
- Sallis, J.F., Conway, T.L., Cain, K.L., Carlson, J.A., Frank, L.D., Kerr, J., et al. Neighborhood built environment and socioeconomic status in relation to physical activity, sedentary behavior, and weight status of adolescents. *Prev Med.* 2018;110:47–54. <https://doi.org/10.1016/j.ypmed.2018.02.009>
- Sallis, J.F., Slymen, D.J., Conway, T.L., Frank, L.D., Saelens, B.E., Cain, K., et al. Income disparities in perceived neighborhood built and social environment attributes. *Health Place.* 2011;17(6):1274–1283. <https://doi.org/10.1016/j.healthplace.2011.02.006>
- Salm, E., Käärik, E., Kaarma, H. The growth charts of Estonian schoolchildren. Comparative analysis. *Papers on Anthropology.* 2013; 22. <https://doi.org/10.12697/poa.2013.22.19>
- Sartorius, K., Sartorius, B., Madiba, T.E., Stefan, C. Does high-carbohydrate intake lead to increased risk of obesity? A systematic review and meta-analysis. *BMJ Open.* 2018; 8(2):e018449. <https://doi.org/10.1136/bmjopen-2017-018449>
- Savva, S.C., Lamnisos, D., Kafatos, A.G. Predicting cardiometabolic risk: waist-to-height ratio or BMI? A meta-analysis. *Diabetes Metab Syndr Obes.* 2013;6:403–419. <https://doi.org/10.2147/DMSO.S34220>
- Schlesinger, S., Neuenschwander, M., Schwedhelm, C., Hoffmann, G., Bechthold, A., Boeing, H., et al. Food Groups and Risk of Overweight, Obesity, and Weight Gain: A Systematic Review and Dose-Response Meta-Analysis of Prospective Studies. *Adv Nutr.* 2019;10(2):205–218. <https://doi.org/10.1093/advances/nmy092>
- Schneider, S., Gruber, J. Neighbourhood deprivation and outlet density for tobacco, alcohol and fast food: first hints of obesogenic and addictive environments in Germany. *Public Health Nutr.* 2013;16(7):1168–1177. <https://doi.org/10.1017/s1368980012003321>
- Schramm, S., Sørensen, T.I.A., Davidsen, M., Tolstrup, J.S. Changes in adult obesity prevalence in Denmark, 1987–2021: age–period–cohort analysis of nationally representative data. *Eur J Public Health.* 2023;33(3):463–467. <https://doi.org/10.1093/eurpub/ckad024>
- Scuteri, A., Sanna, S., Chen, W.-M., Uda, M., Albai, G., Strait, J., et al. Genome-Wide Association Scan Shows Genetic Variants in the FTO Gene Are Associated with Obesity-Related Traits. *PLoS Genet.* 2007;3(7):e115. <https://doi.org/10.1371/journal.pgen.0030115>
- Shah, S.H., Freedman, N.J., Zhang, L., Crosslin, D.R., Stone, D.H., Haynes, C., et al. Neuropeptide Y Gene Polymorphisms Confer Risk of Early-Onset Atherosclerosis. *PLoS Genet.* 2009;5(1):e1000318. <https://doi.org/10.1371/journal.pgen.1000318>
- Shimizu, N., Oomura, Y., Plata-Salamán, C.R., Morimoto, M. Hyperphagia and obesity in rats with bilateral ibotenic acid-induced lesions of the ventromedial hypothalamic nucleus. *Brain Res.* 1987;416(1):153–156. [https://doi.org/10.1016/0006-8993\(87\)91508-3](https://doi.org/10.1016/0006-8993(87)91508-3)
- Shrewsbury, V., Wardle, J. Socioeconomic status and adiposity in childhood: a systematic review of cross-sectional studies 1990–2005. *Obesity.* 2008;16(2):275–284. <https://doi.org/10.1038/oby.2007.35>
- Sianturi, Y., Pardamean, G., Muzasti, R. Role of neuropeptide Y gene rs16147 polymorphism as a risk factor for hypertension [poster presentation]. *J Hypertens.* 2022; 40(Suppl 2):pe4.

