The metabolic syndrome and cardiometabolic risk factors in children and adolescents: Associations between different anthropometric measurements and cardiometabolic risk factors

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Summary

Introduction: The prevalence of pediatric obesity has increased worldwide during the last decades, and is currently a serious health challenge, as it causes extensive health problems in terms of cardiovascular comorbidities and premature mortality. Early detection and treatment of childhood obesity is therefore of major importance.

The Body Mass Index (BMI) is most commonly used to assess adiposity. Although the BMI also is considered to be a good predictor for various adverse effects of adiposity, indicators of central obesity may have a closer link with cardiometabolic risk as the BMI does not describe fat distribution, and visceral fat causes metabolic alterations through multiple pathways.

Objective: This thesis aims to determine the prevalence of the metabolic syndrome (MetS) as defined by Cook et al., and to explore the associations between anthropometric measurements (AM) and cardiometabolic risk factors in a group of severely obese children and adolescents at Haukeland University Hospital.

Materials and methods: Ninety-six obese patients with BMI >IOTF 35kg/m^2 or BMI>30 kg/m^2 with comorbidities, aged 5-18 years were recruited from the Obesity outpatient clinic at Haukeland University Hospital in Bergen. Information was retrieved from the medical records of the participants. Prevalence of the MetS and associations between SD-scores for BMI, waist circumference (WC), waist-to-height-ratio (WHtR), and waist-to-sitting height-ratio (WSHR), and systolic/diastolic blood pressure (SBP/DBP), HDL, LDL, total cholesterol, HbA1c, ALAT, gGT and the MetS were assessed. For correlations and linear regression, blood pressure measurements were categorized according to percentiles adjusted for age, gender and height. AIC was used to compare the different regression models. All models were run with and without adjustment for age and gender.

Results: The prevalence of the MetS in this group of obese children and adolescents was 36.9%. Significant moderate to weak correlations were found between all AM and SBP/DBP; and between BMI and WSHR, and markers of insulin resistance. Logistic regression models adjusted for age and gender showed that BMI, WHtR and WSHR were also significantly associated with a SBP >90^{th} percentile, and WC with DBP. BMI was the only measurement significantly related to the MetS, and had the lowest AIC when investigating both SBP and the MetS. For DBP, WC had the lowest AIC. No significant relations were found with the other biomarkers using linear regression adjusted for age and gender.

Conclusions: A relatively high prevalence of the MetS underlines the importance of screening for cardiometabolic risk factors and providing good treatment for this group of severely obese patients.

Due to weak associations, AM are probably not the main factor affecting the presence of cardiometabolic risk in this group of severely obese children and adolescents except for SBP, which showed significant associations with all AM. Among the investigated AM, BMI was the best to predict cardiometabolic risk.

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Abbreviations

ALAT	Alanine aminotransferase
ASAT	Aspartate aminotransferase
BMI	Body Mass Index (BMI; weight/height2 [kg/m2])
CI	Confidence interval
CRP	C-reactive protein
DBP	Diastolic Blood Pressure
DMT2	Diabetes Mellitus type 2
GGT	Gamma-glutamyltransferase
HDL	High Density Lipoprotein Cholesterol
HOMA-IR	Homeostatic model assessment of insulin resistance
IDF	International Diabetes Federation
IL-6	Interleukin-6
IOTF	International Obesity Task Force
LDL	Low Density Lipoprotein Cholesterol
METS	Metabolic Syndrome
NAFLD	Non-alcoholic fatty liver disease
NCEP ATP	National Cholesterol Educational Program, Adult Treatment Panel
ROS	Reactive Oxygen Species
SBP	Systolic Blood Pressure
SDS	Standard Deviation Score (=z-score)
SH	Sitting height
TNF-α	Tumor necrosis factor alpha
WC	Waist circumference
WHO	World Health Organization
WHtR	Waist-to-Height-Ratio
WSHR	Waist-to-sitting height-Ratio

1 Introduction

1.1 Obesity

1.1.1 Definition and prevalence

Overweight and obesity is normally defined using the Body Mass Index (BMI). For children, the cut-offs for overweight and obesity are age and gender adjusted as the BMI changes during childhood and differs between boys and girls (1, 2). The International Obesity Task Force (IOTF) has developed age- and gender-specific BMI-cutoff points which classify children and adolescents as normal-weight, overweight, and obese. These cutoff points are tied to adult overweight (≥25 kg/m^2) and obesity (≥30 kg/m^2) thresholds (1).

