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Risk Factors, Complications and Characteristics of Metabolic Syndrome in Obese Children and Adolescents

Summary of the Doctoral Thesis for obtaining a doctoral degree “Doctor of Science (*Ph.D.*)”

Sector – Clinical Medicine
Sub-Sector – Paediatrics

Riga, 2022

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Abbreviations used in the Thesis

ACTH	adrenocorticotropic hormone
ALT	alanine aminotransferase
BMI	body mass index
CCUH	Children's Clinical University Hospital
CDC	Centre for Disease Prevention and Control
CI	confidence interval
CVD	cardiovascular diseases
DBP	diastolic blood pressure
DM	diabetes mellitus
h	hour
HDL	high-density lipoproteins
HOMA-IR	homeostatic model assessment for insulin resistance
HbA1c	glycated haemoglobin
HR	hazard ratio
IDF	International Diabetes Federation
IGT	impaired glucose tolerance
IR	insulin resistance
ISPAD	International Society for Paediatric and Adolescent Diabetes
IQR	interquartile range
LDL	low-density lipoproteins
MS	metabolic syndrome
NAFLD	non-alcoholic fatty liver disease
NCEP	National Cholesterol Education Programme in USA
OGTT	oral glucose tolerance test
OR	odds ratio
p	significance level
pc	percentile

PNF1	pediatric NAFLD fibrosis index-1
SBP	systolic blood pressure
tc	tertile
TCh	total cholesterol
TG	triglycerides
T2D	type 2 diabetes mellitus
TTH	thyrotropic hormone
USA	United States of America
WC	waist circumference
WHO	World Health Organisation
z-BMI	standardised body mass index

Introduction

Overweight and obesity not only in adulthood, but currently also in children and adolescents is one of the main health problems of the 21st century in many countries of the world (WHO, 2017a; WHO, 2017b; WHO, 2017c).

Obesity is a global epidemic not only in developed countries, but also in low- and middle-income countries. Children are at increased risk of overfeeding due to calorie-rich foods with high levels of fat, sugar, and salt, while nutrition is poor in terms of nutritional value. The prevalence of overweight in children has increased in all age groups of both genders, as well as in different ethnic and racial groups. Children who are obese in pre-school and school age are also at risk of being obese in adulthood, and the higher the degree of obesity in childhood, the higher the risk of obesity in adulthood (Sahoo et al., 2015; Zhao et al., 2011).

In this context, it is important to recognise preventable and non-preventable risk factors for obesity in children. In particular, it is useful if long-term obesity prevention programmes are launched in the country, as well as for weight management purposes in the working methodology of various multidisciplinary teams. Not only are the promotion of physical activities and healthy diets, including the consumption of fruits and vegetables, important components in the reduction of overweight among children and young people, but also the education of parents is an integral part of the fight against obesity. It is important to educate parents about healthy weight and weight control, pregnancy planning, the need for exclusive breastfeeding and its benefits, infant nutrition and healthy nutrition, physical activity for the whole family. The role of parents in preventing obesity in children and in weight management is irreplaceable, so the goal of weight management programmes is to change lifestyle not only for the child, but for the whole family (Evans et al., 2012; Wilfley et al., 2017; Yan et al., 2014; Zolotarjeva et al., 2018).

The development of screening programmes to help assess obesity-related complications in children and young people allows early initiation of treatment that would improve quality of life, reduce the risk of chronic diseases, and early death (Brook et al., 2010; Tagi et al., 2020).

In obese children, arterial hypertension, dyslipidaemia, insulin resistance (IR), hyperuricaemia, non-alcoholic fatty liver disease, polycystic ovarian syndrome, and other complications are observed at an early age. Many of these disorders are components of metabolic syndrome or diagnostic criteria. Although metabolic syndrome (MS) is a well-known risk factor for cardiovascular disease and type 2 diabetes mellitus (T2D) in adults, it has no similar role in determining the risk in children. The detection of metabolic syndrome in children and adolescents draws attention to a high-risk group of children who require intensive lifestyle correction, multidisciplinary care, often – the use of medication, and in rare cases – considering of bariatric surgery (Reilly et al., 2011; Tagi et al., 2020; Zolotarjeva et al., 2018).

The COVID-19 pandemic had a negative impact on the whole world and changed many daily habits not only for adults, but also for children. Since March 2020, there have been major changes in children's daily lives, imposing countless restrictions, studying at school was replaced by on-line studies at home, reducing the time of direct contact with peers, increasing the screen time, and reducing the physical activity time accordingly. The literature shows a marked increase in body mass index (BMI) in children during the pandemic compared to pre-pandemic (Cushieri et al., 2020). A study done in the United States of America (USA) during 2018–2020 included 432,302 children aged 2 to 19 years where their growth rate of BMI during the pandemic was studied. The study showed that the rate of BMI in children had approximately doubled compared to the pre-pandemic period. The highest increase in BMI was observed in children who had already been overweight or obese before the pandemic, as well as preschool and primary school children. In August 2019, the proportion of obese children in this

cohort was 19.3 %, while in August 2020 the proportion of obese children was 22.4 %. Overall, the monthly growth rate of BMI during the COVID-19 pandemic period was 0.100 kg/m² compared to 0.052 kg/m² pre-pandemic (Lange et al., 2021). The rise in BMI during the pandemic was significantly affected by sedentary lifestyles and the change in eating habits, which could also contribute to the spread of obesity among children and adolescents after the pandemic, affecting the obesity rate of children and causing early health problems and chronic diseases. Therefore, timely weight management, especially in children, would be important to prevent serious health threats that worsen quality of life and have a negative impact on life expectancy (Starvodou et al., 2021; Rundle et al., 2020).

To date, there have been no studies in Latvia on the prenatal and postnatal risk factors of obesity, complications caused by obesity, and the prevalence of metabolic syndrome in children and adolescents. Given that Latvia also has a high proportion of overweight children and adolescents and that possibly the COVID-19 pandemic will further contribute to the overweight of children, it is important to study the risk factors of obesity that would allow for the development of a targeted strategy to combat and prevent overweight in the country. There are many studies in the scientific literature on the risk factors of obesity and their impact on the weight of children and adolescents. However, there is insufficient data on the risk and development of complications of metabolic syndrome. Screening of obesity complications and the study of metabolic syndrome in Latvia would allow the development of a personalised care strategy for high-risk children, which would include education about healthy lifestyles, work of a multidisciplinary team, as well as medical therapy if necessary. Personalised care would increase opportunities for timely weight management, which would clearly reduce the risk of complications in the future, improve quality of life and life expectancy.

Objective of the Thesis

To investigate risk factors, complications and characteristics of metabolic syndrome in obese children and adolescents.

Aim of the Thesis

The following tasks have been set for the achievement of the objective of the Doctoral Thesis:

1. To identify prenatal and postnatal risk factors of obesity in children and adolescents with overweight / obesity and normal weight.
2. To analyse possible early changes in lipids, glucose, and other biochemical parameters in children and adolescents with overweight / obesity and normal weight.
3. To investigate the impact of prenatal and postnatal risk factors of obesity on cardiovascular disease, insulin resistance, metabolic syndrome, non-alcoholic fatty liver disease, and other metabolic complications in obese children and adolescents.
4. To study metabolic syndrome according to International Diabetes Federation consensus and to determine the prevalence of metabolic syndrome in obese children.
5. To investigate the risk of metabolic syndrome in relation to BMI, sexual maturation, and prenatal and postnatal risk factors of obesity.
6. During the Doctoral Thesis, in cooperation with the State Language Centre, to clarify and develop terminology in Latvian for investigation methods and names of syndromes.

Hypothesis of the Thesis

- Prenatal and postnatal risk factors of obesity increase the metabolic syndrome risk in children and adolescents.
- In obese children, the metabolic syndrome risk is associated with sexual maturation stage and the severity of obesity.

Novelty of the Thesis

1. In Latvia, metabolic syndrome in obese children and adolescents has been evaluated for the first time according to criteria of International Diabetes Federation, as well as its prevalence, association with BMI, sexual maturation, and risk factors.
2. During the study, evaluating the features / characteristics of metabolic syndrome in children with obesity, a high-risk group for chronic diseases in the future, which requires a personalised care strategy, has been identified.
3. The paediatric NAFLD fibrosis index (PNFI) has been analysed for the first time in obese and normal weight children, its association with prenatal and postnatal risk factors and metabolic syndrome.
4. Prenatal and postnatal risk factors of obesity have been evaluated in obese and normal weight children and adolescents; knowing and preventing them timely can reduce the risk of childhood obesity in Latvia.
5. Obesity-related comorbidities (arterial hypertension, dyslipidaemia, insulin resistance, non-alcoholic liver fatty disease) have been evaluated in obese and normal weight children and adolescents, which have an early impact on children's quality of life, future chronic disease risk and life expectancy.

1 Materials and methods

The study "Risk Factors, Complications and Characteristics of Metabolic Syndrome in Obesity Children and Adolescents" was launched in 2013 at the Children's Clinical University Hospital (CCUH). By December 2018, the study prospectively included 198 children and adolescents who had visited a paediatric endocrinologist and / or had been at CCUH Outpatient clinic. The processing and analysis of the research data took place in several stages.

1.1 Inclusion and exclusion criteria in the study

The study included children according to inclusion and exclusion criteria.

Inclusion criteria:

- the age of the child from 5 to 18 years;
- there are no signs of acute illness;
- have not been diagnosed with endocrine, psychiatric or genetic diseases;
- do not use glucocorticoids orally or intravenously (with the exception of inhaled glucocorticoids);
- no movement disabilities;
- no seizure (except for a history of febrile seizures);
- agree to participate in the study.

Exclusion criteria:

- children are under 5 years of age;
- there are signs of acute illness;
- there is a known genetic pathology (e.g., Turner or Prader-Willi syndrome, etc.);
- endocrine pathology has been diagnosed (e.g., hypothyroidism, Cushing syndrome, etc.);

- a chronic disease has been diagnosed or medications are used to treat the disease, which can negatively affect the growth of the child and promote weight gain (e.g., severe bronchial asthma, chronic renal failure, etc.);
- diagnosed mental disabilities;
- movement disorders;
- seizure.

1.2 Description of study phases and methods

In the **first phase**, 3 study groups were established taking into account the BMI and age of the child:

1) children aged 10 years and older with obesity – group I (n = 143);
2) children under the age of 10 with obesity – group II (n = 38);
3) children with normal weight – control group (n = 17).

This age breakdown was chosen according to the definition of the metabolic syndrome (MS) by the International Diabetes Federation (IDF). MS can only be diagnosed at the age of 10 years; No MS was established for children under 10 years of age, but diagnostic criteria were analysed separately.

In the **second phase**, only study group I – children aged 10 years and older with obesity were analysed and evaluated. Children were divided into two age groups according to IDF diagnostic criteria for metabolic syndrome:

1) children from 10 to 16 years of age;
2) children aged 16 and over.

During the first phase of the study, participants:

- had their anthropometric data defined – weight, height, waist circumference (WC);
- had their blood pressure measured;
- were assessed for their sexual maturation stage on the Tanner scale;

- had their body mass index calculated and evaluated in BMI percentile charts for children relative to their age and gender;
- a survey of parents or legal representative on prenatal and postnatal risk factors of obesity had been carried out;
- blood tests taken in fasting.

1.2.1 Anthropometric indicators and blood pressure for study respondents

The weight was determined by weighing the children, in light clothes and without shoes, on the scales (*Rice Lake weighting systems*) with an accuracy of 0.1 kg, the height was measured with an accuracy of 0.1 cm using a stadiometer *(Dr Keller I*). The waist circumference (cm) was measured with an accuracy of 0.1 cm, with the rigid tape placed midway between the pelvic bone and the rib arc. During the measurement, the abdomen had to be relaxed and the child should exhale.

The body mass index was calculated for the subjects according to the formula:

$$\text{body weight (kg)} / \text{height (m}^2\text{)}.$$

The BMI was then evaluated using the BMI percentile (pc) curves validated by the Centre for Disease Prevention and Control in relation for age and gender:

- underweight if BMI < 5 pc;
- normal weight if BMI ≥ 5 pc and < 85 pc;
- overweight if BMI ≥ 85 pc and < 95 pc;
- obesity when BMI ≥ 95 pc.

An evaluation of the BMI index in children and adolescents showed that 181 children had a BMI for age and gender greater than 95 pc, corresponding to the definition of obesity, and 17 children had BMI ranging from ≥ 5 pc to < 85 pc, corresponding to the definition of normal weight. None of the children included in the study showed overweight or underweight.

Arterial blood pressure was measured for each patient under standard conditions using a calibrated automatic apparatus with an appropriate cuff size. In the study, blood pressure scores were evaluated only according to the IDF criteria and were not evaluated on blood pressure percentile charts. Increased blood pressure was measured at values above 130/85 mmHg.

1.2.2 Evaluation of sexual maturation stage for study respondents

The sexual maturation for girls and boys is assessed according to the Tanner scale and rated from stage I to V. For girls, breast and *pubic* hair were evaluated, while in boys – *pubic* hair and testicular volume according to Prader's orchidometer.

Sexual maturation was assessed on the Tanner scale according to the following stage:

Stage I – infantilism, can be the first signs of maturation;

Stage II – pituitary stimulation – *thelarche* and *testes* growth;

Stage III – gonadal activation;

Stage IV – maximum level of steroids;

Stage V – the maturity.

1.2.3 Parents' survey on prenatal and postnatal risk factors of obesity

The parents or legal representatives of the children were interviewed about prenatal and postnatal risk factors of obesity.

They were asked about:

1) birth weight – asked to indicate in grams. A birth weight of 4 kg or above (≥ 4 kg) was considered a risk factor (Kleiser et al., 2009; Yu et al., 2020);
2) duration of exclusive breastfeeding – asked to indicate in months. The duration of exclusive breastfeeding less than 6 months (< 6 months) was considered a risk factor (Evans et al., 2012; Qiao et al., 2020; Yan et al., 2014);
3) weight gain during pregnancy for the mother – asked to indicate the weight gain in kilograms. Weight gain during pregnancy 20 kilograms or above (≥ 20 kg) was considered a risk factor (Kleiser et al., 2009);
4) Type 2 diabetes mellitus history in family – diabetes in 1st and / or 2nd degree relatives was considered a risk factor (Annis et al., 2005);
5) parental obesity – non-obese (= normal weight) parents or both obese parents (obese only mother, obese only father) (Martínez-Villanueva et al. 2019; Reilly et al. 2005).

1.2.4 Laboratory measurements for study respondents

Blood samples were taken when the participants entered the CCUH outpatient care department. The participant had to be in fasting in the morning, i.e., 8 hours after the last meal. For all children included in the study, blood samples were taken in the Clinical Laboratory of the Children's Clinical University Hospital.

The following fasting biochemical parameters have been analysed during the study: uric acid, alanine aminotransferase (ALT), total cholesterol (TCh), low-density lipoproteins (LDL), high-density lipoproteins (HDL), triglycerides (TG), glucose, insulin, glycated haemoglobin (HbA1c), prolactin, thyrotropin hormone (TTH), adrenocorticotropic hormone (ACTH), cortisol.

In the enrolled children, an oral glucose tolerance test (OGTT) was performed with glucose calculated at a dose of 1.75 g/kg up to a maximum dose of 75 g. During the test, the glucose and insulin levels were determined at 0 and 120 min after glucose load. OGTT was considered to have failed if the child was unable to drink all the intended glucose or if vomiting was observed after glucose consumption. The collected glucose and insulin data were not analysed in this case.

The HOMA-IR calculated from fasting glucose and insulin levels according to the formula:

$$\text{fasting glucose (mmol/l)} \times \text{fasting insulin (mIU/l)}/22.5.$$

Changes in glucose metabolism are determined:

1) according to the criteria of the International Society for Paediatric and Adolescent Diabetes (ISPAD) and included impaired fasting glucose, impaired glucose tolerance and diabetes:
   - impaired fasting glucose – glucose level 5.6–6.9 mmol/l;
   - impaired glucose tolerance – 2 hours post load glucose 7.8–11.1 mmol/l.
   - Diagnosis of T2D – fasting glucose level ≥ 7.0 mmol/l and / or 2 hours post load glucose ≥ 11.1 mmol/l;

2) Insulin resistance has been evaluated according to HOMA-IR tertile (tc) values:
   - first tertile: HOMA-IR < 2.96;
   - second tertile: HOMA-IR ≥ 2.96 and < 4.46;
   - third tertile: HOMA-IR ≥ 4.46 (Smetanina et al., 2021).

During the study, individual insulin levels were not analysed in children as the value ranges are unclear in children, there is a possible increase in levels during puberty, and there may be so-called physiological insulin resistance.

In children and adolescents, total cholesterol (TCh) and low-density lipoprotein (LDL) levels were assessed against criteria and recommendations developed by the National Lung, Heart, and Blood Institute (NHLBI). TCh was considered to be elevated if it was ≥ 5.2 mmol/l, while LDL levels were considered to be elevated if they were > 3.4 mmol/l.

Other biochemical measurements were evaluated at the CCUH laboratory rapporteur intervals (Table 1.1).

Table 1.1

CCUH laboratory reference intervals for blood biochemical indicators

Indicator	Manufacturer / Analyser	Referent Interval	Method of measurement
Uric acid, µmol/l	Roche / Cobas c501	202.3–416.5	Photometry
ALT, U/l	Roche / Cobas c501	0–24	Photometry
HbA1c, %	Roche / Cobas Integra 400	4.8–5.9	Immune Chemistry
Prolactin, µU/ml	Roche / Cobas e601	0–320	Immune Chemistry
TTH, mU/l	Roche / Cobas e601	0.27–4.2	Immune Chemistry
ACTH, pg/ml	Siemens / Immulite 200 XPI	0–46	Immune Chemistry
Cortisol, µg/dl	Roche / Cobas e601	6.2–19.4	Immune Chemistry

1.2.5 Pediatric non-alcoholic fatty liver disease (NAFLD) fibrosis index (PNFI) in study respondents

For all children included in the study, the PNFIs were calculated using the formula:

$$PNFI = 1/ (1+e^{-lp}) \times 10;$$

$$LP = 6.539 \times \log_e [\text{age (years)}] + 0.207 \times VA \text{ (cm)} +$$

$$+ 1.957 \times \log_e [TG \text{ (mg/dl)}] - 10.074,$$

where:

WC – waist circumference;

TG – triglycerides;

Conversion of TG to mg/dl: mmol/l × 88,57.

When calculating the PNFI, the NAFLD was evaluated according to the calculated score:

- no liver fibrosis: PNFI < 3.0;
- risk for liver fibrosis: PNFI 3.0–8.99;
- predicted liver fibrosis: PNFI ≥ 9.0 (Nobili et al., 2009).

In the **second phase of the study**, metabolic syndrome in group I children and adolescents were diagnosed according to the International Diabetes Federation (IDF) consensus. This definition of MS was chosen due to its simple applicability also in clinical practice (IDF, 2007).

1.2.6 Metabolic syndrome in study respondents

1) MS is not diagnosed in children younger than 10 years;
2) for children between 10 and 16 years, the diagnostic criteria are as follows:
   - central type of obesity – waist circumference of 90 pc and / or BMI, 95 pc in relation to age and gender, and plus any 2 of the following criteria:
     - triglycerides ≥ 1.7 mmol/l;
     - HDL < 1.03 mmol/l;
     - arterial hypertension – systolic blood pressure ≥ 130 mmHg / diastolic blood pressure ≥ 85 mmHg (or antihypertensive therapy)
     - fasting glucose ≥ 5.6 mmol/l (or known T2D);
3) for children older than 16 years, the IDF adult criteria were used for MS diagnosis:
   - central type obesity – waist circumference for men ≥ 94 cm and women ≥ 80 cm and / or BMI > 30 kg/m^2 and 2 of the following criteria:
     - triglycerides ≥ 1.7 mmol/l;
     - HDL < 1.03 mmol/l for men and < 1.29 mmol/l for women (or dyslipidaemia therapy);
     - arterial hypertension – systolic blood pressure ≥ 130 mmHg and diastolic blood pressure ≥ 85 mmHg (or antihypertensive therapy)
     - fasting glucose ≥ 5.6 mmol/l (or known T2D).