- Smillie, L.D., Pickering, A.D., Jackson, C.J. The new reinforcement sensitivity theory: implications for personality measurement. *Pers Soc Psychol Rev.* 2006;10(4):320–335. https://doi.org/10.1207/s15327957pspr1004_3
- Song, S., Wei, Y., Zhang, H., Soundy, A. Effects of different exercise interventions on body composition in women with overweight and obesity: a systematic review and network meta-analysis. *BMJ Open.* 2026;16(6):e113206. <https://doi.org/10.1136/bmjopen-2025-113206>
- Stanley, B.G., Kyrkouli, S.E., Lampert, S., Leibowitz, S.F. Neuropeptide Y chronically injected into the hypothalamus: a powerful neurochemical inducer of hyperphagia and obesity. *Peptides.* 1986;7(6):1189–1192. [https://doi.org/10.1016/0196-9781\(86\)90149-x](https://doi.org/10.1016/0196-9781(86)90149-x)
- Stunkard, A., d'Aquili, E., Fox, S., Filion, R.D. Influence of social class on obesity and thinness in children. *JAMA.* 1972;221(6):579–584. <https://doi.org/10.1001/jama.221.6.579>
- Stutzmann, F., Cauchi, S., Durand, E., Calvacanti-Proença, C., Pigeyre, M., Hartikainen, A.-L., et al. Common genetic variation near MC4R is associated with eating behaviour patterns in European populations. *Int J Obes.* 2009;33(3):373–378. <https://doi.org/10.1038/ijo.2008.279>
- Swinburn, B.A., Sacks, G., Hall, K.D., McPherson, K., Finegood, D.T., Moodie, M.L., et al. The global obesity pandemic: shaped by global drivers and local environments. *Lancet.* 2011;378(9793):804–814. [https://doi.org/10.1016/S0140-6736\(11\)60813-1](https://doi.org/10.1016/S0140-6736(11)60813-1)
- Tan, C.M.J., Green, P., Tapoulal, N., Lewandowski, A.J., Leeson, P., Herring, N. The Role of Neuropeptide Y in Cardiovascular Health and Disease. *Front Physiol.* 2018; 9:1281. <https://doi.org/10.3389/fphys.2018.01281>
- Tao, Y., Maegawa, H., Ugi, S., Ikeda, K., Nagai, Y., Egawa, K., et al. The transcription factor AP-2 β causes cell enlargement and insulin resistance in 3T3-L1 adipocytes. *Endocrinology.* 2006;147(4):1685–1696. <https://doi.org/10.1210/en.2005-1304>
- Tatemoto, K., Carlquist, M., Mutt, V. Neuropeptide Y: A novel brain peptide with structural similarities to peptide YY and pancreatic polypeptide. *Nature.* 1982;296(5858): 659–660. <https://doi.org/10.1038/296659a0>
- Tatnell, D.G., Loxton, N.J., Modecki, K.L., Hamilton, K. Testing a model of reward sensitivity, implicit and explicit drinker identity and hazardous drinking. *Psychol Health.* 2019;34(12):1407–1420. <https://doi.org/10.1080/08870446.2019.1606221>
- Thaker, V.V. Genetic and Epigenetic Causes of Obesity. *Adolesc Med State Art Rev.* 2017;28(2):379–405.
- Thomas, D.M., Bredlau, C., Bosy-Westphal, A., Mueller, M., Shen, W., Gallagher, D., et al. Relationships between body roundness with body fat and visceral adipose tissue emerging from a new geometrical model. *Obesity.* 2013;21(11):2264–71. <https://doi.org/10.1002/oby.20408>
- Thomas, F., Thomas, C., Hooper, L., Rosenberg, G., Vohra, J., Bauld, L. Area deprivation, screen time and consumption of food and drink high in fat, salt and sugar (HFSS) in young people: results from a cross-sectional study in the UK. *BMJ Open.* 2019;9(5):e027333. <https://doi.org/10.1136/bmjopen-2018-027333>
- Timper, K., Brüning, J.C. Hypothalamic circuits regulating appetite and energy homeostasis: pathways to obesity. *Dis Model Mech.* 2017;10(6):679–689. <https://doi.org/10.1242/dmm.026609>
- Tsukada, S., Tanaka, Y., Maegawa, H., Kashiwagi, A., Kawamori, R., Maeda, S. Intronic polymorphisms within TFAP2B regulate transcriptional activity and affect adipo-