The prevalence of pediatric overweight and obesity has increased worldwide during the last decades (3), and excessive bodyweight is currently a serious health problem in the European Region of the World Health Organization (4).

A Norwegian study conducted in 2010 found children aged 2-19 years to have a prevalence of overweight including obesity of 13.8% and of obesity alone of 2.3%, using the IOTF cutoff points (5). These figures are similar to other Western and Northern countries (5).

1.1.2 Etiology

Obesity has a multifactorial etiology. Genetics play an important role in the development of obesity (6), and genetic components have been found to contribute between 40% and 70% to interindividual variation in obesity (7). Nevertheless, environmental issues such as an increased consumption of energy-dense foods and refined carbohydrates combined with a sedentary lifestyle and an over-all decline in energy-expenditure are thought to be of greater importance, as described in the World Health Organization Technical Report on chronic illnesses (8). Further, several non-modifiable risk factors have been identified, including parental obesity, gestational weight gain, birth weight, duration of breastfeeding (9), socioeconomic status (10), prematurity, rapid catch-up growth (11, 12), and early adipose rebound (13). In addition, psychological issues, such as binge- or loss of control eating, can contribute to a further development of obesity in children at risk (14). Also, novel research has proposed altered microbiota as a result of antibiotic exposure in infancy to result in increased BMI in toddlers, and that this may play a role in the development of the obesity epidemic (15).

1.1.3 Consequences

In addition to being a serious psychological challenge for children and adolescents (16), overweight and obesity cause major health problems in terms of cardiovascular comorbidities and premature mortality (17, 18). In this thesis I will focus on the physical consequences of obesity, especially the cardiometabolic factors.

1.1.4 Treatment

There is limited literature regarding treatment of childhood obesity done in randomized controlled trials. Systematical reviews have found that conservative treatment such as combined behavioral lifestyle interventions can result in significant weight reduction compared with standard care or self-help (19), also, educational interventions including behavioral modification can decrease overweight and obesity as well as blood pressure (20).

The use of drug therapy in children and adolescents is currently not recommended in the treatment of overweight and obesity. However, with emergence of new pharmaceutical alternatives, drugs might play a role in the future treatment of overweight and obesity as an adjunct to conservative treatment (21).

Surgical interventions have been applied to adolescents in Norway as a part of the ongoing intervention study "4XL" at the Center for morbid Obesity in HelseSør-Øst (clinicaltrials.gov NCT00923819). Short term results from other countries demonstrate positive effects regarding weight-development and social issues, and a lower complication rate than in adults (22). However, surgical treatment is currently not considered as a treatment option in pediatrics unless life-style treatment has proven inefficient in a metabolic disarranged child or adolescent.

Preventive strategies of overweight and obesity in children and adolescents targeting the family, school, and community can have a small effect on weight outcome, but with questionable clinical relevance according to a systematic review and meta-analysis (23). Further, universal prevention strategies with interventions focusing on the environmental arena with policy interventions improving dietary intake and physical activity are thought to enhance obesity control rather than an individual strategy with clinical intervention (24).

The Obesity outpatient clinic at Haukeland University Hospital offers conservative treatment of obesity. The treatment is interdisciplinary, with teams of pediatricians, a dietitian, a physiotherapist, a psychologist and a specialized nurse. Two treatment methods are used. The first is an educational intervention including follow-ups every 3 months with the specialized

nurse and every 6 months with a pediatrician. The course of treatment is for two years with the possibility of another year if necessary. The other method is based on cognitive behavioral treatment with visits to the clinic every week. This method is family based, and it demands more from the patient and their families, but also offers a closer follow-up from the attending staff and its efficacy is promising.

Inclusion criteria for treatment at the Obesity outpatient clinic at Haukeland University Hospital are having an IOTF BMI above 35 kg/m^2 or above 30 kg/m^2 with obesity related comorbidity, such as reduced glucose tolerance, hyperinsulinism, hypertension, dyslipidemia, sleep apnea, very quick weight gain, or severe concern for weight development (25). When included, the patients undergo a physical examination described in detail in the methods section.