From 10 to 16 years of age, there were 117 children in study Group I and 26 children older than 16 years.

1.3 Design diagram of the study

Figure 1.1 shows the design of the study and the steps described above.

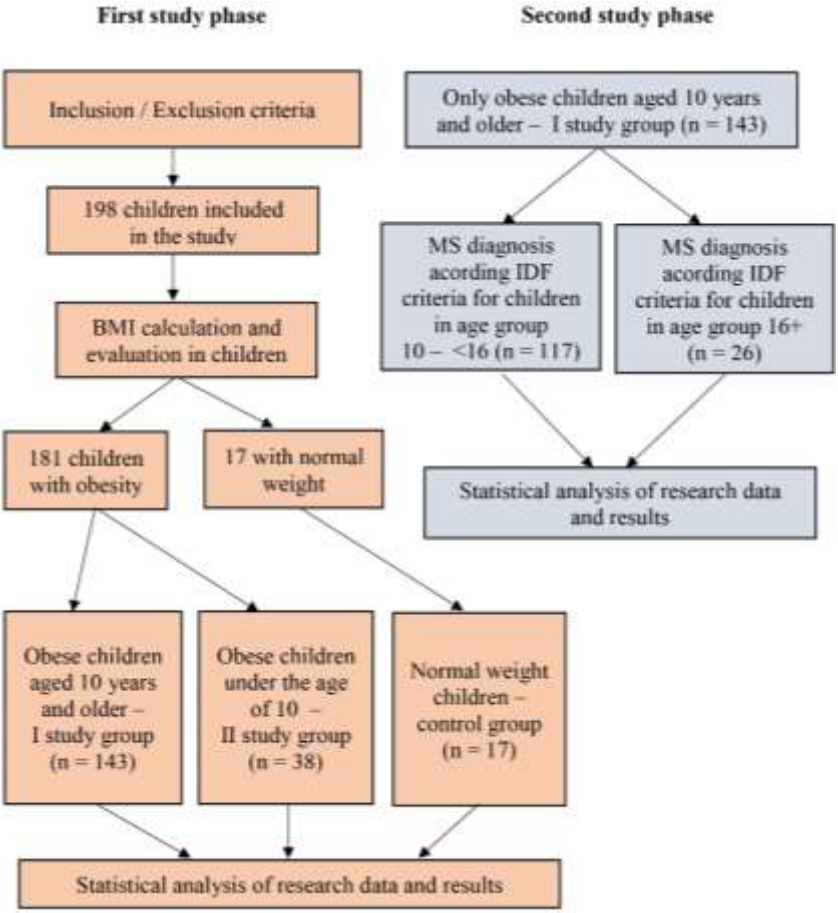

Figure 1.1 **The diagram of study phases**

1.4 The ethical aspects

The study was carried out with the approval of the Ethics Committee of Rīga Stradiņš University, issued on 25 November 2013. The parents or legal representative of the children included in the study signed a written form of consent for the participation of the child in the study.

1.5 Statistical analysis of study data

All data were collected in the *Excel* database and analysed using *RStudio* V.1.4.1103. For continuous data, mean values, the median as a measure of central tendency, and the interquartile range (IQR), the difference between quarter 25 and quarter 75 as the dispersion interval for the population was determined. The differences between the two groups were evaluated using the Mann-Whitney, Wilcoxon, or T tests, between three and more groups – with the Kruskal-Walli's test. In the analysis of variable scales, correlation analyses were used, corresponding to Spearman's correlation coefficients or association measures.

It was assumed that:

- The correlation is weak when the Spearman's correlation coefficient is 0.2–0.4;
- The correlation is moderate close when the coefficient is 0.4–0.7;
- The correlation is strong when coefficient is greater than 0.7 (Akoglu et al., 2018).

To compare the proportions, Pearson's Chi's squared test or Fisher's direct test was used according to their conditions. When analysing possible risk factors for MS, prognostic factors were introduced into a multifactor binary logistic regression model. The differences were considered statistically significantly when the significance level was $p < 0.05$.

2 Results

2.1 Characteristics of the study respondents

There were no differences in gender distribution across all study groups, with 49.7 % (n = 71) in group I, 50 % (n = 19, and 47.1 % (n = 8) in the control group.

No statistically significant differences in the median age between group I and the control group children, respectively 13.1 years (IQR 11.8; 15.1) and 12.7 years (IQR 11.5; 14,2). The median age in group II children was 8.1 years (IQR 7.1; 9,1).

Table 2.1 shows the characteristics of the study population.

Table 2.1

Anthropometric parameters and blood pressure of study respondents (median value with interquartile range)

Indicator	Group I (N = 143)	Group II (N = 38)	Control group (N = 17)
Height, m	1.7 (1.6; 1.7)	1.4 (1.3; 1.5)	1.7 (1.7; 1.8)
Weight, kg	86.0 (71.0; 100.5)	50.0 (43.0; 58.5)	59.0 (50.0; 65.0)
Waist circumference, cm	101.0 (96.0; 110.0)	90.0 (84.2; 94.0)	77.0 (74.8; 82.5)
BMI, kg/m^2	30.8 (28.0; 33.9)	25.9 (21.9; 28.2)	19.3 (17.3; 21.0)
SBP**, mmHg	123.0 (116.0; 132.0)	105.0 (98.0; 111.8)	115.0 (110.0; 120.0)
DBP***, mmHg	78.0 (71.5; 83.0)	65.0 (60.0; 74.0)	70.0 (65.0; 76.0)

* N – number of children;
** SBP – systolic blood pressure;
*** DBP – diastolic blood pressure.

The highest BMI value in group I reached 56.8 kg/m², but 21.7 % (n = 31) of children's BMI exceeded a threshold ≥ 35 kg/m², and it can be considered as severe obesity. The median BMI of the control group was 1.5 times lower than the median BMI of children in group I ($p < 0.001$). Also, the median waist

circumference in the control group children was 1.3 times lower than the median WC of children in group I ($p < 0.001$).

The median waist circumference and BMI were significantly higher in children of group II compared to the control group ($p < 0.001$). In group II, the highest estimated BMI value was 43.3 kg/m², but 7.9 % (n = 3) of children already at this age had BMI above the threshold ≥ 35 kg/m, which can be considered as a very severe degree of obesity.

The cardiovascular disease risk factor, high blood pressure above 130/85 mmHg was not found in any child of control group. Elevated blood pressure above 130/85 mmHg was observed only in children of groups I and II, respectively 17.5 % (n = 25) and 13.2 % (n = 5), respectively.

The highest blood pressure values during the study were observed in group I compared to children of group II and control group ($p < 0.001$).

Children in study group II had statistically significantly lower systolic blood pressure compared to the control group ($p = 0.027$), but no differences were observed between these groups in diastolic pressure ($p = 0.761$).

2.1.1 Evaluation of prenatal and postnatal risk factors of obesity in children included in the study

No statistically significant differences in prenatal risk factors of obesity between groups were found in children included in the study. The lowest median birth weight was observed in children of control group – 3.5 kg (IQR 3.0; 4.0), however, statistically significant differences in birth weight of children in the study groups were not found ($p = 0.530$) (Table 2.2). The largest number of children with birth weight ≥ 4 kg were born in study group II – 39.3 % (n = 11), but in group I – 29.1 % (n = 30 and in control group 37.5 % (n = 3) of children.

All study groups had a high prevalence of women with excessive weight gain during pregnancy (p = 0.787). The prevalence of Type 2 diabetes mellitus in the family was also high between all study groups (p > 0.999).

Table 2.2

Evaluation of prenatal risk factors of obesity in children included in the study*

Risk factor for obesity	Group I	Group II	Control group
Birth weight, kg	3.6 (3.2; 4.1) ** (N = 103)	3.8 (3.5; 4.1) (N = 28)	3.5 (3.0; 4.0) (N = 8)
Weight gain during pregnancy ≥ 20 kg	48.2 % (N = 83)	43.5 % (N = 23)	33.3 % (N = 6)
T2D in ***family	17.0 % (N = 112)	14.8 % (N = 27)	11.1 % (N = 9)

* N – total number of cases analysed;
** Median birth weight with interquartile interval,
*** T2D – Type 2 diabetes mellitus.

In the analysis of postnatal risk factors of obesity, it was found that the lowest median breastfeeding duration was in group I, only 4.0 (IQR 2,0; 8.0) months, in group II breastfeeding duration was 8.0 (IQR 3.0; 18.0) months and in control group 14.0 (IQR 7.5; 22.0) months, but no statistically significant differences of breastfeeding duration were found between study groups (p = 0.120). Exclusive breastfeeding for ≥ 6 months received by 40.3 % (n = 31) of the children in group I, 64.7 % (n = 11) in group II and 66.7 % (n = 2) in the control group.

Only the postnatal risk factor of obesity – parental obesity – has shown a statistically significantly difference between the study groups. When compiling parent survey data on weight only by the principle of obese or non-obese parents, differences in parental weight existed between all study groups (p = 0.004) (Table 2.3). Parents of both study groups I and II had high rates of obesity (p = 0.308).

Table 2.3

Parental obesity in children included in the study*

Study groups	Obesity for parents, %	Normal weight for parents, %
Group I (N = 124)	79.8 %	20.2 %
Group II (N = 27)	63.0 %	37.0 %
Control group (N = 9)	33.3 %	66.7 %

* N – total number of cases analysed.

Both parents were more than 3.5 times likely to be obese in group I than in the control group (p = 0.016) (Figure 2.1). Maternal obesity was more common in group I children, but paternal obesity was more common among group II children. Maternal obesity was not detected in the control group children.

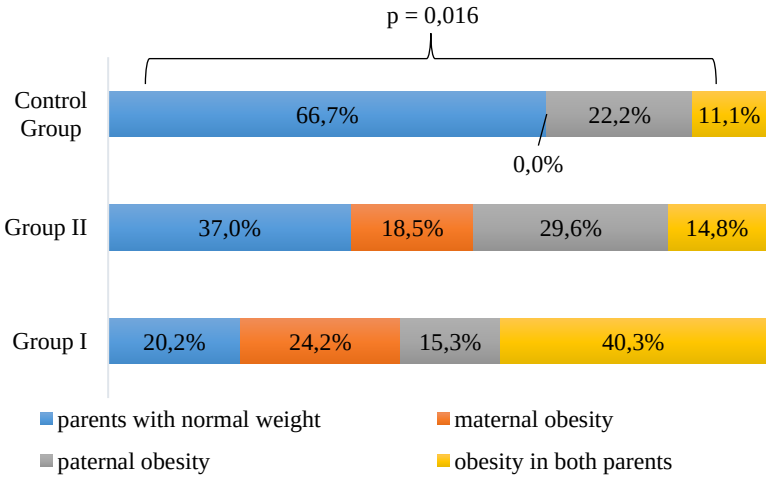

Figure 2.1 **Parental obesity prevalence for children of study groups**

In addition, the analysis of the study groups according to the maternal weight status – obese or non-obese mother –, maternal obesity was found 5.8 times more often of children in group I ($p < 0.001$) compared to control group children, and approximately 2 times more often compared to group II children ($p < 0.001$) (Table 2.4).

Table 2.4

Maternal obesity prevalence in study children*

Study groups	Obese mothers, %	Normal weight mothers, %
Group I (N = 124)	64.5 %	35.5 %
Group II (N = 27)	33.3 %	66.7 %
Control group (N = 9)	11.1 %	88.9 %

* N – total number of cases analysed.

2.1.2 Comparison of biochemical blood measurements between study groups in children

No statistically significant differences between groups were observed in biochemical blood measurements such as TCh ($p = 0.922$), LDL ($p = 0.546$), TTH ($p = 0.124$), ACTH ($p = 0.613$), cortisol ($p = 0.575$).

However, statistically significant differences in biochemical blood rates were observed between all study groups in uric acid ($p < 0.001$), ALT ($p < 0.001$), TG ($p < 0.001$), HDL ($p < 0.001$) and prolactin ($p = 0.007$) levels.

Due to age differences between groups I and II, the biochemical measurements of these groups were studied separately to the control group but were not analysed and taken into account among themselves, although there were statistically significant differences in the levels of biochemical measurements such as uric acid ($p < 0.001$), TG ($p = 0.016$) and prolactin ($p = 0.005$).

In group I children, blood ALT level was 1.7 times higher, and TG level 1.8 times higher compared to control children, while HDL level was 1.5 times lower compared to control children's biochemistry (Table 2.5).

Furthermore, in group II children blood ALT level was 1.5 times higher and HDL level 1.3 times lower compared to control children's blood biochemistry (Table 2.6).

Table 2.5

Comparison of biochemical blood measurements (median value with interquartile range) between I and control group

Indicator	Group I	Control group	P value
Uric acid, μmol/l	341.1 (288.9; 388.5) (N* = 116)	274.8 (242.3; 300.3) (N = 8)	0.067
ALT, U/l	22.5 (16.1; 35.0) (N = 136)	12.9 (15.2; 24.0) (N = 15)	< 0.001
HDL, mmol/l	1.1 (1.0; 1.3) (N = 131)	1.7 (1.6; 1.7) (N = 8)	< 0.001
TG, mmol/l	1.1 (0.8; 1.5) (N = 129)	0.6 (0.4; 0.8) (N = 8)	0.003
Prolactin, μU/ml	209.3 (149.0; 292.0) (N = 107)	224.0 (130.3; 286.5) (N = 9)	> 0.999

* N – total number of cases analysed.

Table 2.6

Comparison of biochemical blood measurements (median value with interquartile interval) between II and control group

Indicator	Group II	Control group	P value
Uric acid, μmol/l	281.8 (253.6; 319.3) (N* = 35)	274.8 (242.3; 300.3) (N = 8)	> 0.999
ALT, U/l	19.2 (15.2; 24.0) (N = 38)	12.9 (15.2; 24.0) (N = 15)	0.004
HDL, mmol/l	1.3 (1.0; 1.5) (N = 31)	1.7 (1.6; 1.7) (N = 8)	0.008
TG, mmol/l	0.8 (0.6; 1.0) (N = 30)	0.6 (0.4; 0.8) (N = 8)	0.140
Prolactin, μU/ml	154.9 (118.8; 181.1) (N = 28)	224.0 (130.3; 286.5) (N = 9)	0.310

* N – total number of cases analysed.

Uric acid above 416.5 μmol/l in blood was in 17.2 % (n = 20) of children in study group I, in 8.6 % (n = 3) in group II and in 12.5 % (n = 1) in control group.

ALT level above 24 U/l was observed in almost half, 44.9 % (n = 61) of children in group I, 26.3 % (n = 10) of children in group II and no increase in the control group.

Total cholesterol and LDL levels in children were analysed as important risk factors for cardiovascular disease (CVD) in children. TCh ≥ 5.2 mmol/l was not elevated in any child in the control group. TCh increased ≥ 5.2 mmol/l was 8.8 % (n = 12) in children in group I and 5.9 % (n = 2) in group II. Blood LDL level above 3.4 mmol/l was not found in any child in the control group. LDL level above 3.4 mmol/l was 16.7 % (n = 22) in children in group I and 6.5 % (n = 2) in group II.

Blood TTH level above 4.2 mU/l was increased in 14.7 % (n = 20) of the children in group I and in 19.4 % (n = 7) of the children in group II and only in 6.2 % (n = 1) of the children in the control group.

Prolactin level above 320 μU/ml was found in almost a quarter of children in group I – 24.3 % (n = 26) – and 22.2 % (n = 2) in the control group. Increased prolactin levels were less common in class II children, – only 3.6 % (n = 1).

Increased morning cortisol level above 19.4 μg/dl was equally common across all study groups: 18.6 % in group I (n = 21), 16.7 % (n = 5) in group II and 22.2 % (n = 2) in the control group.

2.1.3 Impaired glucose metabolism in children included in study

Fasting blood glucose level was statistically significantly higher in children in group I (p = 0.003) compared to other study groups (Table 2.7). However, no significant differences in blood glucose were observed between the group I and the control group (p = 0.167) as well as between the group II and the

control group ($p > 0.999$). Statistically significant differences in fasting blood glucose occurred between study groups I and II ($p = 0.005$).

Table 2.7

Glucose metabolism indicators (median value with interquartile range) in children included in the study

Indicator	Group I	Group II	Control group
Glucose, mmol/l fasting	5.1 (4.8; 5.3) (N = 142)	4.8 (4.7; 5.0) (N = 37)	4.9 (4.6; 5.1) (N = 17)
Insulin, mIU/l fasting	17.2 (11.6; 25.2) (N = 139)	10.6 (5.1; 15.4) (N = 38)	5.4 (3.6; 9.8) (N = 12)
Glucose, mmol/l OGTT after 2 hours	6.3 (5.5; 7.0) (N = 126)	5.9 (5.4; 6.5) (N = 28)	5.3 (4.7; 6.6) (N = 15)
Insulin, mIU/l OGTT after 2 hours	90.5 (62.4; 133.5) (N = 114)	71.2 (46.0; 91.7) (N = 28)	40.6 (24.8; 43.4) (N = 9)
HOMA-IR	3.9 (2.6; 5.6) (N = 138)	2.3 (1.5; 3.4) (N = 16)	1.1 (0.8; 2.1) (N = 12)
HbA1c, %	5.4 (5.3; 5.7) (N = 134)	5.5 (5.4; 5.6) (N = 34)	5.5 (5.4; 5.7) (N = 11)

* N – total number of cases analysed.

In children in group I, fasting insulin level was more than 1.5 times higher than in group II ($p < 0.001$) and 3.2 times higher than in control group ($p < 0.001$). No differences in fasting insulin level were observed between group II and control group children ($p = 0.178$).

In OGTT, no significant differences in glucose level were found between all study groups ($p = 0.168$) after 2 hours, but a higher median glucose of 6.3 (IQR 5.5; 7.0) was found in children in study group I.

In OGTT, after 2 hours, statistically significant differences between study groups were found in insulin level ($p < 0.001$). Insulin level in group I children were 2.2 times higher compared to control group ($p = 0.002$) and 1.7 times higher in group II children compared to control group ($p = 0.023$). But the same high level of insulin in the blood was in children in group I and II after 2 hours post load glucose ($p = 0.080$).

No statistically significant differences in glycated haemoglobin levels were found between groups ($p = 0.808$).

The HOMA-IR index, the surrogate method for assessing insulin resistance, was calculated, analysed, and evaluated concerning possible disruptions between hepatic glucose release and insulin secretion during the study. According to insulin and blood glucose, the HOMA-IR in fasting was 1.7 times higher for children in group I compared to HOMA-IR ($p < 0.001$) in group II children and up to 3.5 times higher than the HOMA-IR ($p < 0.001$) in the control group. No statistically significant differences were observed in the HOMA-IR ratio between the II and control children ($p = 0.109$).

In the analysis of the insulin resistance coefficient according to the tertile classification, in almost all children in control group the HOMA-IR corresponded to the first tertile, but in group I children – only in 31.7 % cases ($p < 0.001$) (Table 2.8).