- cytokine gene expression in differentiated adipocytes. *Mol Endocrinol.* 2006;20(5): 1104–1111. <https://doi.org/10.1210/me.2005-0311>
- Tuck, M.T., Wiehl, P.E., Pan, T. Inhibition of 6-methyladenine formation decreases the translation efficiency of dihydrofolate reductase transcripts. *Int J Biochem Cell Biol.* 1999;31(8):837–851. [https://doi.org/10.1016/s1357-2725\(99\)00041-2](https://doi.org/10.1016/s1357-2725(99)00041-2)
- Vaask, S., Liebert, T., Maser, M., Pappel, K., Pitsi, T., Saava, M., et al. Eesti toitumis- ja toidusoovitused. Tallinn: Tervise Arengu Instituut; 2006.
- Vaht, M., Merenäkk, L., Mäestu, J., Veidebaum, T., Harro, J. Serotonin transporter gene promoter polymorphism (5-HTTLPR) and alcohol use in general population: interaction effect with birth cohort. *Psychopharmacology.* 2014;231(12):2587–2594. <https://doi.org/10.1007/s00213-013-3427-8>
- van Baak, M.A., Pramono, A., Battista, F., Beaulieu, K., Blundell, J.E., Busetto, L., et al. Effect of different types of regular exercise on physical fitness in adults with overweight or obesity: Systematic review and meta-analyses. *Obes Rev.* 2021;22(Suppl 4):e13239. <https://doi.org/10.1111/obr.13239>
- van Rossum, C.T.M., Pijl, H., Adan, R.A.H., Hoebee, B., Seidell, J.C. Polymorphisms in the NPY and AGRP genes and body fatness in Dutch adults. *Int J Obes.* 2006; 30(10):1522–1528. <https://doi.org/10.1038/sj.ijo.0803314>
- Villalobos-Comparán, M., Flores-Dorantes, M.T., Villarreal-Molina, M.T., Rodríguez-Cruz, M., García-Ulloa, A.C., Robles, L., et al. The FTO gene is associated with adulthood obesity in the Mexican population. *Obesity.* 2008;16(10):2296–2301. <https://doi.org/10.1038/oby.2008.367>
- Virtanen, S., Kaprio, J., Viken, R., Rose, R.J., Latvala, A. Birth cohort effects on the quantity and heritability of alcohol consumption in adulthood: a Finnish longitudinal twin study. *Addiction.* 2019;114(5):836–846. <https://doi.org/10.1111/add.14533>
- Visscher, P.M., Wray, N.R., Zhang, Q., Sklar, P., McCarthy, M.I., Brown, M.A., et al. 10 Years of GWAS Discovery: Biology, Function, and Translation. *Am J Hum Genet.* 2017;101(1):5–22. <https://doi.org/10.1016/j.ajhg.2017.06.005>
- Volkow, N.D., Wang, G.-J., Baler, R.D. Reward, dopamine and the control of food intake: implications for obesity. *Trends Cogn Sci.* 2011;15(1):37–46. <https://doi.org/10.1016/j.tics.2010.11.001>
- Wang, L., Wang, H., Zhang, B., Popkin, B.M., Du, S. Elevated Fat Intake Increases Body Weight and the Risk of Overweight and Obesity among Chinese Adults: 1991–2015 Trends. *Nutrients.* 2020;12(11):3272. <https://doi.org/10.3390/nu12113272>
- Wang, M.C., Kim, S., Gonzalez, A.A., MacLeod, K.E., Winkleby, M.A. Socioeconomic and food-related physical characteristics of the neighbourhood environment are associated with body mass index. *J Epidemiol Community Health.* 2007;61(6):491–498. <https://doi.org/10.1136/jech.2006.051680>
- Wang, X., Zhu, L., Chen, J., Wang, Y. mRNA m⁶A methylation down-regulates adipogenesis in porcine adipocytes. *Biochem Biophys Res Commun.* 2015; 459(2):201–207. <https://doi.org/10.1016/j.bbrc.2015.02.048>
- Wardle, J., Llewellyn, C., Sanderson, S., Plomin, R. The FTO gene and measured food intake in children. *Int J Obes.* 2009;33(1):42–45. <https://doi.org/10.1038/ijo.2008.174>
- Wei, J., Liu, F., Lu, Z., Fei, Q., Ai, Y., He, P.C., et al. Differential m⁶A, m⁶A_m, and m¹A Demethylation Mediated by FTO in the Cell Nucleus and Cytoplasm. *Mol Cell.* 2018;71(6):973–985.e5. <https://doi.org/10.1016/j.molcel.2018.08.011>
- Woolcott, O.O., Bergman, R.N. Relative fat mass (RFM) as a new estimator of whole-body fat percentage – A cross-sectional study in American adult individuals. *Sci Rep.* 2018;8(1):10980. <https://doi.org/10.1038/s41598-018-29362-1>