1.2 Anthropometrics

Anthropometry is the most commonly used technique in a clinic setting to determine overweight and obesity. Anthropometric measures are also used as markers for the outcome of treatment. In order to be able to compare anthropometric measurements across age, it is common to use percentiles or to calculate standard deviation scores (SDS).

1.2.1 Body Mass Index

BMI is routinely assessed as a surrogate measure of adiposity, and thereby defining overweight and obesity. It has been validated as a measure of body composition in adults (26-29), and children (30-32), and has the advantage of being feasible because it is simple, safe and inexpensive to obtain (27).

BMI has earlier been considered to be a good predictor for insulin sensitivity, as Travers et al. found that an increasing BMI correlates with increasing insulin levels in children aged 10-15 years (33). Also, Moussa et al. found a significant correlation between BMI and systolic and diastolic blood pressure (SBP and DBP) in children 6-18 years of age (34). However, later research accentuates the fact that BMI does not differentiate fat- and fat free tissues (35-37), and it is claimed not to describe body fat distribution. As an upper body or centralized deposition of body fat is associated with an increased risk for obesity-related metabolic complications such as adverse lipoprotein and fasting insulin concentrations (38, 39), the fat-distribution is of great relevance for assessing this risk.

Although an increased BMI is associated with various adverse biochemical and physiologic effects of excessive adiposity (30), it would be interesting to investigate whether other anthropometric measurements or indexes for children and adolescents have a higher correlation as there are some objections to the use of BMI as a marker for the risk of developing adiposity-related morbidity.

1.2.2 Waist circumference

Waist circumference (WC) has the advantage over BMI that it describes a centralized distribution of fat. A peripheral distribution of excessive fat is likely to have an isolating effect, whereas a centralized distribution is more likely to consist of ectopic fat, that is fat which infiltrates the organs and is metabolically active. There has, however, been some debate as to whether the WC is able to distinguish subcutaneous from ectopic fat or not, as they are both located in the visceral region. It has been proposed by several authors that this measure reflects the intra-abdominal fat which is metabolically active in addition to correspond with total body fatness and general abdominal fat in children (40, 41). WC is also considered a predictor for the metabolic syndrome (MetS) (42).

Other anthropometric measures including the WC has also been proposed as better markers for metabolic changes as they take into account the distribution of fat. For instance the ratio between WC and height, waist-to-height-ratio (WHtR), has been demonstrated to be superior to BMI in predicting cardiovascular disease (39, 43, 44).

1.2.3 Sitting height

For many years there has been a focus on the WC, however, a research topic which has not been explored in particular is whether the height may be of importance when assessing metabolic risk. Both BMI and WHtR involve height, but they compose the entire height, without consideration of different body parts. Sitting height on the other hand focuses to a greater extent on the truncus. Sitting height has been reported to be significantly higher in dyslipidemic Chinese children (45), and to correlate with overweight and obesity in Brazilian children (46), but beyond this, little is known of its impact on cardiometabolic risk.

When taking into account that metabolic changes are associated with a fat-accumulation in the visceral region of the body, it would be plausible to suggest that anthropometric measures including the WC and sitting height may be a stronger predictor for these changes. Therefore, there is a need to establish whether other anthropometric measurements than BMI better predict obesity-related health risk among children and adolescents. If so, it would have

important implications as to whether other measures than height and weight should be assessed in the clinical setting.

1.3 Cardiovascular risk factors and the metabolic syndrome

1.3.1 Cardiometabolic risk factors

Cardiometabolic risk factors entail alterations increasing the risk for cardiovascular disease and metabolic disturbances. Overweight and obesity are associated with an altered metabolic state, which increases the risk of cardiovascular disease and a reduced life expectancy (47, 48).

1.3.2 The metabolic syndrome

The MetS is a clustering of selected cardiometabolic risk factors. To date no single international standardized criteria have been established to identify the MetS in children. However, all existing definitions tend to share these parameters: (1) an obesity estimate, such as BMI or WC, (2) elevated blood pressure, (3) altered blood lipids, such as decreased HDL, elevated LDL or triglycerides, and (4) a diabetes-related risk factor , such as HOMA-IR, elevated fasting glucose or insulin levels, with different cut-off values (49).