Table 2.8

Distribution of children included in the study according to HOMA-IR tertile groups *

Risk factors of obesity	Group I	Group II	Control group
First Tertile: < 2.96 %	31.9 % (n = 44)	64.9 % (n = 24)	91.7 % (n = 11)
Second Tertile: 2.96–4.46 %	27.5 % (n = 38)	21.6 % (n = 8)	8.3 % (n = 1)
Third Tertile: > 4.46 %	40.6 % (n = 56)	13.5 % (n = 5)	0.0 %

* N – total number of cases analysed.

In the control group no child had a HOMA-IR above 4.46, which corresponds to the third tertile. However, there were 3 times fewer children in the study group compared to the study group I, who had a HOMA-IR ratio above 4.46.

Fasting blood glucose > 5.6 mmol/l was observed only in 7.0 % (n = 10) of group I children and no hyperglycaemia were observed in group II and control populations.

Impaired glucose tolerance (IGT) was observed in 11.9 % (n = 15) of children in study group I two hours post load glucose with glucose levels ranging from 7.8 to 11.1 mmol/l, 7.1 % (n = 2) in children in study group II and 13.3 % (n = 2) in control group. Impaired glucose tolerance was more common in boys at 73.3 % (n = 11) in group I and only 26.6 % (n = 4) in girls (p = 0.046) (Table 2.9). Children with IGT were older (p = 0.048) compared to children without IGT. No statistically significant differences in anthropometric rates were observed in children with or without IGT. However, children with IGT had statistically significantly higher levels of SBP (p = 0.015), DBP (p = 0.031), uric acid (p = 0.047), ALT (p = 0.003), HbA1c (0.040), glucose (p < 0.001) 2 hours post load glucose and insulin (p < 0.001) 2 hours post load glucose and HOMA-IR index (p = 0.050) compared to children without IGT.

Table 2.9

Children with and without impaired glucose tolerance (median value with interquartile interval)

Indicator	Impaired glucose tolerance	
	No (N = 111)	Yes (N = 15)
Age, years	13.1 (11.4; 15.1)	14.5 (13.4; 15.4)
Waist circumference, cm	102.0 (96.0; 110.0)	108.0 (100.5; 114.5)
BMI, kg/m^2	30.9 (28.4; 34.9)	33.3 (31.2; 34.7)
SBP, mmHg	122.0 (115.5; 132.0)	135.0 (123.5; 146.0)
DBP, mmHg	77.0 (70.5; 83.0)	81.0 (75.0; 92.0)
Glucose, mmol/l fasting	5.1 (4.8; 5.2)	5.2 (5.0; 5.4)
Insulin, mIU/l fasting	17.0 (11.1; 24.1)	17.3 (17.1; 30.3)
HOMA-IR index	3.6 (2.4; 5.5)	4.1 (3.4; 7.1)
Glucose, mmol/l OGTT after 2 h.	6.2 (5.4; 6.7)	8.4 (7.9; 9.0)
Insulin, mIU/l OGTT after 2 h.	86.4 (60.7; 119.5)	197.0 (136.6; 300.0)
ALT, U/l	21.3 (15.6; 31.0)	38.5 (28.4; 53.2)
Uric acid, μmol/l	336.3 (289.0; 390.9)	366.1 (342.4; 438.5)
TCh, mmol/l	3.9 (3.5; 4.6)	4.6 (3.6; 5.4)
LDL, mmol/l	2.5 (2.2; 3.1)	3.1 (2.1; 3.8)

Table 2.9 continued

Indicator	Impaired glucose tolerance	
	No (N = 111)	No (N = 111)
HDL, mmol/l	1.1 (1.0; 1.3)	1.1 (1.0; 1.2)
TG, mmol/l	1.1 (0.8; 1.5)	1.0 (0.7; 1.5)
HbA1c, %	5.4 (5.3; 5.7)	5.7 (5.5; 5.7)

* N – number of children.

Analysis of prenatal and postnatal risk factors of obesity in children with and without IGT did not show statistically significant differences in birth weight ($p > 0,999$), excessive weight gain in mothers during pregnancy ($p > 0.999$), positive family history of T2D ($p = 0.085$), duration of exclusive breastfeeding ($p > 0.999$) and parental obesity ($p = 0.205$).

In the OGTT study, no child had glucose levels ≥ 11.1 mmol/l 2 hours post load glucose no diagnosis of T2D was confirmed.

2.1.4 Relationship between prenatal and postnatal risk factors of obesity and insulin resistance

Controversial data were obtained regarding the prenatal risk factor of obesity – birth weight. Statistically significantly higher ($p = 0.034$) median HOMA-IR index – 3.8 (IQR 2,5; 5.4) – was in children with a birth weight of less than 4 kg and children born over 4 kg had a median HOMA-IR index of 2.6 (IQR 1.9; 4,9).

The value of the HOMA-IR index was not statistically significantly influenced by other prenatal risk factors of obesity – positive T2D anamnesis ($p = 0.779$) in the family and excessive weight gain in the mother during pregnancy ($p = 0.599$).

The postnatal risk factor of obesity, the duration of exclusive breastfeeding, also did not have a statistically significantly impact on the value of the HOMA-IR index ($p = 0.094$).

A statistically significantly effect of parental weight (p = 0.027) was observed when considering the possible association of prenatal and postnatal risk factors of obesity to insulin resistance. The highest median t HOMA-IR index – 4,7 (IQR 2,7; 6.3) – was observed in children with both obese parents, while the lowest median ratio – 2.9 (IQR 1.8; 4.3) – in children whose parents were of normal weight, i.e., non-obese (Figure 2.2).

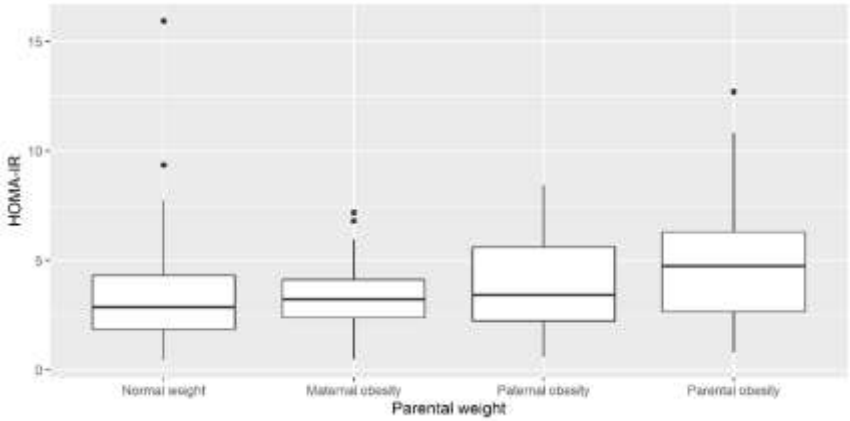

Figure 2.2 **HOMA-IR index for children depending on the parental weight**

2.1.5 Sexual maturation and HOMA-IR index in children of study

The highest median HOMA-IR index – 4,5 (IQR 3.1; 6.8) – was observed in children whose sexual maturity corresponded to Tanner V stage and the lowest median index of 2.4 (IQR 1.2; 3.1) – was in children in Tanner I stage (p = 0.002) (Figure 2.3). Possibly due to physiological insulin resistance, a higher median HOMA-IR index of 4.1 (IQR 2.5; 5.3) – was observed in children in Tanner III stage.

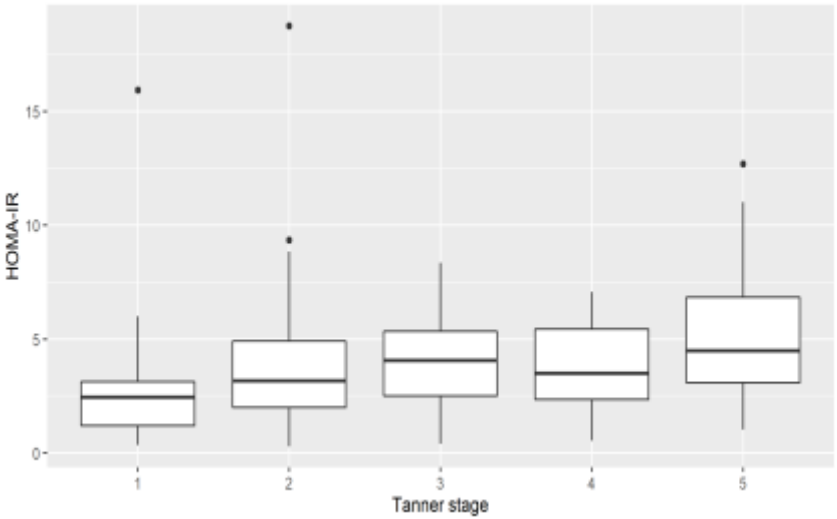

Figure 2.3 **HOMA-IR index depending on the Tanner stage**

2.1.6 Correlation of the HOMA-IR index with anthropometric and biochemical blood parameters

Between the anthropometric parameters and the HOMA-IR index, a moderate correlation was found in weight ($r = 0.472$, $p < 0.001$), waist circumference ($r = 0.462$; $p < 0.001$) and BMI ($r = 0.450$; < 0.001) (Figure 2.4). The resulting correlation may indicate the effect of direct anthropometric indicators on insulin resistance.

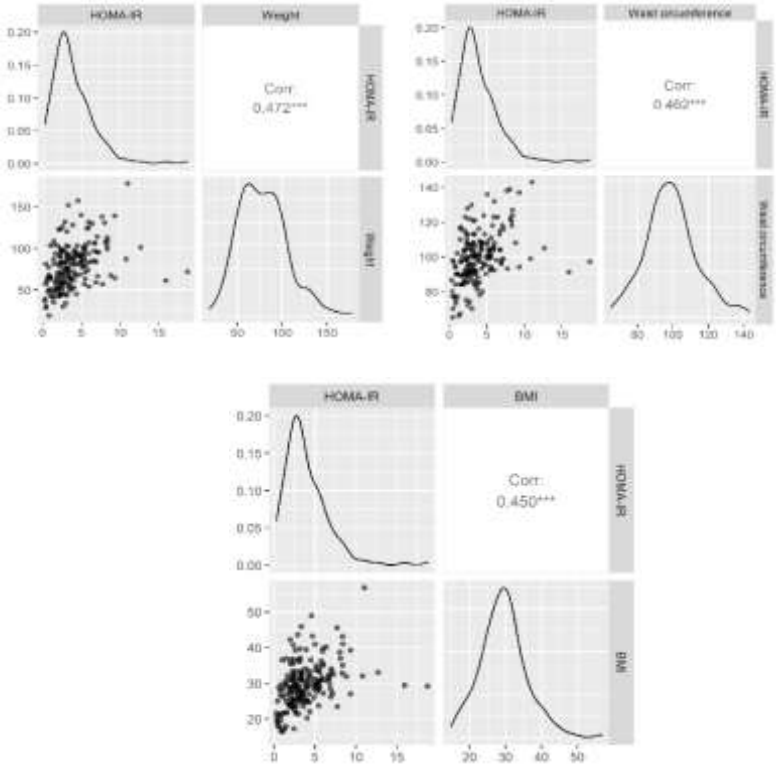

Figure 2.4 **Correlation of the HOMA-IR index with anthropometric parameters**

A weak correlation between the HOMA-IR index and uric acid ($r = 0.396$, $p = 0.018$), prolactin ($r = 0.277$, $p < 0.001$) and cortisol ($r = 0.227$, $p < 0.001$) was observed in biochemical blood tests. There was a moderate correlation between the HOMA-IR ratio and ALT ($r = 0.407$; $p < 0.001$) (Figure 2.5).

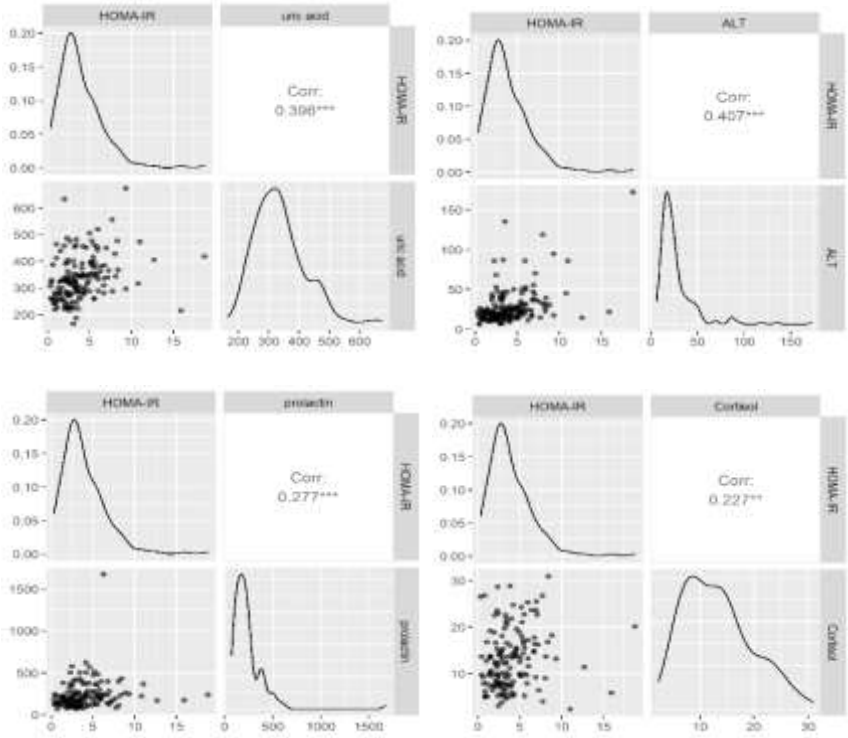

Figure 2.5 **HOMA-IR factor correlation with biochemical blood**

When analysing the diagnostic criteria of MS – blood pressure, TG and HDL, a weak correlation was observed between the HOMA-IR index and the SBP ($r = 0.361$; $p < 0.001$) as well as DBP ($r = 0,360$; $p < 0.001$). A moderate correlation was observed for the HOMA-IR ratio and blood TG level ($r = 0.460$; $p < 0.001$) (Figure 2.6).

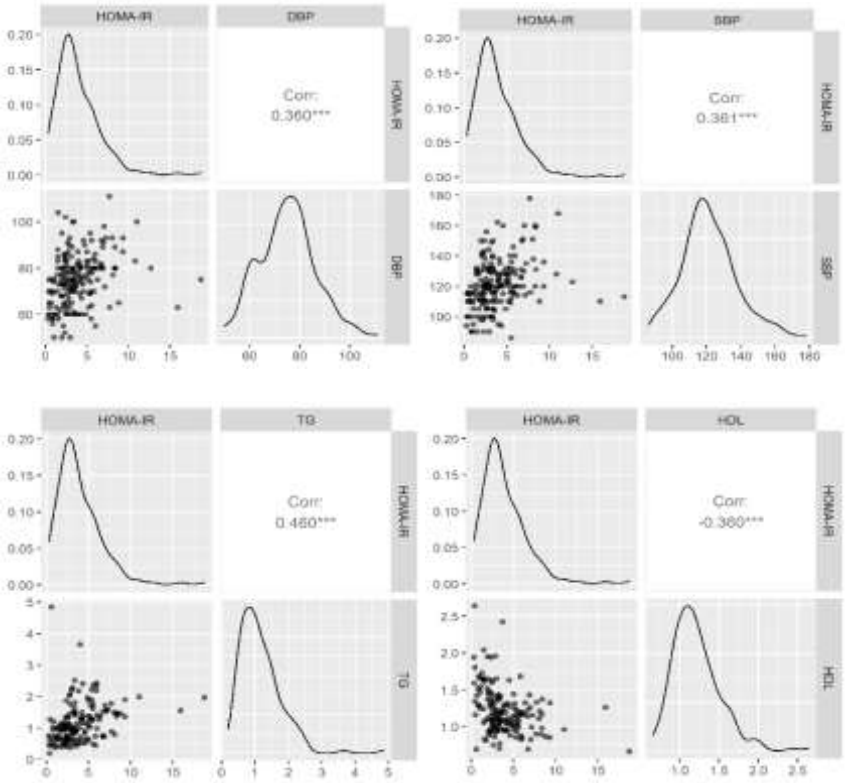

Figure 2.6 **Correlation of the HOMA-IR index with the diagnostic MS criteria**

A weak negative correlation in studied children was observed between the HOMA-IR index and blood HDL level ($r = -0.360$, $p < 0.001$): the lower the HDL level in the blood, the higher the estimated HOMA-IR index in children included in the study.

2.1.7 Pediatric NAFLD fibrosis index (PNFI) in children included in the study

When analysing the paediatric NAFLD fibrosis index between study groups, statistically significantly ($p < 0.001$) predicted liver fibrosis was higher for children in group I compared to control group. No risk of liver fibrosis or predicted liver fibrosis was found in the control group children (Table 2.10).

Table 2.10

PNFI score and risk of liver fibrosis in study group children*

Risk of liver fibrosis	THE PNFI		
	Group I, n	Group II, n	Control group, n
No liver fibrosis	4 (3.1 %)	0 (0.0 %)	8 (100 %)
Risk for liver fibrosis	31 (24.0 %)	7 (23.3 %)	0 (0.0 %)
Predicted liver fibrosis	94 (72.9 %)	23 (76.7 %)	0 (0.0 %)

* N – number of cases analysed.

The median PNFI score for group I was 9.7 (IQR 8.9; 9.9 and II – 9.7 (IQR 9.2; 9.9) and in the control group only 0.4 (IQR 0.2; 0.7) ($p < 0.001$). The risk of liver fibrosis and predicted liver fibrosis was observed in almost all subjects in study groups I and II ($p > 0.999$).

There were statistically significantly gender differences: boys had the highest median PNFI in group I – 9.9 (IQR 9.3; 10.0) compared to girls – 9.5 (IQR 8.4; 9.9) ($p = 0{,}002$). However, there were no statistically significantly gender differences in PNFIs in the study group II ($p = 0.525$).

2.2 Prenatal and postnatal risk factors of obesity in study group I children

During the study, the prenatal and postnatal risk factors of obesity in study group I were analysed separately and their effect on several parameters – both anthropometric and biochemical blood indicators in case of obesity.

In group I, the positive T2D history in the family was 17.0 % (n = 19) of children: 57.9 % (n = 11) boys and 42.1 % (n = 8) girls. The birth weight ≥ 4 kg was 29.1 % (n = 30) of children: 56.7 % (n = 17) boys and 43.3 % (n = 13) girls. Excessive weight gain in mothers in group I, ≥ 20 kg during pregnancy, was 48.2 % (n = 40) of children: 45.0 % (n = 18) mothers of boys and 55.0 % (n = 22) of girls' mothers.

Exclusive breastfeeding ≥ 6 months received 40.2 % (n = 31) of group I children: 45.2 % (n = 14) boys and 54.8 % (n = 17) girls. In the family, at least one or both parents with obesity had 79.8 % (n = 99) of children: 52.5 % (n = 52) of the parents of boys and 47.5 % (n = 47) of the parents of girls.

2.2.1 Prenatal risk factors of obesity

In children in group I, who had a positive family history of T2D, the risk of central obesity was significantly higher because BMI ($p = 0.006$) and waist circumference ($p = 0.005$) were significantly higher than in children with no positive history of diabetes in the family. An increased CVD risk was observed in children with a positive history of diabetes in the family, with both systolic ($p = 0.030$) and diastolic ($p = 0.009$) pressure significantly higher than in children who had no positive history of T2D in the family. Other biochemical blood parameters were not affected by family history of T2D in group I children (Table 2.11).