- World Health Organization. Obesity: Preventing and Managing the Global Epidemic. Report of a WHO Consultation. World Health Organ Tech Rep Ser. 2000;894:i–xii, 1–253.
- World Health Organization. Waist Circumference and Waist-Hip Ratio: Report of a WHO Expert Consultation. Geneva: World Health Organization; 2008.
- World Health Organization. WHO Child Growth Standards: Growth Velocity Based on Weight, Length and Head Circumference: Methods and Development. Geneva: World Health Organization; 2009.
- World Health Organization. Physical Activity: Fact Sheet. Geneva: World Health Organization; 2020a.
- World Health Organization. WHO Guidelines on Physical Activity and Sedentary Behaviour. Geneva: World Health Organization; 2020b.
- World Health Organization. Noncommunicable Diseases Progress Monitor 2025. Geneva: World Health Organization; 2025.
- Wu, R., Liu, Y., Yao, Y., Zhao, Y., Bi, Z., Jiang, Q., et al. FTO regulates adipogenesis by controlling cell cycle progression via m⁶A-YTHDF2-dependent mechanism. *Biochim Biophys Acta Mol Cell Biol Lipids*. 2018;1863(10):1323–1330. <https://doi.org/10.1016/j.bbalip.2018.08.008>
- Wu, R., Yao, Y., Jiang, Q., Cai, M., Liu, Q., Wang, Y., et al. Epigallocatechin gallate targets FTO and inhibits adipogenesis in an mRNA m⁶A-YTHDF2-dependent manner. *Int J Obes*. 2018;42(7):1378–1388. <https://doi.org/10.1038/s41366-018-0082-5>
- Yengo, L., Sidorenko, J., Kemper, K.E., Zheng, Z., Wood, A.R., Weedon, M.N., 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):3641–3649. <https://doi.org/10.1093/hmg/ddy271>
- Yeung, E.H., Zhang, C., Chen, J., Bowers, K., Hu, F.B., Kang, G., et al. Polymorphisms in the neuropeptide Y gene and the risk of obesity: findings from two prospective cohorts. *J Clin Endocrinol Metab*. 2011;96(12):E2055–E2062. <https://doi.org/10.1210/jc.2011-0195>
- Yoo, C. The Birth Cohorts Difference in Depression. *Child Indic Res*. 2023;16(3):997–1017. <https://doi.org/10.1007/s12187-022-09985-7>
- Yoo, C., Chung, I.-J. A Comparative Study of Cohorts for Children's Body Mass Index Changes. *Soc Work Public Health*. 2020;35(4):213–222. <https://doi.org/10.1080/19371918.2020.1768196>
- Yu, J.H., Kim, M.-S. Molecular mechanisms of appetite regulation. *Diabetes Metab J*. 2012;36(6):391–398. <https://doi.org/10.4093/dmj.2012.36.6.391>
- Zain, S.M., Mohamed, Z., Jalaludin, M.Y., Fauzi, F., Hamidi, A., Zaharan, N.L. Comprehensive evaluation of the neuropeptide Y gene variants in the risk of obesity: a case-control study and meta-analysis. *Pharmacogenet Genomics*. 2015;25(10):501–510. <https://doi.org/10.1097/FPC.0000000000000164>
- Zhang, M., Zhang, Y., Ma, J., Guo, F., Cao, Q., Zhang, Y., et al. The Demethylase Activity of FTO (Fat Mass and Obesity Associated Protein) Is Required for Pre-adipocyte Differentiation. *PLoS One*. 2015;10(7):e0133788. <https://doi.org/10.1371/journal.pone.0133788>
- Zhang, X., Wei, L.-H., Wang, Y., Xiao, Y., Liu, J., Zhang, W., et al. Structural insights into FTO's catalytic mechanism for the demethylation of multiple RNA substrates. *Proc Natl Acad Sci U S A*. 2019;116(8):2919–2924. <https://doi.org/10.1073/pnas.1820574116>

- Zhao, X., Yang, Y., Sun, B.-F., Shi, Y., Yang, X., Xiao, W., et al. FTO-dependent demethylation of N⁶-methyladenosine regulates mRNA splicing and is required for adipogenesis. *Cell Res.* 2014;24(12):1403–1419. <https://doi.org/10.1038/cr.2014.151>
- Zhou, Z., Zhu, G., Hariri, A.R., Enoch, M.-A., Scott, D., Sinha, R., et al. Genetic variation in human NPY expression affects stress response and emotion. *Nature.* 2008; 452(7190):997–1001. <https://doi.org/10.1038/nature06858>