In this thesis a definition of the MetS based on the definition proposed by Cook et al. (50) has been used. The definition is a modification of the adult criteria, specified by the National Cholesterol Educational Program, Adult Treatment Panel III (NCEP ATP III) (51), with the closest representative values obtainable from pediatric data. A review found that in the pediatric setting, this is the definition most commonly used (52). Also, for other definitions, such as the one proposed by the International Diabetes Federation (IDF) (53), the adaption does not apply for children younger than 10 years, which makes it unsuitable for the present study sample.

1.3.3 Pathophysiology of the metabolic syndrome

Although the pathophysiology of the MetS is not completely understood, there are some main factors thought to impact on the development.

Insulin resistance with hyperinsulinemia seems to be a central factor in the pathogenesis of the MetS. An insulin-resistant state interferes with the hormonal actions taking place in the liver. Insulin produced in the β-cells of the pancreas travels quickly to the liver via the portal vein, and in the presence of the MetS, insulin has a selective dysfunction so that it does not

diminish the hepatic glucose output, but rather increases it, and still, like in the normal state, increases the de novo lipogenesis, thereby releasing triglycerides to the circulation, causing dyslipidemia (54). Further, insulin resistance causes increased renal sodium reabsorption and stimulate the sympathetic nervous system which can result in hypertension (55).

Another factor contributing to the development of the MetS is excessive nutrient intake. Nutrient processing in the mitochondria cause ROS formation which can alter the mitochondrial function and endoplasmic reticulum which again will lead to defective insulin secretion and Diabetes Mellitus type 2 (DMT2) (56). Also, increased excretion of uric acid as a result of excessive intake of fructose is thought to cause metabolic alterations, which are even more evident in a hyperinsulemic or hypertriglyceridemic state (57). Moreover, excessive nutrient intake can result in obesity, defined as the presence of excessive adipose tissue, which also contribute to the development.

Visceral fat is particularly unfortunate as it secrets the inflammatory cytokines TNF-α and IL-6 and little anti-inflammatory adiponectin as a result of activation and infiltration of macrophages in the adipose tissue, while subcutaneous fat first serves as an isolation agent. The production of cytokines with pro-inflammatory effects in adipose tissue contributes to an increase in lipolysis and hypertriglyceridemia (58, 59), and the lipolysis is further increased when insulin resistance is present, and more free fatty acids are released into the circulation (60). This becomes part of a vicious circle as an elevated concentration of free fatty acids again is thought to cause insulin resistance (60, 61). Altogether, this underpins the allegation that increased visceral fat is associated with metabolic alterations.

There is, however, some debate as to whether insulin resistance and obesity is the cause or a consequence of the metabolic alterations as they interfere in a fashion making cause and effect hard to differentiate.

A longitudinal study conducted by Weiss et al. (62) concluded that among severely obese children, the absence of the MetS is likely to remain unless further weight gain is achieved, which suggest a genetic component in the development of the MetS. This underpin that some are susceptible to the MetS to a greater extent than others. A genetic susceptibility for both central obesity and for the development of the MetS is probably an underlying cause of the development (63). This susceptibility is further reasoned when considering ethnicity, as youth of ethnic minorities have been shown to be more obese and more insulin resistant compared with their Caucasian counterparts (64).

Moreover, for the development of the MetS in adolescence the impact of a temporary insulin resistance which occurs during puberty, may be relevant. This state is possibly a result of increasing levels of growth hormone and insulin-like growth factor 1 (65). The change can worsen the insulin-resistant state in obese youth and accelerate the development of DMT2, or the MetS (66).

1.3.4 Consequences of the metabolic syndrome

The presence of the MetS entails an increased risk for mortality from cardiovascular diseases and all causes in adults (47, 48), and an increase in DMT2 and cardiovascular disease in juvenile age (67). Children with obesity are also at increased risk of adolescent and adult obesity (17, 68, 69), which again increases the risk of cardiovascular disease in later life.

The metabolic syndrome is further associated with polycystic ovary syndrome, obstructive sleep apnea, hypogonadism and some forms of cancer (70, 71).