Table 2.11

Comparison of anthropometric and biochemical parameters (median value with interquartile interval) in group I children* with and without positive history of T2D in the family

Indicator	Positive diabetes anamnesis in family	
	There is no (N = 93)	**There is (N = 19)**
Waist circumference, cm	100.0 (93.0; 106.0)	113.0 (99.5; 119.5)
BMI, kg/m^2	29.7 (27.1; 33.3)	32.5 (29.8; 36.9)
SBP, mmHg	121.0 (116.0; 131.0)	128.0 (121.0; 142.5)
DBP, mmHg	76.0 (70.0; 80.0)	83.0 (76.0; 91.0)
Glucose, mmol/l fasting	5.1 (4.8; 5.3)	5.1 (4.9; 5.2)
Insulin, mIU/l fasting	18.1 (11.8; 25.1)	15.5 (10.2; 28.6)
HOMA-IR index	4.0 (2.7; 5.6)	3.3 (2.3; 7.0)
Glucose, mmol/l OGTT after 2 h.	6.3 (5.4; 6.8)	6.2 (5.0; 7.1)
Insulin, mIU/l OGTT after 2 h.	89.6 (62.4; 133.8)	89.9 (57.5; 218.0)
ALT, U/l	21.3 (16.0; 31.4)	27.6 (20.1; 43.0)
Uric acid, μmol/l	337.8 (283.8; 383.9)	349.7 (322.8; 427.3)
TCh, mmol/l	3.9 (3.5; 4.6)	4.2 (3.6; 4.8)
LDL, mmol/l	2.5 (2.1; 3.1)	2.9 (2.2; 3.3)
HDL, mmol/l	1.1 (1.0; 1.3)	1.2 (1.1; 1.3)
TG, mmol/l	1.1 (0.8; 1.5)	1.0 (0.7; 1.5)

* N – number of children.

During the study, a statistically significantly higher glucose level ($p = 0.020$) in fasting was observed in children born ≥ 4 kg than in children born with weight < 4 kg. No other statistically significant differences in anthropometric or other biochemical measurements were found between children born with weight < 4 kg or ≥ 4 kg. However, in children whose mothers had a weight gain of up to 20 kg during pregnancy, blood uric acid levels were significantly higher than in children whose mothers had a weight gain ≥ 20 kg during pregnancy ($p = 0.043$). No other statistically significant differences in anthropometric or other biochemical measurements related to weight gain during pregnancy were observed in mothers.

2.2.2 Postnatal risk factors of obesity

There were no statistically significant differences in anthropometric, blood pressure or biochemical parameters when analysing the differences between children in group I with exclusive breastfeeding up to 6 months or more.

Significantly higher BMI ($p = 0.003$) and waist circumference ($p < 0.001$), higher blood pressure values of SBP ($p = 0.002$) and DBP ($p = 0.002$), and higher blood levels of ALT ($p = 0.018$) and uric acid ($p = 0.035$) were observed in group I children with obesity compared to children with normal weight in the parents. No statistically significant differences were found in other biochemical measurements (Table 2.12).

Table 2.12

Group I children* whose parents were non-obese or obese, comparison of anthropometric and biochemical measurements (median value with interquartile interval)

Indicators	Obesity of parents	
	There is no (N = 25)	There is (N = 99)
Waist circumference, cm	95.0 (91.0; 102.0)	104.0 (97.0; 114.0)
BMI, kg/m^2	27.7 (25.0; 31.4)	31.1 (28.6; 34.9)
SBP, mmHg	116.0 (112.0; 125.0)	126.0 (118.5; 135.5)
DBP, mmHg	73.0 (63.0; 78.0)	80.0 (73.0; 83.0)
Glucose, mmol/l fasting	5.0 (4.7; 5.2)	5.1 (4.9; 5.3)
Insulin, mIU/l fasting	17.4 (11.2; 22.2)	17.3 (11.6; 25.7)
HOMA-IR index	4.1 (2.5; 4.6)	3.9 (2.7; 5.9)
Glucose, mmol/l OGTT after 2 h.	6.0 (5.2; 6.5)	6.3 (5.6; 7.0)
Insulin, mIU/l OGTT after 2 h.	65.7 (55.5; 98.9)	90.4 (62.6; 143.1)
ALT, U/l	17.7 (14.8; 23.4)	24.0 (18.2; 36.6)
Uric acid, µmol/l	311.8 (285.4; 347.5)	344.0 (289.8; 393.2)
TCh, mmol/l	3.8 (3.5; 4.4)	4.0 (3.5; 4.8)
LDL, mmol/l	2.5 (1.8; 3.0)	2.5 (2.2; 3.4)
HDL, mmol/l	1.1 (1.0; 1.3)	1.1 (1.0; 1.3)
TG, mmol/l	1.1 (0.9; 1.3)	1.1 (0.8; 1.6)

* N – number of children.

2.3 Comparison of anthropometric parameters, blood pressure and biochemical measurements in study group I children according to their belonging to a particular HOMA-IR tertile group

The children whose HOMA-IR ratio corresponded to the third tertile were statistically significantly taller ($p = 0.008$), with greater weight ($p < 0.001$) and BMI ($p = 0.005$), as well as waist circumference ($p = 0.007$) (Table 2.13). When evaluating blood pressure parameters, there were no statistically significant differences in SBP ($p = 0.165$) parameters, but there were significant differences in DBP (0.032) parameters, when comparing children according to HOMA-IR tertile groups.

Table 2.13

Comparison of anthropometric parameters, blood pressure and biochemical measurements (median value with interquartile interval) in group I children* according to HOMA-IR tertile groups

HOMA-IR index	The first tc < 2.96 (N = 44)	The second tc = 2.96–4.46 (N = 38)	Third tc > 4.46 (N = 56)
Weight, kg	81.0 (63.0; 97.2)	82.0 (68.8; 92.0)	94.5 (82.8; 107.2)
Height, m	1.6 (1.5; 1.7)	1.6 (1.6; 1.7)	1.7 (1.6; 1.8)
Waist circumference, cm	98.5 (92.0; 108.5)	101.0 (92.2; 107.5)	104.0 (99.0; 118.0)
BMI, kg/m^2	29.4 (27.0; 32.9)	30.6 (27.0; 32.5)	32.2 (29.7; 35.6)
SBP, mmHg	121.0 (114.2; 131.2)	123.5 (116.0; 132.0)	127.0 (120.0; 135.2)
DBP, mmHg	75.5 (68.8; 83.0)	75.0 (71.2; 80.0)	80.0 (75.0; 86.2)
ALT, U/l	18.7 (14.2; 26.6)	20.3 (15.1; 30.0)	26.6 (20.4; 40.2)
Uric acid, umol/l	322.0 (275.9; 343.6)	327.8 (281.9; 351.5)	366.7 (335.6; 431.1)
TCh, mmol/l	3.9 (3.5; 4.5)	3.9 (3.5; 4.7)	3.9 (3.5; 4.7)
HDL, mmol/l	1.2 (1.0; 1.5)	1.1 (1.0; 1.2)	1.1 (1.0; 1.2)
LDL, mmol/l	2.6 (2.1; 3.2)	2.5 (2.2; 3.1)	2.5 (2.2. 3.2)
TG, mmol/l	1.0 (0.6; 1.2)	1.0 (0.8; 1.5)	1.4 (0.9; 1.7)

* N – number of children; tc – tertile.

No significant differences in blood levels of total cholesterol (p = 0.890), HDL (p = 0.229) and LDL (p = 0.976) were found in the HOMA-IR index tertile groups. Children in the third tertile had statistically significantly higher biochemical levels of lipid profile, triglycerides (p = 0.005), as well as levels of ALT (p = 0.003) and uric acid (< 0.001) in the blood.

The HOMA-IR index is directly dependent on fasting glucose and insulin levels, which is reflected in the HOMA-IR index in the tertile groups. This was also the case when evaluating insulin level in OGTT 2 hours post load glucose, the insulin level in the third tertile group was 1.7 times higher compared to the first tertile group (p < 0.001) (Table 2.14).

Table 2.14

Glucose and insulin levels by performing OGTT in fasting and 2 hours post load glucose in children* according to HOMA-IR tertile groups

Indicator	HOMA-IR index		
	The first tc < 2.96 (N = 44)	**The second tc = 2.96–4.46 (N = 38)**	**Third tc > 4.46 (N = 56)**
Glucose, mmol/l in fasting	5.0 (4.7; 5.1)	4.9 (4.7; 5.2)	5.2 (5.0; 5.4)
Insulin, mIU/l in fasting	9.7 (8.5; 11.6)	17.0 (15.4; 17.4)	25.9 (23.1; 30.9)
Glucose, mmol/l OGTT after 2 h.	5.8 (5.1; 6.5)	6.5 (5.8; 7.4)	6.4 (5.8; 7.1)
Insulin, mIU/l OGTT after 2 h.	68.6 (38.5; 90.2)	98.9 (68.3; 132.0)	119.0 (84.4; 193.0)

* N – number of children; tc – tertile.

When evaluating the HOMA-IR index in group I children (n = 138) according to the stage of puberty, there was an observer tendency for lower median HOMA-IR index in early puberty stages – in Tanner stage I children it was 3.6 (IQR 2.8; 5.2) and Tanner stage II children 3.2 (IQR 2.5; 5.4). The highest median HOMA-IR index was 4.5 (IQR 3.0; 7.3) in Tanner stage V children, however in Tanner stage III children was 4.2 (IQR 3.1; 5.5) and in

Tanner stage IV children 3.8 (IQR 2.5; 5.6) but no statistically significant differences were found in children according to the Tanner stages (p = 0.628).

2.4 Prenatal and postnatal risk factors of obesity and PNFI in study group I children

The predicted liver fibrosis rates were equally high in study I group in both children with positive T2D history in the family and without diabetes history (p = 0.454). The median PNFI in children with positive T2D history in the family was 9.9 (IQR 8.7; 10.0), while in children without history of diabetes it was 9.7 (IQR 8.8; 9.9) (p = 0,109).

In group I children, predicted liver fibrosis was equally common in children with birth weight < 4 kg and those with birth weight ≥ 4 kg (p = 0.411). The median PNFI for children with birth weight < 4 kg was 9.5 (IQR 8.6; 9.9) but in children with birth weight ≥ 4 kg, it was 9.8 (IQR 9.4; 9.9) (p = 0.545).

Furthermore, this prenatal risk factor of obesity – excessive weight gain in mothers during pregnancy – did not affect liver fibrosis scores in group I children (p > 0.999). For children whose mothers had a weight gain during pregnancy up to 20 kg, the median PNFI was 9.5 (IQR 8.7; 9.9), but for children whose mothers had ≥ 20 kg weight gain during pregnancy, it was 9.8 (IQR 9.1; 9,9) (p = 0,167).

The postnatal risk factor of obesity – duration of exclusive breastfeeding – had no effect on predicted liver fibrosis in group I children (p = 0.452). The median PNFI for children with an exclusive breastfeeding period of < 6 months was 9.7 (IQR 9.0; 9.9 but in children with a breast-feeding time ≥ 6 months, it was 9.7 (IQR 8.4; 9.9) (p = 0.833).

A statistically significantly difference in rates of predicted liver fibrosis (p = 0.007) was observed between children with obese and normal weight parents (Figure 2.7). Children with both obese parents had a median PNFI

of 9.8 (IQR 9.3; 9.9) and children with normal weight parents had a median PNFI of 8.8 (IQR 7.4; 9.7) (p = 0.002).

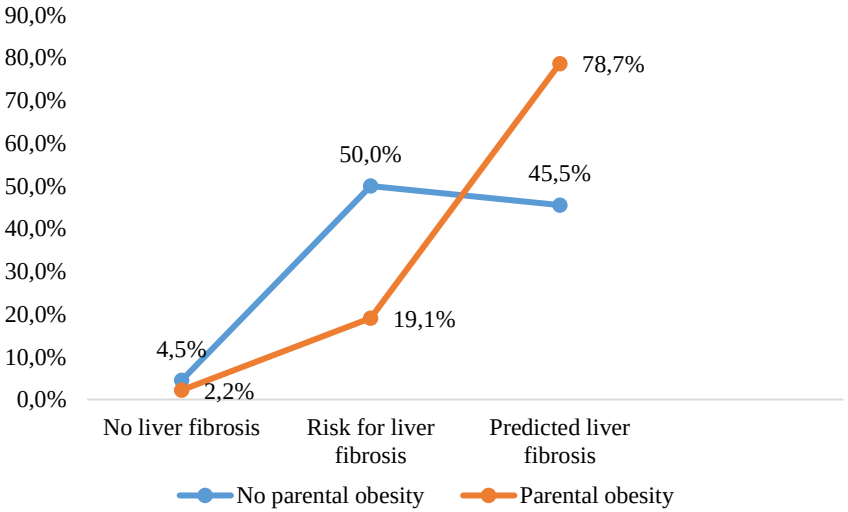

Figure 2.7 **Parental obesity and PNFI rates in study group I children**

2.5 Metabolic syndrome

Studying the diagnostic criteria for metabolic syndrome, it was found that there was no such diagnostic factor in the control group. In study group II, no MS diagnostic criteria were found in 68.4 % (n = 26) of children, one diagnostic criterion was 28.9 % (n = 11) and a set of two criteria was found in 2.6 % (n = 1) of children.

Considering the criteria for diagnosis of metabolic syndrome of the International Diabetes Federation (*IDF*) and age ≥ 10 years, MS was further studied in study group I children only.

In group I, the diagnostic criteria for MS were not found in 53.1 % (n = 76) of the children, but all 4 criteria for MS were found only in 0.7 % (n = 1) of children (Figure 2.8).

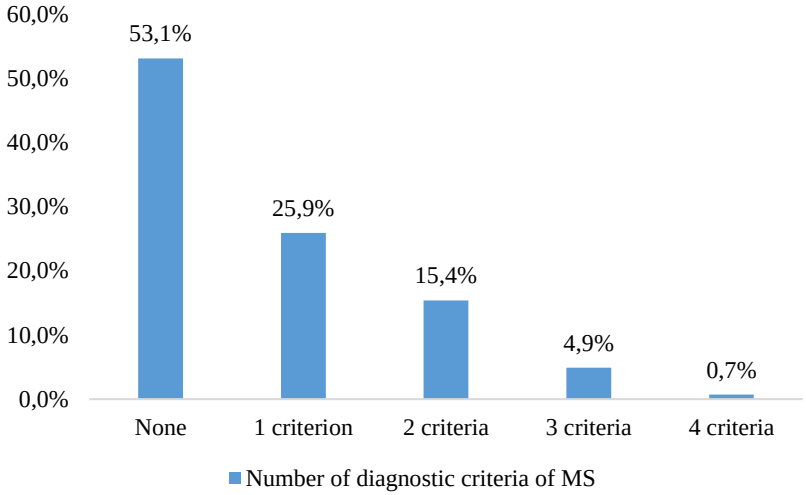

Figure 2.8 **Metabolic syndrome diagnostic criteria for children in study group I**

Metabolic syndrome was diagnosed in 21.0 % (n = 30) of children in study group I according to the IDF criteria. The incidence was higher in children aged 16 years and older when assessing diagnostic criteria of MS according to age; in this group, MS was diagnosed in 38.5 % (n = 10) of children, while 17.1 % (n = 20) of children aged 10 to 16 years were diagnosed with MS.

The most common diagnostic criterion for MS was a decreased HDL level in children under 16 years of age and children 16 years of age and older (Figures 2.9 and 2.10).

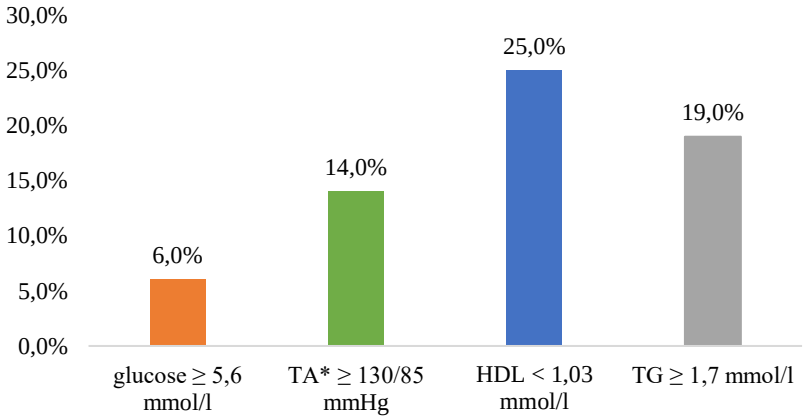

Figure 2.9 **MS diagnostic criteria in children from 10 to 16 years**

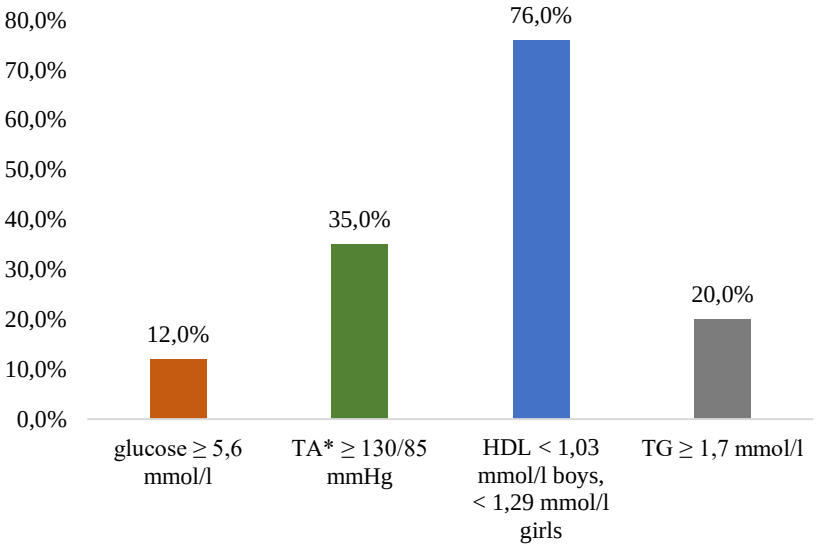

Figure 2.10 **MS diagnostic criteria in children 16 years of age and older**

* TA – arterial blood pressure (Latin *tensia arterialis*).

During the study, children aged 16 years were more likely to experience increased blood pressure ≥ 130/85 mmHg and glucose ≥ 5.6 mmol/l compared to children under 16 years of age.

2.5.1 Prenatal and postnatal risk factors of obesity and metabolic syndrome

Studying the role of obesity risk factors in the development of MS in children in group I, it showed that prenatal risk factors – positive T2D history in the family ($p = 0.519$), excessive weight gain in the mother during pregnancy ($p = 0.625$) and child's birth weight ($p = 0.145$) – did not have a statistically significantly effect on the distribution of MS among children in this group.

The median birth weight for children without MS was 3.6 kg (IQR 3.3; 4.1) and 3.3 kg for children with MS (IQR 3.1; 3.7) ($p = 0.072$).

The postnatal risk factor of obesity in children – duration of exclusive breastfeeding ($p > 0,999$) – also did not affect the prevalence of MS, like all prenatal risk factors of obesity mentioned above. The median duration of exclusive breastfeeding in chaildren without MS was 4.0 months (IQR 2.0; 8.0) and children with MS – 6.0 months (IQR 2.0; 6.0) ($p = 0.994$).

The only risk factor for obesity that affected the prevalence of MS in children of study group I was parental obesity ($p = 0.036$) (Figure 2.11). In children with non-obese parents, MS was diagnosed in only 4.3 % ($n = 1$) of cases, while other children with MS were characterised by parental obesity.