SUMMARY IN ESTONIAN

Geneetilised, käitumuslikud ja elukeskkonnast tulenevad tegurid ülekaalu, rasvumise ja insuliinresistentsuse väljakujunemisel

Mittenakkushaigused, nagu südame-veresoonkonnahaigused, vähk, diabeet ja kroonilised hingamisteede haigused, on ülemaailmselt peamised surmapõhjused. Mittenakkushaiguste riskitegurite hulka kuuluvad ebatervislik toitumine, vähene kehaline aktiivsus, alkoholi tarvitamine, tubaka- ja nikotiinitoodete tarvitamine, ülekaal ja rasvumine, kõrgeenenud vererõhk ning suurenenud vere kolesteroolisisaldus. Ülekaal ja rasvumine on olulised rahvatervise probleemid. 2021. aastal oli ligikaudu 2,1 miljardit täiskasvanut ülekaalulised või rasvunud. Samal aastal seostati ülekaaluga 3,7 miljonit surmajuhtu ja 129 miljonit tervisekaoga kohan-datud eluaastat.

Ülekaal ja rasvumine kujuneb kui energiatarbimine ja energiakulutamine ei ole tasakaalus. Ülekaalu ja rasvumise väljakujunemisse panustavad erinevad tegurid sh geneetilised-, bioloogilised-, psühholoogilised-, elukeskkonnast tulenevad-, sotsiaal-majanduslikud-, ja käitumuslikud tegurid.

Käesolevas doktoritöös analüüsisime valitud geneetiliste- (transkriptsiooni-faktor AP-2 beeta [*TFAP2B*], rasvamassi ja rasvumisega seotud geen [*FTO*] ning neuropeptiid Y [*NPY*]) ja psühhobioloogiliste tegurite (hüvehimulisus) seoseid ülekaalu ja rasvumise ning nendega seotud seisunditega (nt insuliinresistentsus), arvestades samaaegselt vanuse, soo, toitumise, kehalise aktiivsuse, sotsiaal-majandusliku staatuse ja sünnikohordi võimalikke koosmõjusid.

Uuringu valim moodustati algselt Euroopa Noorte Südameuuringu (ENSU) tarbeks 1998/1999 ning kaasati hiljem longituudsesse Eesti laste isiksuse, käitu-mise ja tervise uuringusse (ELIKTU). ENSU valimi moodustamise ühikuks olid koolid. Valimisse kaasati kõik Tartu maakonna koolid, kes nõustusid uuringus osalema (54 kooli 56-st), ning neist valiti 25 kooli (tõenäosusliku valimi põhi-mõttel). Uuringusse kutsuti valitud koolidest kõik 3. klassi (9-aastased) ja 9. klassi (15-aastased) õpilased; algses uuringus osales 79,1% kutsututest (vastavalt $n = 583$ ja $n = 593$). Noorema sünnikohordi järgmised uuringulained toimusid 2004. aastal (15-aastased, $n = 483$), 2007. aastal (18-aastased, $n = 454$), 2014. aastal (25-aastased, $n = 441$) ning 2022. aastal (33-aastased, $n = 428$). Vanema sünnikohordi järgmised uuringulained toimusid 2001. aastal (18-aastased, $n = 417$, lisaks kaasati 62 uut uuritavat), 2008. aastal (25-aastased, $n = 541$) ning 2016. aastal (33-aastased, $n = 504$).

TFAP2B geeni teises intronis paiknev VNTR-polümorfism oli seotud rasvu-mist, kõhupiirkonna rasvumist ja insuliinresistentsust peegeldavate näitajatega nii mees- kui ka naissoost uuritavatel. Seos ei olnud tingitud erinevusest toidu-energi tarbimises, mis viitab vajadusele käsitleda muid bioloogilisi mehha-nisme. *FTO* rs1421085 polümorfism oli seotud rasvumist peegeldavate näitaja-tega, kuid see seos ei olnud põhjendatav erinevusega toiduenergia tarbimises ja/või kehalises aktiivsuses. Naissoost uuritavatel ilmnis *FTO* rs1421085 geno-tüübi ja sotsiaal-majandusliku staatuse vaheline koostoime. *NPY* geenivariandid

olid seotud rasvumist peegeldavate näitajatega vanusest sõltuval moel. Kõik neli uuritud *NPY* üksiknukleotiidi polümorfismi olid seotud vererõhuga. Seos ei olnud põhjendatav erinevusega toiduenergi tarbimises ja/või füüsilises aktiivsuses. Tulevastes hüvehimulisust käsitlevates uuringutes tuleks arvesse võtta selle sisemist struktuuri. Meie tulemuste kohaselt olid rasvumist peegeldavad näitajad seotud hüvehimulisusega üksnes selle hüvedele küllastamatuse komponendi kaudu. Lisaks leidsime seose sünnikohordi, rasvumist peegeldavate näitajate ja ainevahetuse vahel. Seda seost selgitas vähemalt osaliselt suurem päevane toiduenergia tarbimine, eriti suurem süsivesikute osakaal päevasest toiduenergiast.

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APPENDICES

Supplementary table 1. The Reward Openness and Insatiability Scale (ROIS) by subscales, with original sources for related items (Pulver et al., 2020)

Openness to Reward scale		Original source
Excitement and Novelty subscale		
1.	Enjoys exciting adventures	AMIS
2.	Gets thrilled easily	IPIP
3.	Is fascinated by novelty	IPIP
4.	Is open to new things	IPIP
5.	Enjoys new experiences	ANPS
6.	Dislikes routine	IPIP
7.	Avoids dangerous activities	IPIP
Social experiences subscale		
8.	Is modest in socializing	IPIP
9.	Uneasy in social situations	IPIP
10.	Enjoys big parties	IPIP
11.	Is easily amused	ANPS
12.	Does not enjoy playing games with others	ANPS
13.	Is action-oriented	AMIS
14.	Does not enjoy joking around	ANPS
Insatiability by Reward scale		
Excessive spending subscale		
15.	Spends more than earns	BIS
16.	Has spending under control	IPIP
17.	Spends more than can afford	BIS
18.	Is saving oriented	BIS
19.	Does not spend extravagantly	IPIP
20.	Spends money pointlessly	AMIS
21.	Spends money on impulse	BIS
Giving in to cravings subscale		
22.	Succumbs to ones's cravings	AMIS
23.	Finds it difficult to set limits	IPIP
24.	Has strong self-control	IPIP
25.	Has insufficient control of appetite	AMIS
26.	Gets addicted easily	IPIP
27.	Is prone to overindulgence	IPIP
28.	Keeps cravings under control	BIS

AMIS, Adaptive and Maladaptive Impulsivity Scale; ANPS, Affective Neuroscience Personality Scale; BIS, Barratt Impulsivity Scale; IPIP, International Personality Item Pool NEO

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2. **Joost U**, Villa I, Comasco E, Orelund L, Veidebaum T, Harro J. Association between Transcription Factor AP-2B genotype, obesity, insulin resistance and dietary intake in a longitudinal birth cohort study. *Int J Obes*. 2019;43:2095–2106.
3. **Katus U**, Villa I, Ringmets I, Vaht M, Mäestu E, Mäestu J, Veidebaum T, Harro J. Association of FTO rs1421085 with obesity, diet, physical activity, and socioeconomic status: A longitudinal birth cohort study. *Nutr Metab Cardiovasc Dis*. 2020;30:948–959.
4. **Katus U**, Villa I, Ringmets I, Pulver A, Veidebaum T, Harro J. The role of reward sensitivity in obesity and its association with Transcription Factor AP-2B: A longitudinal birth cohort study. *Neurosci Lett*. 2020;735:135158.
5. **Katus U**, Villa I, Ringmets I, Veidebaum T, Harro J. Neuropeptide Y gene variants in obesity, dietary intake, blood pressure, lipid and glucose metabolism: A longitudinal birth cohort study. *Peptides*. 2021;139:170524.
6. Volke V, **Katus U**, Johannson A, Toompere K, Heinla K, Rünkorg K, Uusküla A. Systematic review and meta-analysis of head-to-head trials comparing sulfonylureas and low hypoglycaemic risk antidiabetic drugs. *BMC Endocr Disord*. 2022;22:251.
7. Sakala K, Kasearu K, **Katus U**, Veidebaum T, Harro J. Association between platelet MAO activity and lifetime drug use in a longitudinal birth cohort study. *Psychopharmacology*. 2022;239:327–337.
8. Sakala K, **Katus U**, Kiive E, Veidebaum T, Harro J. Is low platelet MAO activity associated with antisocial behavior? evidence from representative samples of longitudinally observed birth cohorts. *Brain Res*. 2023;1804:148249.
9. Reinap M, Nathan NL, Muscat NA, Laisaar KT, **Katus U**, Schünemann HJ. Strengthening guideline contextualization in the WHO European Region. *Bull World Health Organ*. 2024;102(10):715–721.
10. Tskhvarashvili G, Aher K, Sveide I, **Katus U**, Westerlund A, Hoti F, Wennerström C, Hassan F, Lee J, Hermanrud C, Johnsson I, Passey A, Nissinen R, Polesie S, Mätkönen T, Saarelainen L. Persistence of advanced systemic pharmacological treatment of moderate-to-severe psoriasis among bio-naïve patients-A retrospective register-based cohort study in Finland and Sweden. *J Eur Acad Dermatol Venereol*. 2025;39 Suppl 1(Suppl 1):50–64.
11. Kiive E, **Katus U**, Eensoo D, Villa I, Mäestu J, Veidebaum T, Harro J. Parsing reward sensitivity reveals distinct relationships with energy intake,