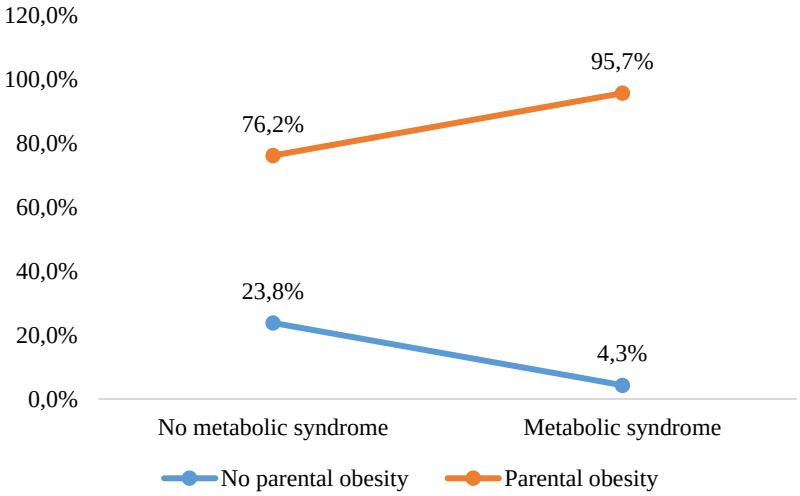

Figure 2.11 **Obesity in parents and metabolic syndrome in children**

2.5.2 Relationship of metabolic syndrome with puberty stage

There were significant differences in the prevalence of MS when assessing the stage of puberty of children (p = 0.013) (Table 2.15).

Table 2.15

Prevalence (%) of metabolic syndrome in children* on the Tanner stage scale (Stage I–V)

Metabolic syndrome	Stage I (N* = 11)	Stage II (N = 31)	Stage III (N = 41)	Stage IV (N = 34)	Stage V (N = 26)
No (n = 113)	7.1 %	25.7 %	31.9 %	19.5 %	15.9 %
Yes (n = 30)	10.0 %	6.7 %	16.7 %	40.0 %	26.6 %

* N – number of children.

More than half of children, up to 66.6 % (n = 20), were diagnosed with MS in late puberty stages, i.e., IV and V Tanner stages.

2.5.3 Evaluation of anthropometric parameters, blood pressure, glucose metabolism, PNFI and other biochemical measurements in children with and without metabolic syndrome

Children with MS were statistically significantly taller ($p < 0.001$) and, these children had higher weight ($p < 0.001$), which directly affected BMI ($p = 0.006$). BMI and statistically significantly higher waist circumference ($p = 0.003$) in children with MS confirmed the central obesity tendency. CVD risk factors – systolic blood pressure ($p < 0.001$) and diastolic blood pressure ($p < 0.001$) – were also statistically significantly higher in children with MS than in children without MS (Table 2.16).

Table 2.16

Anthropometric parameters, blood pressure and biochemical measurements in children* with or without metabolic syndrome

Indicator	No MS (N = 113)	MS (N = 30)
Height, m	1.6 (1.6; 1.7)	1.8 (1.7; 1.8)
Weight, kg	83.0 (69.0; 96.8)	99.0 (89.0; 125.0)
BMI, kg/m^2	30.1 (27.3; 33.4)	32.8 (30.4; 38.3)
Waist circumference, cm	100.0 (93.0; 108.0)	107.5 (99.2; 117.5)
SBP, mmHg	121.0 (115.0; 130.8)	132.0 (123.0; 140.0)
DBP, mmHg	75.5 (70.0; 80.0)	87.0 (80.0; 92.0)
Glucose, mmol/l fasting	5.0 (4.8; 5.3) (N = 112)	5.2 (4.9; 5.4) (N = 30)
Insulin, mIU/l fasting	16.7 (11.2; 24.1) (N = 110)	20.6 (16.4; 25.7) (N = 29)
Glucose, mmol/l OGTT after 2 h.	6.3 (5.5; 7.0) (N = 99)	6.2 (5.6; 7.0) (N = 27)
Insulin, mIU/l OGTT after 2 h.	85.0 (57.5; 115.5) (N = 88)	124.5 (89.5; 187.8) (N = 26)
HOMA-IR index	3.6 (2.5; 5.4) (N = 109)	5.0 (3.4; 6.0) (N = 29)
HbA1c, %	5.5 (5.2; 5.7) (N = 104)	5.4 (5.3; 5.6) (N = 30)
ALT, U/l	21.7 (15.2; 31.4) (N = 107)	26.3 (20.3; 36.4) (N = 29)

Table 2.16 continued

Indicator	No MS (N = 113)	MS (N = 30)
TCh, mmol/l	3.9 (3.5; 4.5) (N = 107)	4.5 (3.8; 5.1) (N = 30)
HDL, mmol/l	1.2 (1.1; 1.3) (N = 102)	0.9 (0.8; 1.0) (N = 29)
LDL, mmol/l	2.5 (2.1; 3.0) (N = 103)	2.9 (2.5; 3.5) (N = 29)
TG, mmol/l	1.0 (0.7; 1.4) (N = 100)	2.0 (1.5; 2.2) (N = 29)

* N – total number of cases analysed.

There was no difference in fasting glucose in children without and with MS ($p = 0.093$) and after 2 hours post load glucose ($p = 0.894$). However, children with MS had statistically significantly higher insulin levels on both fasting ($p = 0.041$) and after 2 hours post load glucose ($p = 0.005$).

When calculating the HOMA-IR insulin resistance index directly influenced by fasting blood glucose and insulin levels, insulin resistance was more common in children with MS ($p = 0.039$). The ALT level in children with MS were also significantly higher than in children without MS ($p = 0.002$).

Other risk factors for CVD, lipids levels in the blood – total cholesterol ($p = 0.01$), LDL (0.005) and TG ($p < 0.001$) were significantly higher in children with MS compared to children without MS. On the other hand, HDL levels in children with MS were statistically significantly lower ($p < 0.001$).

Pediatric NAFLD fibrosis index was significantly higher in children with MS, with a median PNFI of 9.9 (IQR 9.8; 10.0) while in children without MS the median PNFI was 9.5 (IQR 8.3; 9.9) ($p < 0.001$). Predicted liver fibrosis was expected in almost all children 93.3 % with MS. Significantly lower predicted liver fibrosis rates of only 66.0 % were observed in children without MS ($p = 0.003$) (Figure 2.12).

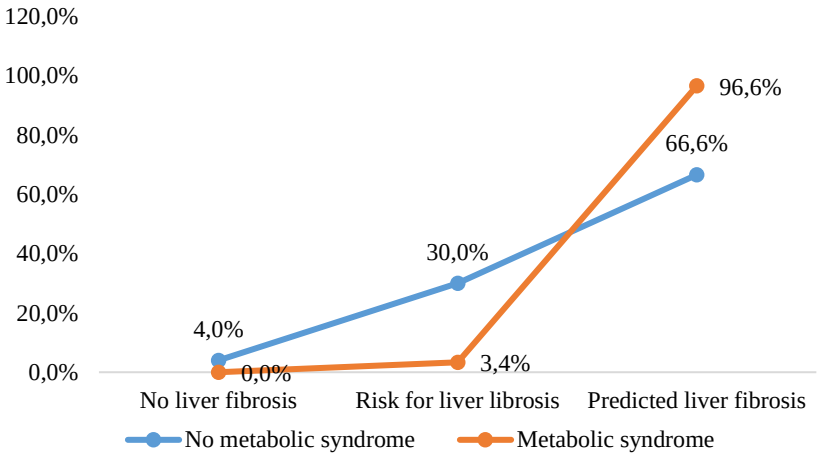

Figure 2.12 **Metabolic syndrome and PNFI in children**

2.5.4 Metabolic syndrome risk in obese children

By inserting a number of parameters into the logistic regression model, it was established that age, BMI, SBP, waist circumference, ALT, insulin levels taking OGTT after 2 hours and paternal obesity increased the metabolic syndrome risk in children.

With the increase in BMI, the risk of MS increased by 1.12 times, but paternal obesity increased this risk by up to 11.13 times compared to children whose parents had normal weight (Table 2.17). The risk of metabolic syndrome in children was not increased by prenatal risk factors of obesity such as high birth weight and positive T2D history in family.

Table 2.17

Risk of metabolic syndrome in study group I children

Indicator	B*	OR**	value of Z	value of P
Boys *(Reference: the girls)*	0.49	1.64	1.183	0.273
Age *(Step: 1 year)*	0.32	1.38	3.25	**0.001**
BMI, kg/m^2 *(Step: 1 unit)*	0.11	1.12	3.007	**0.003**
Waist circumference, cm *(Step: 1 cm)*	0.05	1.05	3.248	**0.001**
SBP, mmHg *(Step 1 mmHg)*	0.05	1.05	3.4	**0.001**
HOMA-IR index *(Reference: first tertile)*	0.17	1.19	0.527	0.275
ALT *(Step: 1 unit)*	0.02	1.02	2.213	**0.027**
Insulin OGTT after 2 hours. *(Step: 1 unit)*	0.01	1.01	2.138	**0.032**
Birth weight ≥ 4 kg *(Reference: birth weight < 4 kg)*	−1.11	0.33	−1.399	0.162
Positive T2D history in the family *(Reference: no T2D in family)*	−0.78	0.46	−0.987	0.324
Obesity in the family: *(Reference: normal weight for parents)*				
Parental obesity	1.79	5.99	1.659	0.097
Paternal obesity	2.41	11.13	2.122	**0.034**
Maternal obesity	1.79	5.99	1.603	0.109

* B – regression factor;
** OR – odds ratio.

3 Discussion

The hypothesis of the development of the metabolic syndrome and its relevance to the weight of the child was confirmed during the study. As the body mass index increases, the likelihood of metabolic syndrome has also been observed. This indicates that any child and adolescent with significant overweight should be assessed as a high-risk patient for obesity complications. During the study, it has also been observed that more metabolic syndrome is diagnosed in children at late stages if puberty which correspond to the proposed hypothesis about the relationship between puberty and metabolic syndrome. These two research questions were already extensively studied and analysed by researchers, but the result of the study points to the main national goal of combating childhood obesity – it is the prevention of obesity and early management of excess weight even before serious complications occur.

The hypothesis of the effect of prenatal and postnatal risk factors of obesity on the risk of metabolic syndrome was only partially confirmed. The positive history of T2D in the family and the child's birth weight did not increase the risk of developing metabolic syndrome. Only the postnatal risk factor of obesity – parental obesity (especially paternal) – increased the risk of metabolic syndrome in children. The uncovered fact about the influence of paternal obesity on the risk of metabolic syndrome opens up new research questions: about the mechanism of inheritance of metabolic complications, the possible different role of parents in the process of chronic complications, and the influence of environmental factors and father's habits on the child's weight and risk of complications.

Prevalence and diagnostic criteria of metabolic syndrome in the paediatric population

In recent years, important data have been accumulated on risk factors for cardiovascular diseases and metabolic syndrome in children with obesity. However, the definition of MS in children and adolescents is still unclear, as there is no golden standard of diagnostic criteria for the paediatric population (Al-Hamad et al., 2017). Most studies analysed blood lipid levels (TCh, HDL, LDL, TG), blood pressure (SBP and DBP) and glucose metabolism (fasting glucose, uncommonly glycated haemoglobin). Although studies have shown that metabolic syndrome is more common in children with severe rather than mild obesity, only a few studies have been focused on whether severe obesity poses an increased risk of metabolic syndrome compared to mild obesity (Calcaterra et al., 2008; Skinner et al., 2015; Tavares Giannini et al., 2014). The prevalence of MS has also been found to be significantly higher in high-income countries due to the increasing number of obese children (Agudelo et al., 2014; Friend et al., 2013; Swinburn et al., 2019). The meta-analysis by Bitew et al. revealed that the prevalence of MS in the paediatric population is variable and depends on the chosen diagnostic criteria for MS. When assessing MS according to the diagnostic criteria of the IDF and the National Cholesterol Education Programme in the United States (NCEP), it was established in 25.25 % and 24.47 % of children, respectively. Using the MS diagnostic criteria of Ferranti et al. and Weiss et al., it has been found that prevalence among children is much higher, 39.41 % and 33.36 % respectively (Bitew et al., 2021). The study by Smetanina et al. found that 21.3 % of overweight children in Lithuania have MS evaluated according to the IDF diagnostic criteria, and 6.9 % of children have fasting hyperglycaemia (Smetanina et al., 2021). It should be noted that the definitions of values of biochemical blood measurements vary significantly between studies, and the incidence of at least one MS criterion in severely obese children ranged from 67 to 86 % of cases (Bendor et al., 2020). In the meta-analysis

of Bitew et al., the most common diagnostic criterion for MS in children was high blood pressure 27.50 %, low HDL 23.41 %, increased TG – 19.05 %. Increased fasting glucose was found only in a small number of children, 7.16 % of children according to NCEP criteria and 1.63 % by the World Health Organisation (WHO) (Bitew et al., 2021).

The data of the conducted study correspond with the literature data on the prevalence of MS in obese children. According to the IDF diagnostic criteria, MS was found in 21 % of obese children aged 10 years and older. At least one MS diagnostic criterion was identified in 46.9 % of children aged 10 years with obesity and in 31.5 % of children younger than 10 years. The most common diagnostic criterion for MS was decreased level of HDL in blood, a total of 32.6 % of obese children under 10 years. From the age of 16, decreased level of HDL in blood was found in 76 % of children and 25 % of children aged 10 to 16 years. The second most common diagnostic criterion was high blood pressure, with 17.5 % of children aged 10 years and older, and 35 % of children aged 16 years and older and 14 % of children aged 10 to 16 years. Elevated glucose levels ≥ 5.6 mmol/l were observed in a total of 7 % of obese children aged 10 years and older, consistent with the meta-analysis data of Bitew et al., for the incidence of diagnostic criteria of MS.

Risk factors for metabolic syndrome in children and adolescents with obesity

Several studies have attempted to clarify and identify risk factors for metabolic syndrome. Data suggest that the risk of MS is related to BMI, waist circumference and fasting insulin level. A study published by Jung et al. found that BMI is the best prognostic factor to identify metabolic syndrome and its diagnostic criteria (Jung et al., 2010). The study conducted by Smetanina et al. also demonstrates the direct effect of BMI on the prevalence of MS in children.

MS was found in 10.7 % of children with overweight; 22.8 % with obesity; 25.9 % with severe obesity degree (Smetanina et al., 2021).

Several studies have also shown a genetic predisposition to the development of the syndrome and certain ethnic groups that are at increased risk of MS. The conducted studies also confirm the importance of the intrauterine environment (Hadjiyannakis, 2005).

Birth weight – both too small and too large for gestational age – is associated with metabolic complications during life. The long-term consequences of the large birth weight related to MS have been studied only in a few studies. Early obesity and MS risk are believed to be directly related to large birth weight (Hong et al., 2021). The risk of MS was 2 times higher for children with large birth weight (HR 2.19; 95 % CI: 1.25–3.82). There was an increased risk of MS not only in children with large birth weight, but also in children who were exposed to effects of maternal diabetes or obesity in the intrauterine environment (Boney et al., 2005; Romero-Velarde et al., 2016).

Researchers in a study conducted in a large cohort of obese children in Italy found that a high waist-to-hip ratio, positive family history of T2D and *acanthosis nigricans* were associated with a high risk of metabolic syndrome and prediabetes. Each of the three clinical markers studied has been shown to be associated with an increased risk of metabolic syndrome and prediabetess / diabetes. In addition, it is simple to obtain each of these markers during the first clinical examination (Santoro et al., 2013). Guerrero-Romero et al. reported that children with a positive family history of diabetes and large or low birth weight are at high risk of metabolic syndrome. The risk of MS is higher in children with a positive maternal, but not paternal history of diabetes (Guerrero-Romero et al., 2010). Other studies have also shown that the prevalence of MS is significantly higher in children whose family member has diabetes, hypertension, coronary heart disease or dyslipidaemia. This indicates not only the impact of genetic factors, but it can also indicate similar environmental conditions, dietary habits,

socio-economic family status, and sedentary lifestyle (Sangun et al., 2010). In Americans of Mexican origin family history of diabetes was the most accurate prognostic risk factor for the development of metabolic syndrome (Hadjiynnakis, 2005).

Studies have reported that breastfeeding may have a beneficial effect and reduce the risk of developing individual components of metabolic syndrome in children and adolescents, but it is not known whether there is a relationship between breastfeeding and metabolic syndrome in general. The Wisnieski et al. review showed a limited number of high-quality studies on the relationship between breastfeeding and the development of metabolic syndrome in children and adolescents with obesity. The evidence provided in this review suggests that breastfeeding may protect against MS, but further research is needed. When planning studies on breastfeeding and MS, the duration of breastfeeding, the course of pregnancy and delivery, maternal diseases and weight status should be specified which would allow for a more targeted analysis of the factors that may influence breastfeeding and its role in development of MS (Wisnieski et al., 2018).

Ornellas et al. review of literature indicates that paternal obesity causes insulin resistance / T2D and increased levels of cortisol in the blood of the umbilical cord in the newborn, which affects risk factors for cardiovascular diseases. There is also a link between parental obesity and the risk of obesity in their daughters (Ornellas et al., 2010). Parental obesity is not only a risk factor for overweight in their offspring, but also for insulin resistance, which begins to develop already in the prepubertal period. If parents are not only obese, but also have hypertension, then their children have higher insulin resistance, higher blood pressure, serum cholesterol and triglycerides than control subjects (Hadjiynnakis, 2005).

Only a few studies have tested the association between maternal weight before pregnancy or excessive weight gain during pregnancy with cardiovascular disease and risk of metabolic syndrome in children. For the most part, this applies to BMI and blood pressure. It has been found that maternal weight before pregnancy is more consistently associated with child's obesity and cardiovascular disease risk than excessive weight gain during pregnancy. This finding supports initiatives aimed at maintaining healthy weight in women of reproductive age. And pregnancy can be an opportunity to change the mother's diet and physical activity habits. In addition, limiting excessive weight gain during pregnancy may help break the cycle of obesity between generations, but the benefits of less weight gain need to be compared with possible risks (e.g., growth retardation of offspring if the mother's weight dynamics during pregnancy are not sufficient). Further long-term follow-up of these children is necessary to assess the impact of maternal excessive weight gain during pregnancy on the cardiometabolic risk in adolescence and adulthood (Fraser et al., 2010; Gaillard et al., 2016; Hrolfsdottir et al., 2015; Tam et al., 2018).

The results of this study show that the risk of MS increases with an increase in BMI. The MS risk was also associated with biochemical parameters such as ALT level in the blood and insulin level after 2 hours post load glucose. This may indicate an increased excretion of glucose from the liver due to an increase ALT level in the blood, and an excessive release of insulin into the pancreas. These changes are the pathogenetic mechanism for the early development of insulin resistance, CVD, and T2D. Parental obesity significantly increased the risk of metabolic syndrome in obese children from the age of 10 years. These results confirm the results of the above-mentioned studies and allow to identify the group of children and adolescents who are at high risk of developing CVD and T2D in the future. Childhood obesity treatment should be personalised, considering the growth and sexual maturation process. And the

primary goal of treatment in children and adolescents would be to normalise the balance of energy intake and consumption.

Identifying and managing weight problems in children among primary healthcare professionals and parents

According to the established inclusion and exclusion criteria, 198 children were included in the study. When children were included in the study, BMI was not calculated and evaluated in percentile charts according to the child's age and gender immediately. Later, when calculating and evaluating children's BMI in percentile chart during the study, there was an alarming trend – 91.4 % of the included children were found to be obese, but no child was found to be overweight during the study and 8.6 % of children were of normal weight. This might suggest that children and adolescents are referred to the child endocrinologist only when the degree of obesity is already significant and complications of obesity have developed, which require careful examination, follow-up, and initiation of treatment. However, it would be much more important to notice their overweight or rapid weight gain in time, even before the obesity complications occur in children. Two factors would be important here – the timely response of primary care professionals and parents to the weight problems of the child, as well as the referral to the weight management programme to initiate lifestyle changes.