- metabolic markers, physical activity and fitness. *Acta Neuropsychiatr.* 2025; 37:e8.
12. **Katus U**, Villa I, Ringmets I, Eensoo D, Mäestu J, Veidebaum T, Harro J. Birth cohort effects on obesity, glucose metabolism, diet, and fitness: evidence from a longitudinal study. *Nutr Metab Cardiovasc Dis.* 2026;36(7): 104638.

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2. **Joost U**, Villa I, Comasco E, Orelund L, Veidebaum T, Harro J. Association between Transcription Factor AP-2B genotype, obesity, insulin resistance and dietary intake in a longitudinal birth cohort study. *Int J Obes*. 2019;43: 2095–2106.
3. **Katus U**, Villa I, Ringmets I, Vaht M, Mäestu E, Mäestu J, Veidebaum T, Harro J. Association of FTO rs1421085 with obesity, diet, physical activity, and socioeconomic status: A longitudinal birth cohort study. *Nutr Metab Cardiovasc Dis*. 2020;30:948–959.
4. **Katus U**, Villa I, Ringmets I, Pulver A, Veidebaum T, Harro J. The role of reward sensitivity in obesity and its association with Transcription Factor AP-2B: A longitudinal birth cohort study. *Neurosci Lett*. 2020;735:135158.
5. **Katus U**, Villa I, Ringmets I, Veidebaum T, Harro J. Neuropeptide Y gene variants in obesity, dietary intake, blood pressure, lipid and glucose metabolism: A longitudinal birth cohort study. *Peptides*. 2021;139:170524.
6. Volke V, **Katus U**, Johannson A, Toompere K, Heinla K, Rünkorg K, Uusküla A. Systematic review and meta-analysis of head-to-head trials comparing sulfonylureas and low hypoglycaemic risk antidiabetic drugs. *BMC Endocr Disord*. 2022;22:251.
7. Sakala K, Kasearu K, **Katus U**, Veidebaum T, Harro J. Association between platelet MAO activity and lifetime drug use in a longitudinal birth cohort study. *Psychopharmacology*. 2022;239:327–337.
8. Sakala K, **Katus U**, Kiive E, Veidebaum T, Harro J. Is low platelet MAO activity associated with antisocial behavior? evidence from representative samples of longitudinally observed birth cohorts. *Brain Res*. 2023;1804: 148249.
9. Reinap M, Nathan NL, Muscat NA, Laisaar KT, **Katus U**, Schünemann HJ. Strengthening guideline contextualization in the WHO European Region. *Bull World Health Organ*. 2024;102(10):715–721.
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11. Kiive E, **Katus U**, Eensoo D, Villa I, Mäestu J, Veidebaum T, Harro J. Parsing reward sensitivity reveals distinct relationships with energy intake, metabolic markers, physical activity and fitness. *Acta Neuropsychiatr*. 2025; 37:e8.

12. **Katus U**, Villa I, Ringmets I, Eensoo D, Mäestu J, Veidebaum T, Harro J. Birth cohort effects on obesity, glucose metabolism, diet, and fitness: evidence from a longitudinal study. *Nutr Metab Cardiovasc Dis.* 2026;36(7): 104638.

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