Studies have shown that primary care professionals do not assess and solve children's weight problems in time. Physicians interviewed in several studies have identified childhood obesity as an increasingly important problem with potential long-term health effects. However, the majority did not consider it to be a medical problem or did not consider its management as a responsibility of general practitioner (O'Donnell et al., 2017). The research found that only 25.7 % of physicians reported a problem of overweight or inadequate weight gain to parents. Although70.6 % of physicians reported that they had discussed eating

and physical activity habits with parents of overweight or obese children, only 19.4 % indicated that they had given these parents the necessary advice to change eating habits and promote physical activity. Less than half (41.7 %) of physicians reported that they had determined that parents were willing to make minor changes for their overweight or obese child (Holt et al., 2011).

Studies on parent's perception of their child's weight have shown that parents deliberately or unconsciously deny their child's weight problems. In any case, parents more often objectively perceived the child's underweight than obesity. During the studies it was found that parents did not assess the child's overweight if "he is active, and the child has a good appetite". This may indicate that most parents do not perceive their child's overweight or obesity as a serious health problem that can lead to complications and chronic diseases in the future (He at al., 2007). In a systematic review by Rietmeijer-Mentink et al. tried to determine the discrepancy between parent's perception and the child's actual weight. Of the 35 000 children included in the study, 32.9 % were overweight, but only 37 % of parents correctly perceived the child's overweight problem. This systematic review indicates that a large proportion of parents do not recognise the child's weight problem, and this is especially true for the parents of children aged 2–6 years. Subgroup analysis revealed that even 86 % of parents of 2–6 years old children deny that their child is overweight (Rietmeijer-Mentink et al, 2013).

In clinical practice, the child's weight category of a child is determined by evaluating BMI percentile charts according to the child's gender and age. Excess weight in children is divided into two categories – as overweight and obesity. This is different from adults for whom obesity is divided into three degrees of severity, where, for example, the third BMI group > 40 kg/m^2 is considered as severe obesity. In children the degree of obesity is not determined in everyday clinical practice, but several researchers are trying to identify a group

of children with significant BMI, who would be at particularly at high risk of chronic diseases and obesity complications.

Strategies for grading severe obesity in children vary widely in the scientific literature and are often difficult to apply in clinical practice (CDC, 2020; Jung et al., 2010). A BMI threshold of > 120 % of the 95th percentile derived from the growth charts of the Centre for Disease Prevention and Control is currently used to define the degree of severe obesity in children. This allows for an individual assessment of each child's BMI status. There is also evidence from studies that this strategy for detecting severe obesity helps identify children at high risk of metabolic syndrome. However, since the establishment of this strategy in 2013, these cut-off values have been used only in half of the published studies. Many other methods of defining severe obesity are also commonly used, such as using absolute BMI cut-off values, z-BMI and ≥ 99 percentile (Bendor et al., 2020; CDC, 2020; Jung et al., 2010).

A study by Israeli researchers on the severity, prevalence and risk factors of childhood obesity included 1027 children who attended a weight management clinic (mean age 10.8 years; 41.8 % for boys). This study found that 55 % of children were severely obese and its prevalence increased from 54 % in 2008 to 69 % in 2017. Severe obesity was more common in boys ($p = 0.002$) at an early age compared to girls ($p < 0.001$). These boys were characterised by familial obesity ($p = 0.002$), as well as higher incidence of obesity-related co-morbidities (systolic hypertension, dyslipidaemia, obstructive sleep apnoea and non-alcoholic fatty liver disease) ($p < 0.001$) (Avnieli et al., 2019). This finding by Israeli researchers reflects trends in the general paediatric population and encourages changes in policy regarding paediatric weight management clinics. Children are referred to weight management clinics late, already with a severe degree of obesity and co-morbidities. In this case, weight management is difficult, requires intensive intervention in the family environment and regular visits to the clinic.

The results of the study show that 7.9 % of children under 10 years of age and 21.7 % of children over 10 years of age had BMI ≥ 35 kg/m². Evaluating the degree of obesity of the children included in the study by the BMI value ≥ 35 kg/m² and using the severe obesity detection method proposed by the *CDC*, a numerical BMI of > 120 % of the 95th percentile for children under 18 would correspond to 35.4 kg/m². All study children with BMI ≥ 35 kg/m² can be considered as severely obese children, especially children under 10 years of age. This means that these children are at high risk of chronic diseases and obesity complications in the future. Special attention should be paid to the fact that a total of 29.6 % of the children in the study had a severe degree of obesity and these children had not started weight management. It is possible that also in Latvia, the number of children with severe obesity is increasing and solving of weight problems is delayed. Delayed solving of weight problems in Latvia can be related to passive involvement of primary care specialists and the availability of underdeveloped multidisciplinary programmes for children and adolescents. Until now, there is no nationally developed weight management programme, which would be divided into successive stages. According to the obesity prevention and care guidelines developed by Katzmarzyk et al., weight management is initiated and implemented by primary care professionals in the first and second stages. In the third stage, weight management is carried out by a multidisciplinary team in a paediatric clinic, while in the fourth stage children with severe obesity and chronic diseases are referred, when not only lifestyle correction is required, but also pharmacotherapy and in rare cases even bariatric surgery (Katzmarzyk et al., 2014).

The lower prevalence of severe obesity in the study population can be explained by the fact that children visited a paediatric endocrinologist in the outpatient department and the weight level in these children had not been previously evaluated, but in a study conducted by Israeli researchers, children

attended a weight management clinic when the fact of obesity was already known.

Prenatal and postnatal risk factors of obesity

As the prevalence of obesity in children increases worldwide, not only obesity-related complications are studied, but also risk factors that increase not only the risk of obesity, but also the possibility of early complications. These factors are categorised, for example, by exposure time – before or after birth – and constitute prenatal and postnatal obesity risk factors. The following are identified as prenatal risk factors: T2D history in the family, excessive weight gain in pregnancy, birth weight, etc., on postnatal risk factors: duration of exclusive breastfeeding, parental obesity, parental education level, socio-economic family status, etc. Obesity risk factors are further divided into preventable factors such as sedentary lifestyle, unhealthy eating habits, smoking, etc., and non-preventable factors such as age, gender, ethnicity, etc. Research and awareness of these risks allows for the targeted development of anti-obesity tactics and prevention programmes for children.

Many studies provide evidence that confirms the hypothesis that child's birth weight is associated with disease risk later in life. Such associations are well identified, especially for birth weight and the risk of coronary heart disease, diabetes, hypertension, and stroke in adulthood. Many researchers have reported that a birth weight > 4000 g is associated with a higher risk of obesity compared to the birth weight < 4000 g. The role of low birth weight, i.e., < 2500 g, on obesity risk in children is currently controversial. Several researchers have observed a positive linear relationship between birth weight and obesity. Analyses that considered subgroups representing different stages of growth and puberty (pre-school children, school-age children and adolescents) showed that large birth weight was associated with a higher risk of obesity from childhood to early adulthood (Schellong et al., 2012; Yu et al., 2011). Research data show, for

example, that each 100 g increase in birth weight is associated with a higher risk of obesity in the future (Zhao et al., 2012). However, there are also studies with conflicting data regarding birth weight and obesity risk. For example, birth weight has been found to be directly related to the BMI percentile; however, no significant differences were found in birth weight between overweight / obese and normal body weight children (Baran et al., 2019).

The German Health Interview and Examination Survey for Children and Adolescents (KIGGS*)* showed that the highest risk of obesity in children was associated with parental obesity, low socio-economic status, maternal smoking during pregnancy, excessive weight gain in pregnancy, large birth weight, excessive screen time and poor sleep quality. This study found that the children of normal weight mothers who gained ≥ 20 kg during pregnancy were 2.8 times more likely to be overweight or obese (HR 2.81; 95 % CI: 1.6–50.0). Parental obesity showed the strongest association with childhood obesity risk. In children, the risk of obesity was 11.2 times higher when both parents were obese compared to children whose parents were non-obese (HR 11.24; 95 % CI: 6.4–19.7) (Kleiser et al., 2009). Many other authors described similar observations. Excessive weight gain during pregnancy clearly increased the risk of obesity in children from early childhood to preschool and school age (Baran et al., 2020; Sridhar et al., 2014). A study by Shao et al. showed that maternal obesity before pregnancy (HR 2.01; 95 % CI: 1.53–2.65) and excessive weight gain during pregnancy (HR 1.65; 95 % CI: 1.35–2.03) increases the risk of obesity in children, while underweight before pregnancy is a protective factor for childhood obesity (HR 0.49; 95 % CI: 0,39–0.62) (Shao et al., 2016). The data from analysis by Leonard et al. showed that the risk of obesity among children was the lowest in the group whose mothers had low body weight. The difference in the risk of obesity was highest after the age of five and persisted in adolescence. Furthermore, if the mother was already overweight before pregnancy, the risk of obesity in children aged 6 to 11 years doubled (Leonard et al., 2017).

Short duration of exclusive breastfeeding may also be a risk factor for obesity in children, while optimal breastfeeding duration may reduce the risk of childhood overweight / obesity in childhood. Meta-analyses suggest that breast-feeding longer than 6 months can reduce the obesity risk by 13–31 % (Horta et al., 2015). However, although the relationship between the obesity risk and the duration of breastfeeding in children has long been discussed, unfortunately no agreement has been reached on this issue (Qiao et al., 2020). Many studies have identified breastfeeding as a protective factor, while other studies have failed to establish an association between breastfeeding and childhood obesity risk (Yan et al., 2014). For example, Toschke et al. reported no association between breastfeeding for up to 6 months and obesity in their study, and other studies have also found no increased risk of obesity in children who had been exclusively breastfed for less than 4 months (Huus et al., 2008; Toschke et al., 2007).

A positive family history of T2D has been recognised as an important risk factor for diseases in children. Children with diabetes in the family are 2–6 times more likely to develop T2D than children of no family history of diabetes. Of the comprehensive risk assessment, it is the use of family history in children that can be crucial for the prevention, early detection and treatment of T2D. At population level, a family history can help to adapt health promotion intervention to specific population groups (Annis et al., 2005; Yoon et al., 2003). A positive family history of diabetes is very common in young people with T2D. Many young people with T2D live with an adult family member who also has diabetes and obesity. However, it should be noted that for young people the consequences of a common DM experience in the family can be both positive and negative. Several qualitative studies have been addressed to this issue (Pulgaron et al., 2014). In one study, parents reported a controversial role regarding their child's diabetes management: while parents recognised the opportunity to provide support and serve as positive examples, they also reported difficulties in setting

a good example of changes in healthy lifestyles. Family members with T2D can have a negative impact on young people because they accept diabetes-related health complications. If family members have had health disorders due to chronic hyperglycaemia, such as retinopathy, nephropathy, extremity amputations and premature death, young people may perceive these complications as an inevitable course of diabetes (Mulvaney et al., 2006; Jones, 1998).

Several studies have analysed the impact of parental obesity on the risk of obesity in childhood and the risk of early complications of obesity. Most studies link parental BMI and overweight / obesity to the risk of obesity in their offspring, both in childhood and adulthood (Martínez-Villanueva et al., 2019; Reilly et al., 2005). Family predisposition to obesity appears to be particularly important in the development of obesity in preschool children. In studies in obese and normal weight children under 10 years of age, parental overweight / obesity was an important predictor of obesity in adulthood. For example, a 1958 British birth cohort study (n = 16794, offspring n = 2908) shows that an increased risk of overweight and obesity in offspring is associated with an increased parental BMI and parental rapid weight gain in both childhood and adulthood (Li et al., 2009; Nielsen et al., 2015).

Studies linking parental BMI to child obesity risk have observed different effects of maternal and paternal weight: high paternal BMI increases the risk of overweight / obesity in both boys and girls, while increased maternal BMI reduces the risk of obesity among adolescent girls. In contrast, a stronger effect of maternal obesity on the child has been observed in a small longitudinal study (n = 197) specifically of 5 to 7 years old girls, as well as in other studies in Indian and Pima Indian children. However, children from families where both parents are overweight or obese are at the highest risk of child overweight / obesity (Nielsen et al., 2015; Shafaghi et al., 2014, Veena et al., 2014, Whitaker et al, 2010).

Parents and their weight influence not only the risk of obesity in children, but also the outcome of weight management. A large proportion of parents have a misconception about their children's weight, which increases the likelihood of overweight up to 12 times and delegates the child's overweight problems to public institutions, schools and doctors. Studies in which children and adolescents are involved in weight loss programmes with their parents show that normal weight parents better understand the basic principles of obesity treatment, have better communication with the weight management team, they listen more carefully to advice and follow recommendations. At the same time, there are also studies that show that weight management programmes are less successful for children whose parents or siblings are overweight. Some researchers have described a poorer response to lifestyle modification in association to maternal obesity. Other studies have found that parental weight loss in obese children has a significant effect on weight management outcomes (Danielsson et al., 2012; Eliakim et al., 2004). In general, only a small number of studies have analysed how parental obesity can affect the results of weight management in children and adolescents, the degree of obesity and the risk of chronic diseases (Holm et al., 2011; Nielsen et al., 2015).

When comparing the literature data with the results of the conducted study, the obtained results on the risk factors for obesity in children and adolescents do not overlap in part. The results show that birth weight in obese and normal weight children do not differ, although a large birth weight trend in children under ten years of age was observed. However, in all study groups, the proportion of children with a birth weight ≥ 4 kg was high. The duration of exclusive breastfeeding also did not differ between obese and normal weight children. Only 40.3 % of obese children aged 10 years and older received exclusive breastfeeding for 6 months or more, but no statistically significant differences in breastfeeding duration were demonstrated. Positive family history of T2D and excessive weight gain during pregnancy were equally common in

obese and normal weight children. The study found that in obese and normal weight children, only the prevalence of parental obesity varied. Parental obesity was found in 79.8 % of obese children and only in 33.3 % of normal weight children. In children with normal weight were not found maternal obesity.

Analysis of prenatal and postnatal risk factors of obesity showed that only for 10 years of age and older obese children positive family history of T2D had a negative impact on anthropometric parameters. These children had a significantly higher waist circumference, BMI and blood pressure compared to children without diabetes history in the family. Only fasting glucose level was significantly different between children with birth weight < 4 kg and ≥ 4 kg. Children with a birth weight ≥ 4 kg had higher glucose level in the blood. Although no statistically significant differences were found for fasting insulin level and after 2 hours post load glucose or for insulin resistance HOMA-IR index. The study showed an interesting trend that both fasting and after 2 hours post load glucose insulin levels were lower in children with birth weight ≥ 4 kg, respectively, the HOMA-IR insulin resistance index also was lower in these children. Perhaps, this may be explained by the fact that the higher proportion of children with a birth weight ≥ 4 kg was directly in the group of children under 10 years of age who had not started physiological insulin resistance. Excessive weight gain during pregnancy in the mother and duration of exclusive breastfeeding for 10 years and older in obese children did not show significant differences in anthropometric, blood pressure or biochemical parameters. Parental obesity negatively affected anthropometric, blood pressure and biochemical parameters in these children. Children whose parents were of normal weight had lower waist circumference and BMI, as well as SBP and DBP, ALT and uric acid levels in the blood.

Obesity-related chronic diseases

The European Society for Paediatric Endocrinologists, the North American Pediatric Association and many other international guidelines clearly indicates the importance of assessing both complications and co-morbidities associated with overweight. These guidelines generally recommend screening for hypertension in all children and adolescents with overweight and obesity. For example, the US Expert Committee on Adolescents Overweight recommends assessing blood pressure in all children with BMI above the 85th percentile. Despite the clinical evidence underlying these guidelines, overweight adolescents are difficult to assess in clinical practice. However, it should be noted that 33.6 % of 12–19-year-olds are overweight (August et al., 2008; Bendor et al., 2020; Kelly et al., 2015).

The diagnosis of obesity in children increases the risk (experience rate = 2.61) to determine early diagnosis of arterial hypertension between the ages of 8 and 19. This suggests that paediatricians and general practitioners are aware that hypertension is an important complication in overweight children and adolescents (Hansen et al., 2007). In most studies, the correlation between BMI and blood pressure in adolescence is moderate or strong, and the strongest correlation is in children with severe obesity. The mechanisms involved in the development of hypertension in overweight adolescents are currently not fully understood; however, it is clear that a number of preventable and non-preventable risk factors are involved. Some clinical and biochemical markers, including family history of hypertension and hyperinsulinemia indicates a high risk of hypertension in overweight adolescents. These indicators may prove useful for stratifying overweight adolescents into a high or low risk groups of developing hypertensions.

The treatment of hypertension related to obesity in the paediatric population is based on two main methods: lifestyle modification and pharmacotherapy (Blüher et al., 2013; Kelly et al., 2015). In a study by

Blüher et al., elevated blood pressure was observed in 26.5 % of children included in the German / Austrian / Swiss Obesity Register; 36.7 % of children had an elevated one or more lipid parameters in the blood; prevalence of dyslipidaemia ($p = 0.0329$) and hypertension ($p = 0.0076$) was higher among boys; the prevalence of dyslipidaemia increased with age ($p = 0.0700$), but the prevalence of hypertension was not affected by age in children ($p = 0.1000$) (Blüher et al., 2013).

Our study also showed that both systolic and diastolic blood pressure is higher in obese children aged 10 years and older compared to normal weight children's blood pressure. In obese children, blood pressure above 130/85 mmHg was found in 17.5 % of cases. Blood pressure values were negatively influenced by positive family history of T2D and parental obesity. Duration of exclusive breastfeeding, excessive weight gain in the mother during pregnancy and birth weight ≥ 4 kg did not influence blood pressure in the study population. Perhaps the higher prevalence of hypertension in children in the Blüher et al., study can be explained by a different definition of elevated blood pressure. In our study, blood pressure values were assessed according the IDF criteria, and in the Blüher et al., study according to the American Heart Association criteria.

Factors contributing to insulin resistance include central obesity, sedentary lifestyle, age, puberty, family history of T2D, ethnicity, intrauterine environment – too small or large birth weight for gestational age, gestational diabetes in the mother and eating habits. Studies on anthropometric parameters and their relationship with cardiovascular diseases and metabolic syndrome risk factors have shown that insulin resistance seems to be stronger correlated to BMI, whereas levels of uric acid, HDL, ALT in the blood are stronger correlated with waist circumference (WCA). However, the correlation between blood pressure, metabolic markers, and anthropometric parameters – BMI and WC – showed only minor differences. This suggests that BMI detection is a sufficiently accurate method to predict the risk of CVD and metabolic syndrome in obese

children. Minor benefits in the assessment of waist circumference do not justify the mandatory introduction of this measurement into routine practice in the children's population. There is a fact that the correlation between all parameters is the strongest among puberty. In obese children just at puberty, anthropometric parameters (BMI and WC) are the best predictors of CVD and metabolic syndrome risk (Blüher et al., 2013; Freedmann et al., 2004; Al Hourani et al., 2021).

The study carried out confirmed observations on the correlation of the insulin resistance HOMA-IR index with anthropometric measurements, as there was moderate correlation with both weight and BMI, as well as with waist circumference.

Many studies have shown that the most significant clinical risk factor for T2D in children and adolescents is severe obesity. The mean BMI in children with T2D in published reports ranges from 35 to 39 kg/m^2; but approximately one third of children with T2D were found to have a BMI greater than 40 kg/m^2 and 17 % BMI greater than 45 kg/m^2 (Jung et al., 2010; Pinhas-Hamiel et al., 2005). A national wide cross-sectional study of adolescents in Israel, in 1.5 % of children with severe obesity were diagnosed with diabetes. In addition, the risk of diabetes was reported to increase in adolescents with severe obesity (HR 19.1; 95 % CI: 12.3–29.6) and those with very severe obesity respectively (HR 38.0; 95 % CI: 22.6–64.0) compared to mild obesity (HR 5.59; 95 % CI: 3.66–8.54) (Twig et al., 2019). The published paper (Weiss et al., 2005) on a two-year longitudinal study in obese children revealed that 8 out of 117 (6.8 %) children developed T2D. In this study, 84 children had no altered glucose metabolism and mean BMI was 35.5 kg/m², while 33 (28.2 %) children had impaired glucose tolerance and mean BMI was 36.6 kg/m². In all children who developed T2D, impaired glucose tolerance was initially observed. In this study, severe obesity, impaired glucose tolerance and African Americans were the strongest predictors of diabetes. On the other hand, fasting blood glucose, insulin and C-peptide

levels were not associated with the development of diabetes. Changes in insulin sensitivity were strongly correlated with weight changes and had significant effect on glucose level during OGTT (Weiss et al., 2005).

No child was diagnosed with diabetes during the study. In children aged 10 years and older, fasting hyperglycaemia was observed in 7.0 % and impaired glucose tolerance in 11.9 % of obese children. The lower prevalence of impaired glucose tolerance in the study population can be explained by a lower median BMI, which was 30.8 kg/m². Impaired glucose tolerance was more common in boys – 73.3 % of cases, which coincide with literature data, since male gender is considered as risk factor in diabetes development. No differences in anthropometric parameters were found between children with or without impaired glucose tolerance (IGT), but children with IGT were older than children without IGT. Changes in biochemical parameters were observed in children with IGT, these children had higher levels of uric acid and ALT in the blood and higher blood pressure compared to children without IGT.

Several studies have reported a prevalence of NAFLD between 3 to 10 % in general paediatric population, with a significant increase in prevalence to 70 % in individuals with metabolic complications of obesity. Differences in the incidence and prevalence of NAFLD are strongly related to the diagnostic method used and the selection of the study population. In the first studies that assessed the prevalence of NAFLD in children based on aminotransferase level and ultrasound, the prevalence was estimated to range from 3 to 7 % in the general population. In addition, studies conducted in obese children demonstrated that elevated ALT level ranged from 8 to 42 % of children. In contrast, diffuse hyperechogenicity in liver was found in ultrasonography in 1.7 to 77 % of children included in the studies (Fraser et al., 2007). Regardless of the degree of obesity, it has been shown that the risk of developing NAFLD is higher in males and it is one of the most important risk factors for NAFLD in both children and adults. In addition, data from the US National Health and

Nutrition Examination Survey of children aged 12 to 19 years showed that 12.4 % of males included in this study had an unexplained elevated ALT, compared with only 3.5 % of females (Fraser et al., 2007). Gender differences could be explained by the protective role of oestrogens in the liver in women, as well as by the well-documented negative impact of androgens in the development of NAFLD (Fraser et al., 2007; Nobili et al., 2009; Liu et al., 2021).

Recent meta-analyses also show a higher prevalence of NAFLD in obese children compared to general population studies, and also show that it mainly affects men, with a progressive increase in the prevalence as the child's BMI increases. The same meta-analysis was unable to detect an association between NAFLD and ethnicity, as each of the assessed studies did not have sufficient qualitative information to draw meaningful conclusions. However, paediatric studies have demonstrated that, for example, Native American and Hispanic boys are at an increased risk of NAFLD compared to girls and boys of Caucasian and African-American race (Liu et al., 2021; Mărginean et al., 2021). Children whose parents are obese and have diagnosed NAFLD, insulin resistance and / or T2D should be carefully assessed for NAFLD risk (Liu et al., 2021).

The results of our study were consistent with the results of studies described in the literature – 34.2 % of children aged 10 years and older had signs of non-alcoholic fatty liver disease in ultrasound and elevated ALT level – 44.9 % of children. When evaluating the paediatric NAFLD fibrosis index, predictive liver fibrosis was found in 72.9 % of children. The PNFI index was significantly higher in the boys included in the study than in girls.

Limitations and challenges of the study

The study data is limited by inconsistencies in absolute numbers of prenatal and postnatal risk factors of obesity, as they are not always correct or not reported at all in the parent survey. Also, in the analysis of biochemical data, there may be inconsistencies in absolute numbers due to technical or other

reasons. These data were presented as non-existent in the analysis of the study. The small sample of respondents also limits the collection, analysis, and interpretation of research data. However, the obtained results made it possible to achieve the research goals and provided an opportunity to compare with data of other studies, which indicate a qualitative research result. Further research would be needed, especially on the interaction between parent and child obesity and its impact on chronic diseases risk, pathogenetic mechanisms and complications in the future.

Conclusions

1. Parental obesity was the only postnatal risk factor of obesity, that differed significantly between obese and normal weight children. No maternal obesity was found in children with normal weight. No differences in other prenatal and postnatal risk factors of obesity were found between obese and normal weight children in the study.
2. Obese children had elevated blood pressure, ALT, TG, fasting glucose and insulin levels, insulin resistance HOMA-IR index, insulin level after 2 hours post load glucose and decreased HDL level compared to normal weight children. TCh $\geq$ 5.2 mmol/l and LDL > 3.4 mmol/l as well as fasting hyperglycaemia were not observed in normal weight children.
3. A positive family history of Type 2 diabetes mellitus and parental obesity had a negative impact on anthropometric and blood pressure parameters in obese children aged 10 years and older. Children with obese parents had a significantly higher ALT and uric acid levels, as well as PNFIs, compared to children with normal weight parents. Birth weight $\geq$ 4 kg had a negative impact on fasting blood glucose. Excessive weight gain during pregnancy in the mother and the duration of exclusive breastfeeding did not affect the anthropometric, blood pressure and blood biochemical parameters of the children.
4. Although only one diagnostic criterion of metabolic syndrome was present in 46.9 % obese children aged 10 years and older, it was in 31.6 % of the children under 10 years of age. Almost a quarter (21.0 %) of obese children aged 10 years and older had defined metabolic syndrome according to IDF diagnostic criteria.
5. The risk of metabolic syndrome was significantly increased by the increase in BMI and parental obesity.

6. The term “hyperinsulinemic-euglycemic clamp” has been reproduced in Latvian as “hiperinsulinēmiskas normoglikēmijas uzturēšana”. The names of several syndromes in Latvian have been clarified.

Practical recommendations and suggestions

Primary care professionals must carefully monitor the growth and maturation process of the child. If trends of overweight are observed, a preventive conversation with parents about the child's nutrition and physical activities should be carried out. If necessary, you should be encouraged to contact a nutritionist or dietician to help start changing dietary habits.

Primary care professionals should routinely screen overweight and obese children for obesity complications. All children with BMI above the 95th percentile should be evaluated as a high-risk group for the development of arterial hypertension, dyslipidaemia, insulin resistance, metabolic syndrome, non-alcoholic fatty liver disease, etc. After screening for chronic diseases in children, the family should be referred to a multidisciplinary weight management programme to initiate an intensive lifestyle modification. The paediatric endocrinologist consultation is necessary only if weight management has not been successful in the primary care and in case of chronic diseases it is necessary to initiate pharmacotherapy.

Special attention should be paid to families with parental obesity or if a positive history of T2M is observed. These families should be considered as a high-risk group for the development of childhood obesity and children should be regularly screened for early complications of obesity. Primary care specialists should regularly discuss the maintenance of healthy weight of the child, physiological weight gain according to the age of the child, the formation of healthy habits and motivation for the parents themselves to carry out weight management. Special attention should be paid to maternal health, encouraging women to maintain healthy weight both before and during pregnancy, and after childbirth. The weight gain of the mother during pregnancy should be carefully monitored in order to reduce excessive weight gain, the woman should be

motivated to be physically active and adhere to the basic principles of a healthy diet.

A national strategy should be developed that would allow the child and family to be included in a programme that promotes the introduction of healthy eating habits, motivates to be physically active and raises awareness of the health of the child. Several levels of care should be created to address the problem of overweight by encouraging family participation and including a number of specialists who, with different behavioural techniques, would stimulate the family to start changes in daily habits of children. Special paediatric offices should be created, which in case of a child's overweight or rapid weight gain, followed the growth and maturation process of the child, drew parent's attention to the weight problem and motivated them to start changing habits. It would be essential to establish weight management programmes in the regions of Latvia to ensure better access to the service for families.

Publications and reports on the theme of the Thesis

Scientific publications included in international databases:

1. Gailite, J., Mikilpa-Mikgelba, A., Siliņa, I., Kirillova, I., Lauga-Tuņina, U., Dzīvīte-Krišāne, I. & Gardovska, D. 2018. Type 2 Diabetes Mellitus, Impaired Glucose Tolerance and Associated Comorbidities in Children During 2002–2013 in Children's Clinical University Hospital, Latvia. *Proceedings of the Latvian Academy of Sciences. Section B. Natural, Exact, and Applied Sciences.* 72(6) 322–326.

2. Gailite, J., Apela, D., Dzīvīte-Krišāne, I. & Gardovska, D. 2019. Short-Term Predictors for Weight Correction Success of the First Paediatric Weight Correction Programme in Children's Clinical University Hospital in Riga. *Medicina*. *55*(3), 75.

Scientific articles in international peer-reviewed publications:

1. It's a great way to get rid of a lot of money, but it's not a good idea. Parental Weight Status, Birth Weight and Depression Signs Influence on Child's z-BMI. *Journal of Student Research, 8*(1).

2. Gailite, J., Nora Urbane, U. N, Lauga-Tunina, U., Kirillova, I., Dzivite-Krisane, I. 2014. Congenital Hyperinsulinism: Cases Review in Latvia 1992–2013. *Baltic Endocrinology*, Volume 8, Number 1, 2: 53–55.

Scientific articles in peer-reviewed publications issued in Latvia:

1. Gailite, J., Dzivite-Krisane, I. 2013. Assessment of risk factors for cardiometabolic syndrome in adolescents with obesity in Latvia. RSU Scientific Papers (2): 29–37.

2. Gailite, J., Mikilpa-Mikgelba, A., Lauga-Tunina, U., Kirillova, I., Dzivite-Krisane, I. 2014. Characteristics of children with glucose tolerance disorders and type 2 diabetes mellitus in Latvia from 2002 to 2013. RSU Scientific Papers (2): 56–59.

Reports at conferences published in scientific publications included in international databases:

1. Mikilpa-Mikgelba, A., Dzivite-Krisane, I., Gailite, J. 2015. Description of associated chronic comorbidities in children with type 2 diabetes mellitus and impaired glucose tolerance. *Appetite.* Volume 89, p. 312.

2. Gailite, J., Urbane, U., Dzivite-Krisane, I., Gardovska, D. 2015. Lifestyle survey of healthcare personnel in University Children's Hospital in Riga, Latvia. *Appetite.* Volume 89, p. 326.

3. Napituhina, I., Maslova, O., Tase, I., Agadzayan, K., Vetra, A., Dzivite-Krisane, I., Gailite, J. 2015. Physical activity improves functional exercise capacity for children and adolescents with obesity. *Obesity Facts.* 8, Suppl. 1, p. 109.

4. Maslova, O., Napituhina, I., Tase, I., Agadzayan, K., Vetra, A., Dzivite-Krisane, I., Gailite, J. 2015. Children and adolescents with obesity and with physical activities out of school have unbalanced diet risk. *Obesity Facts.* 8, Suppl. 1, p. 104.

5. Maslova, O., Napituhina, I., Tase, I., Agadzayan, K., Vetra, A., Gluza, O., Dzivite-Krisane, I., Gailite, J. 2015. Eating habits and lifestyle of overweight children and adolescents. *ACTA Paediatrica.* 104, Suppl. 466, p. 24

6. Gailite, J., Urbane, U.N., Salijuma, E., Arnicane, L., Terjajev, L., Erts, R., Dzivite-Krisane, I., Gardovska, D. 2016. Lifestyle Survey of Doctors, Medical Residents and Medical Students in Latvia. *Hormone Research in Paediatrics.* 86, Suppl. 1, p. 328.

7. Agadzanyan, K., Napituhina, I., Upmina, I., Lubina, O., Sprudzane, I., Dzivite-Krisane, I., Gailite, J. 2016. EVALUATION OF SIGNS OF DEPRESSION IN CHILDREN AND ADOLESCENTS WITH OBESITY**.** *ACTA Paediatrica, International Journal of Paediatrics.* 106, Suppl. S468, p. 35

8. Lubina, O., Napituhina, I., Agadzanyan, K., Dzivite-Krisane, I., Sprudzane, I., Vetra, A., Gailite, J. 2017. Children's birth weight and parental obesity as risk factors of children obesity. *Obesity Facts.* 10, Suppl. 1, p. 227.

Theses and reports at local conferences:

1. Lubina, O., Gailite, J., Napituhina I., Agadjanjana, K., Tāse I., Sētra A., brine E., Living-Krišane, I. 2016. Differences in eating habits for overweight and children with normal weight, Poster paper, RSU Scientific Conference, 17–18 March 2016.

2. Gailite, J., brine, E., Lubina, O., Napituhina, I., Agadjanjana, K., Kirillova I., Lauga-Tuniņa, U., Live-Krišane, I. 2016. Model factor for insulin homeostasis for overweight girls and boys, Poster paper, RSU Scientific Conference, 17–18 March 2016.

3. Gailite, J., Valdmane, S., Gavrilovs, G., Lubina, O., Napituhina, I., Agadjanyan, K., Sprudzāne, I., A., Vētra, Living-Krišane I. 2017. Effect of birth weight on the body mass index of children and adolescents, Poster paper, RSU Scientific Conference, 6–7 April 2017.

Theses and reports at international conferences:

1. Gailite, J., Strele, I., Lauga-Tunina, U., Kirillova, I., Gardovska, D., Dzivite-Krisane, I. 2013. Synergy between adiposity, glucosae and inflammation markers level in blood in adolescents; 2nd Baltic Paediatric Congress in Parnu, Estonia, 30 May – 1 June 2013.

2. Gailite, J., Strele, I., Lauga-Tunina, U., Kirillova, I., Gardovska, D., Dzivite-Krisane, I. 2013. The number of smoked cigarettes per day influences adverse blood pressure and lipid levels in adolescents with obesity; ESPE, Milan, Italy, 19–22 September 2013.

3. Gailite, J., Strele, I., Lauga-Tunina, U., Kirillova, I., Gardovska, D., Dzivite-Krisane, I. 2013. Adverse influence of the number of smoked cigarettes per day on blood pressure and lipid levels in adolescents with obesity; ESPE, Milan, Italy, 19–22 September 2013.

4. Gailite, J., Nora Urbane, U. N., Dzivite-Krisane, I., Gardovska, D. 2014. Lifestyle Survey of Healthcare Personnel in University Children's hospital in Riga, Latvia; ECOG, Salzburg, Austria, 13–15 November 2014.

5. Gailite, J., Mikilpa-Mikgelba, A., Lauga-Tunina, U., Kirillova, I., Dzivite-Krisane, I. 2014. Anthropometric characteristics of children with impaired glucose tolerance and type 2 diabetes mellitus in Latvia during a period from 2002–2013; FIDS and Ceda, Jurmala, Latvia, 26–28 June 2014.

6. Gailite, J., Urbane, U. N., Strele, I., Erts, R., Lauga-Tunina, U., Kirillova, I., Gardovska, D., Dzivite-Krisane I. 2014. Evaluation of the risk of dyslipidaemia in adolescents with obesity; ESPE, Dublin, Ireland, 18–20 September 2014.

7. Mikilpa-Mikgelba, A., Dzivite-Krisane, I., Gailite, J. 2014. Description of associated chronic comorbidities in children with type 2 DM and IGT; ECOG, Salzburg, Austria, 13–15 November 2014.

8. Maslova, O., Napituhina, I., Tase, I., Agadzayan, K., Vetra, A., Dzivite-Krisane, I., Gailite, J. 2015. Children and adolescents with obesity and with physical activities out of school have unbalanced diet risk; Eco, Prague, Czech Republic, 6–9 May, 2015.

9. Napituhina, I., Maslova, O., Tase, I., Agadzayan, K., Vetra, A., Dzivite-Krisane, I., Gailite, J. 2015. Physical activity improves functional exercise capacity for children and adolescents with obesity; Eco, Prague, Czech Republic, 6–9 May 2015.

10. Mikilpa-Mikgelba, A., Dzivite-Krisane, I., Gailite, J. 2015. Anthropometric characteristics of children with impaired glucose tolerance and type 2 diabetes mellitus in Latvia; 3rd Baltic Paediatric Congress, Riga, Latvia, 19–21 August 2015.

11. Maslova, O., Napituhina, I. Tase, I., Agadzayan, K., Vetra, A., Gluza, O., Dzivite-Krisane, I., Gailite, J. 2015. Eating habits and lifestyle of overweight children and adolescents; ECOG, Stockholm, Sweden, 13–14 October 2015.

12. Gailite, J., Urbane, U. N., Salijuma, E., Arnicane, L., Terjajeva, L., Erts, R., Dzivite-Krisane, I., Gardovska, D. 2016. Lifestyle Survey of Doctors, Medical Residents and Medical Students in Latvia, ESPE, Paris, France, 10–12 September 2016.

13. Gailite, J., Lubina, O., Salijuma, E., Napituhina, I., Agadzanyan, K., Stundzane, I., Kirillova, I., Lauga-Tunina, U., Vetra, A., Dzivite-Krisane I. 2016. Insulin resistance for adolescents with obesity in Latvia; ESPE, Paris, France, 10–12 September 2016.

14. Agadzanyan, K., Napituhina, I., Upmina, I., Lubina, O., Sprudzane, I., Dzivite-Krisane, I., Gailite J. 2017. Evaluation of signs of depression in children and adolescents with obesity, ECOG, Thessaloniki, Greece, 6–8 October 2017.

15. Lubina, O., Napituhina, I., Agadzanyan, K., Dzivite-Krisane, I., Sprudzane, I., Vetra, A., Gailite, J. 2017. Children's birth weight and parental obesity as risk factors of children obesity, ECO2017, Porto, Portugal, 17–20 May 2017.

Bibliography

1. Agudelo, G. M., Bedoya, G., Estrada, A. et al. 2014. VARIATIONS in the prevalence of metabolic syndrome in adolescents according to different criteria used for diagnosis: which definition should be chosen for this age group? *Metabolic Syndrome and Related Disorders*. 12(4), 202–209.

2. Akoglu, H. 2018. User's guide to correlation coefficients. *Turkish Journal of Emergency Medicine*. 18(3), 91–93.

3. Al-Hamad, D., Raman, V. 2017. Metabolic syndrome in children and adolescents. *Translational Pediatrics*. 6(4), 397.

4. Al Hourani, H., Atoum, M., Alzoughool, F. et al. 2021. Screening for non-invasive risk factors of type 2 diabetes in overweight and obese schoolchildren. *Endocrinologia, Diabetes y Nutricion*. S2530-0164(21)00074-4. Advance online publication.

5. Annis, A. M., Caulder, M. S., Cook, M. L. et al. 2005. Family history, diabetes, and other demographic and risk factors among participants of the National Health and Nutrition Examination Survey 1999–2002. *Preventing Chronic Disease*. 2(2), A19.

6. August, G. P., Caprio, S. Endocrine Society. 2008. Prevention and treatment of pediatric obesity: an endocrine society clinical practice guideline based on expert opinion. *The Journal of Clinical Endocrinology and Metabolism*. 93(12), 4576–599.

7. Avnieli Velfer, Y., Phillip, M., Shalitin, S. 2019. Increased Prevalence of Severe Obesity and Related Comorbidities among Patients referred to a Pediatric Obesity Clinic during the Last Decade. *Hormone Research in Paediatrics*. 92(3), 169–178.

8. Baran, J., Weres, A., Czenczek-Lewandowska, E. et al. 2019. Relationship between Children's Birth Weight and Birth Length and a Risk of Overweight and Obesity in 4–15-Year-Old Children. *Medicina (Kaunas, Lithuania)*. 55(8), 487.

9. Bendor, C. D., Bardugo, A., Pinhas-Hamiel, O. et al. 2020. Cardiovascular Morbidity, diabetes and cancer risk among children and adolescents with severe obesity. *Cardiovasc Diabetol*. 19, 79.

10. Bitew, Z. W., Alemu, A., Tenaw, Z. et al. 2021. Prevalence of metabolic syndrome among children and adolescents in high-income countries: A systematic review and meta-analysis of observational Studies. *Biomed Research International*. Article ID 6661457, 24.

11. Blüher, S., Molz, E., Wiegand, S., adiposity Patients Registry Initiative and German Competence Net Obesity 2013. Body mass index, waist circumference, and waist-to-height ratio as Predictors of cardiometabolic risk in childhood obesity depending on pubertal development. *The Journal of Clinical Endocrinology and Metabolism*. 98(8), 3384–3393.

12. Boney, C. M., Verma, A., Tucker, R. et al. 2005. Metabolic syndrome in childhood: Association with birth weight, maternal obesity, and Gestational diabetes mellitus. *Pediatrics*. 115(3), e290–e296.

13. Brook, C. G. D., Clayton, P. E., Brown, R. S. 2010. *Brook's Clinical Pediatric Endocrinology: Sixth edition.* John Wiley & Sons Ltd.

14. Calcaterra, V., Klersy, C., Muratori, T., et al., 2008, Prevalence of metabolic syndrome (MS) in children and adolescents with Varying degrees of obesity. *Clinical Endocrinology*. 68: 868–872.

15. THE CDC. 2020. Healthy Weight, Nutrition and Physical Activity https://www.CDc.gov/healthyweight/assessing/bmi/childrens_bmi/about_childrens_bmi.html.

16. Cuschieri, S., Grech, S. 2020. COVID-19: a one-way ticket to a global childhood obesity crisis? *Journal of Diabetes and metabolic Disorders*. 19(2), 1–4.

17. Danielsson, P., Kowalski, J., Ekblom, Ö. et al. 2012. Response of severely obese children and adolescents to behavioural treatment. *Archives of Pediatrics & adolescent medicine*. 166(12), 1103–1108.

18. Eliakim, A., Friedland, O., Kowen, G. et al. 2004. Parental obesity and higher pre-intervention BMI reduce the likelihood of a multidisciplinary childhood obesity program to succeed – a clinical observation. *Journal of Pediatric Endocrinology & Metabolism: JPEM*. 17(8), 1055–1061.

19. Evans, G. W., Jones-Rounds, M. L., Belojevic, G. et al. 2012. Family income and childhood obesity in eight European cities: the mediating roles of neighbourhood characteristics and physical activity. *Social Science & Medicine (1982)*. 75(3), 477–481.

20. Fraser, A., Longnecker, M. P., Lawlor, D. A. 2007. Prevalence of elevated alanine aminotransferase among US adolescents and associated factors: NHANES 1999–2004. *Gastroenterology*. 133(6), 1814–1820.

21. Fraser, A., Tilling, K., Macdonald-Wallis, C. et al. 2010. Association of maternal weight gain in pregnancy with offspring obesity and metabolic and vascular traits in childhood. *Circulation*. 121(23), 2557–2554.

22. Freedman, D. S., TCan, L. K., Serdula, M. K. et al. 2004. Inter-relationships among childhood BMI, childhood height, and adult obesity: the Bogalusa Heart Study. *International Journal of Obesity and Related Metabolic Disorders: Journal of the International Association for the Study of Obesity*. 28(1), 10–16.

23. Fried, M., Yumuk, V., Oppert, J. M. et al. 2013. Interdisciplinary European Guidelines on metabolic and bariatric surgery. *OBES Facts*. 6(5), 449–468.

24. Gaillard, R., Welten, M., Oddy, W. H. et al. 2016. Associations of maternal prepregnancy body mass index and Gestational weight gain with cardio-metabolic risk factors in adolescent offspring: a prospective cohort study. *BJOG: an International Journal of Obstetrics and gynaecology*. 123(2), 207–216.

25. Guerrero-Romero, F., Aradillas-García, C., Simental-Mendia, L. E. et al. 2010. Bird weight, family history of diabetes, and metabolic syndrome in children and adolescents. *The Journal of Pediatrics*. 156(5), 719–723.e1.

26. Hadjiyannakis, S. 2005. The metabolic syndrome in children and adolescents. *Paediatrics & Child Health*. 10(1), 41–47.

27. Hansen, M. L., Gunn, P. W., Kaelber, D. C. 2007. Underdiagnosis of hypertension in children and adolescents. *JAMA*. 298(8), 874–879.

28. He, M., Evans, A. 2007. Are parents aware that their children are overweight or obese? Do they care? *Canadian family physician Medecin de famille canadien*. 53(9), 1493–1499.

29. Holm, J. C., Gamborg, M., Bille, D. S. et al. 2011. Chronic care treatment of obese children and adolescents. *International Journal of Pediatric Obesity: IJPO: an Official Journal of the International Association for the Study of Obesity*. 6(3–4), 188–196.

30. Holt, N., Schetzina, K. E., Dalton, W. T., 3rd, et al. 2011. Primary care practice addressing child overweight and obesity: a survey of primary care physicians at four clinics in southern Appalachia. *Southern Medical Journal*. 104(1), 14–19.

31. Hong, Y. H., Lee, J. E. 2021. Large for Gestational Age and Obesity-Related Comorbidities. *Journal of obesity & metabolic syndrome*. 30(2), 124–131.

32. Horta, B. L., Loret de Mola, C., Victora, C. G. 2015. Long-term implications of breastfeeding on cholesterol, obesity, Systolic blood pressure and type 2 diabetes: a systematic review and meta-analysis. *ACTA Paediatrica (Oslo, Norway: 1992)*. 104(467), 30–37.

33. Hrolfsdottir, L., Rytter, D., Olsen, S. F. et al. 2015. Gestational weight gain in normal weight women and offspring cardio-metabolic risk factors at 20 years of age. *International Journal of Obesity (2005)*. 39(4), 671–676.

34. Huus, K., Ludvigsson, J. F., Enskär, K. et al. 2008. Exclusive breastfeeding of Swedish children and its possible influence on the development of obesity: a prospective cohort study. *BMC Pediatrics*. 8, 42.

35. IDF consensus definition of metabolic syndrome in children and adolescents 2007. https://www.idf.org/e-library/consensus-statements/61-idf-consensus-definition-of-metabolic-syndrome-in-children-and-adolescents.html.

36. Jones, K. L. 1998. Non-insulin dependent diabetes in children and adolescents: the therapeutic challenge. *Clinical Pediatrics.* 37(2), 103–110.

37. Jung, C., Fischer, N., Fritzenwanger, M. et al. 2010. Anthropometric indices as Predictors of the metabolic syndrome and its components in adolescents. *Pediatrics International: Official Journal of the Japan Pediatric Society*. 52(3), 402–409.

38. Katzmarzyk, P. T., Barlow, S., Bouchard, C. et al. 2014. An Evolving scientific basis for the prevention and treatment of pediatric obesity. *International Journal of Obesity (2005)*. 38(7), 887–905.

39. Kelly, R. K., Magnussen, C. G., Sabin, M.A., et al. 2015. Development of hypertension in overweight adolescents: a review. *Adolescent Health, Medicine and Therapeutics*, *6*, 171–187.

40. Kleiser, C., Schaffrath Rosario, A., Mensink, G. B. et al. 2009. Potential determinants of obesity among children and adolescents in Germany: results from the cross-sectional KiGGS Study. *BMC Public Health*. 9, 46.

41. Lange, S. J., Kompaniyets, L., Freedman, D. S. et al. 2021. Longitudinal Trends in Body Mass Index Before and During the COVID-19 Pandemic Among Persons Aged 2–19 Years – United States, 2018–2020. *MMWR. Morbidity and Mortality Weekly Report*. 70(37), 1278–1283.

42. Leonard, S. A., Rasmussen, K. M., King, J. C. et al. 2017. Trajectories of maternal weight from before pregnancy through Postpartum and associations with childhood obesity. *The American Journal of Clinical Nutrition*. 106(5), 1295–1301.

43. Li, L., Law, C., Lo Conte, R. et al. 2009. Intergenerational influences on childhood body mass index: the effect of parental body mass index trajectories. *The American Journal of Clinical Nutrition*. 89(2), 551–557.

44. Liu, J., Mu, C., Li, K. et al. 2021. Stimulating Global Prevalence of Metabolic Dysfunction-Associated Fatty Liver Disease in Overweight or obese Children and Adolescents: Systematic Review and Meta-Analysis. *International Journal of Public Health*. 66, 1604371.

45. Mărginean, C. O., Meliț, L. E., Săsăran, M. O. 2021. Metabolic Associated Fatty Liver Disease in Children-From Atomistic to Holistic. *Biomedicines*. 9(12), 1866.

46. Martínez-Villanueva, J., González-Leal, R., Argente, J. et al. 2019. La obesidad parental se asocia con la gravedad de la obesidad infantil y de sus comorbilidades is associated with the severity of childhood obesity and its comorbidities. *Anals de Pediatria*. 90(4), 224–231.

47. Mulvaney, S. A., Schlundt, D. G., Mudasiru, E. et al. 2006. Parent perceptions of caring for adolescents with type 2 diabetes. *Diabetes care*. 29(5), 993–997.

48. Nielsen, L. A., Nielsen, T. R., Holm, J. C. 2015. The Impact of Familial Predisposition to Obesity and Cardiovascular Disease on Childhood Obesity. *Obesity Facts*. 8(5), 319–328.

49. Nobili, V., Alisi, A., Vania, A., Tiribelli, C. et al. 2009. The pediatric NAFLD fibrosis index: a predictor of liver fibrosis in children with non-alcoholic fatty liver disease. *BMC Medicine*. 7, 21.

50. Nobili, V., Reale, A., Alisi, A. et al. 2009. Elevated serum ALT in children presenting to the emergency unit: Relationship with NAFLD. *Digestive and Liver Disease: Official Journal of the Italian Society of Gastroenterology and the Italian Association for the Study of the Liver*. 41(10), 749–752.

51. O'Donnell, J. E., Foskett-Tharby, R., Gill, P. S. 2017. General practice views of managing childhood obesity in primary care: a qualitative analysis. *JRSM Open*. 8(6), 2054270417693966.

52. Ornellas, F., Carapeto, P. V., Mandarim-de-Lacerda, C. A. et al. 2017. Obese fathers lead to an altered metabolism and obesity in their children in Adulthood: review of experimental and human studies. *Jornal de Pediatria*. 93, 551–559.

53. Pinhas-Hamiel, O., Zeitler, P. 2005. Advances in epidemiology and treatment of type 2 diabetes in children. *Advances in Pediatrics*. 52, 223–259.

54. Pulgaron, E. R., Delamater, A. M. 2014. Obesity and type 2 diabetes in children: epidemiology and treatment. *Current Diabetes Reports*. 14(8), 508.

55. Qiao, J., Dai, L. J., Zhang, Q., Ouyang, Y. Q. 2020. A Meta-Analysis of the Association Between Breastfeeding and Early Childhood Obesity. *Journal of Pediatric Nursing*. 53, 57–66.

56. Reilly, J. J., Armstrong, J., Dorosty, A. R. Avon Longitudinal Study of Parents and Children Study Team. 2005. Early life risk factors for obesity in childhood: Cohort study. *BMJ (Clinical Research ed.)*. 330(7504), 1357.

57. Reilly, J. J., Kelly, J. 2011. Long-term impact of overweight and obesity in childhood and adolescence on Morbidity and premature mortality in Adulthood: systematic review. *International Journal of Obesity (2005)*. 35(7), 891–898.

58. Rietmeijer-Mentink, M., Paulis, W. D., van Middelkoop, M. et al. 2013. Difference between parental perception and actual weight status of children: a systematic review. *Maternal & Child Nutrition*. 9(1), 3–22.

59. Romero-Velarde, E., Aguirre-Salas, L. M., Álvarez-Román, Y. A. et al. 2016. Prevalencia de síndrome metabólico y Factores ASOCIADOS en niños y adolescentes con obesidad. *Revista medica del Instituto Mexicano del Seguro Social*. 54(5), 568–575.

60. Rundle, A. G., Park, Y., Herbstman, J. B. et al. 2020. COVID-19-Related School closings and Risk of Weight Gain Among Children. *Obesity (Silver Spring, Md.)*. 28(6), 1008–1009.

61. SAHOO, K., SAHOO, B., Choudhury, A. K. et al. 2015. Childhood obesity: causes and consequences. *Journal of Family Medicine and Primary Care*. 4(2), 187–192.

62. Sangun, Ö., Dündar, B., Köşker, M. et al. 2011. Prevalence of metabolic syndrome in obese children and adolescents using three different criteria and evaluation of risk factors. *Journal of Clinical Research in Pediatric Endocrinology*. 3(2), 70–76.

63. Santoro, N., Amato, A., Grandone, A. et al. 2013. Predicting metabolic syndrome in obese children and adolescents: Look, measure and ask. *Obesity Facts*. 6(1), 48–56.

64. Schellong, K., Schulz, S., Harder, T. et al. 2012. Bird weight and long-term overweight risk: systematic review and a meta-analysis including 643,902 persons from 66 studies and 26 countries globally. *PLoS One*. 7(10), e47776.

65. Shafaghi, K., Shariff, Z. M., TAIB et al. 2014. Parental body mass index is associated with adolescent overweight and obesity in Mashhad, Iran. *Asia Pacific Journal of Clinical Nutrition*. 23(2), 225–231.

66. Shao, T., Tao, H., Ni, L. et al. 2016. Maternal pre-pregnancy body mass index and Gestational weight gain with preschool children's overweight and obesity. *Zhonghua yu fang yi xue za zhi [Chinese Journal of Preventive Medicine]*. 50(2), 123–128.

67. Skinner, A. C., Perrin, E. M., Moss, L. A. et al. 2015. Cardiometabolic Risks and Severity of Obesity in Children and Young Adults. *The New England Journal of Medicine*. 373(14), 1307–1317.

68. Smetanina, N., Valickas, R., Vitkauskiene, A. et al. 2021. Prevalence of Metabolic Syndrome and Impaired Glucose Metabolism among 10- to 17-Year-Old Overweight and obese Lithuanian Children and Adolescents. *Obesity Facts*. 14(3), 271–282.

69. Sridhar, S. B., Darbinian, J., Ehrlich, S. F. et al. 2014. Maternal Gestational weight gain and offspring risk for childhood overweight or obesity. *American Journal of Obstetrics and Gynecology*. 211(3), 259.e1–259.e2598.

70. Stavridou, A., Kapsali, E., Panagouli, E. et al. 2021. Obesity in Children and Adolescents during COVID-19 Pandemic. *Children (Basel, Switzerland)*. 8(2), 135.

71. Swinburn, B. A., Kraak, V. I., Allender, S. et al. 2019. The Global Syndemic of Obesity, Undernutrition, and Climate Change: The Lancet Commission report. *Lancet (London, England)*. 393(10173), 791–846.

72. Tagi, V. M., Samvelyan, S., Chiarelli, F. 2020. Treatment of Metabolic Syndrome in Children. *Hormone Research in Paediatrics*. 93(4), 215–225.

73. Tam, C., Ma, R., Yuen, L. Y. et al. 2018. The impact of maternal Gestational weight gain on cardiometabolic risk factors in children. *Diabetologia*. 61(12), 2539–2558.

74. Tavares Giannini, D., Caetano Kuschnir, M. C., SZKLO, M. 2014. Metabolic syndrome in overweight and obese adolescents: a comparison of two different diagnostic criteria. *Annals of Nutrition & Metabolism*. 64(1), 71–79.

75. Toschke, A. M., Martin, R. M., von Kries, R. et al. 2007. Infant feeding method and obesity: body mass index and dual-energy X-ray absorptiometry measurements at 9–10 y of age from the Avon Longitudinal Study of Parents and Children (ALSPAC). *The American Journal of Clinical Nutrition*. 85(6), 1578–1585.

76. Twig, G., Reichman, B., Afek, A. et al. 2019. Severe obesity and cardio-metabolic comorbidities: a nationwide study of 2.8 million teenagers. *International Journal of Obesity (2005)*. 43(7), 1391–1399.

77. Veena, S. R., Krishnaveni, G. V., Karat, S. C. et al., 2013. Testing the fetal overnutrition hypothesis; the relationship of maternal and paternal adiposity to

adiposity, insulin resistance and cardiovascular risk factors in Indian children. *Public Health Nutrition*. 16(9), 1656–1666.

78. Weiss, R., Taksali, S. E., Crochetlane, W. V. et al. 2005. Predictors of changes in glucose tolerance status in obese youth. *Diabetes Care*. 28(4), 902–909.

79. Whitaker, K. L., Jarvis, M. J., Beeken, R. J. et al. 2010. Comparing maternal and paternal intergenerational transmission of obesity risk in a large population-based sample. *The American journal of clinical nutrition*. 91(6), 1560–1567.

80. WHO. 2017a. Commission on Ending Childhood Obesity. *Who*. http://www.who.int/end-childhood-obesity/en/

81. WHO. 2017b. Diet and physical activity: a public health priority. *Who*. http://www.who.int/dietphysicalactivity/childhood/en/

82. WHO. 2017c. Obesity and overweight. *Who*. http://www.who.int/mediacentre/factsheets/fs311/en/

83. Wilfley, D. E., Staiano, A. E., Altman, M. et al. 2017. Improvement access and systems of care for evidence-based childhood obesity treatment: Conference key findings and next steps. *Obesity (Silver Spring).* 25(1), 16–29.

84. Wisnieski, L., Kerver, J., Holzman, C. et al. 2018. Breastfeeding and Risk of Metabolic Syndrome in Children and Adolescents: A Systematic Review. *Journal of human lactation: Official Journal of International Lactation Consultant Association*. 34(3), 515–525.

85. Yan, J., Liu, L., Zhu, Y. et al. 2014. The association between breastfeeding and childhood obesity: a meta-analysis. *BMC Public Health*. 14, 1267.

86. Yoon, P. W., Scheuner, M. T., Khoury, M. J. 2003. Research priorities for evaluating family history in the prevention of common chronic diseases. *American Journal of Preventive Medicine*. 24(2), 128–135.

87. Yu, Z. B., Han, S. P., Zhu, G. Z. et al. 2011. Bird weight and subsequent risk of obesity: a systematic review and meta-analysis. *Obesity Reviews: an Official Journal of the International Association for the Study of Obesity*. 12(7), 525–542.

88. Zhao, J., Grant, S. F. 2011. Genetics of childhood obesity. *Journal of Obesity*, *2011*. 845148. 57.

89. Zhao, Y., Wang, S. F., Mu, M. et al. 2012. Bird weight and overweight/obesity in adults: a meta-analysis. *European Journal of Pediatrics*. 171(12), 1737–1746.

90. Zolotarjova, J., Ten Velde, G., Vreugdenhil, A. 2018. Effects of multidisciplinary interventions on weight loss and health outcomes in children and adolescents with morbid obesity. *Obesity Reviews: An Official Journal of the International Association for the Study of Obesity*. 19(7), 931–946.

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