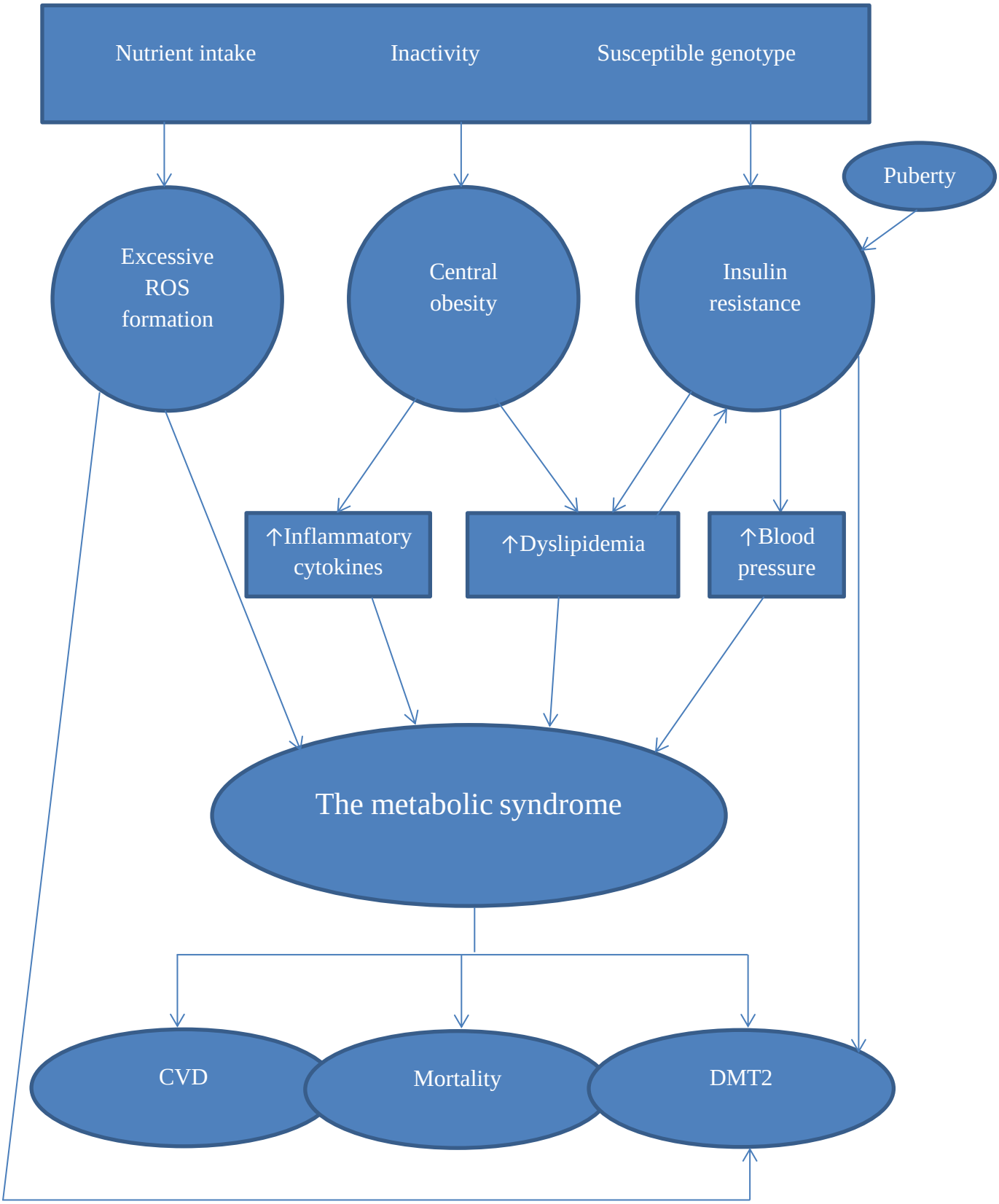

Figure 1 *Mechanisms of obesity-related morbidities.*

Abbreviations: CVD, cardiovascular disease; DMT2, diabetes mellitus type 2; ROS, reactive oxygen species

1.3.5 NAFLD

Another change occurring, also associated with overweight, obesity and insulin resistance is the infiltration of fat to the liver. Non-Alcoholic Fatty Liver Disease (NAFLD) is defined as the presence of steatosis in more than five percent of hepatocytes in the absence of significant alcohol consumption, drug use or hereditary diseases (72). Liver transaminases, especially ALAT, are commonly considered a surrogate marker for NAFLD and because of its close relation to cardiovascular risk factors (73), NAFLD has been suggested to be 'the hepatic manifestation of the MetS' (66).

1.4 Aims of the investigation

a) To determine the prevalence of the MetS among obese children and adolescents at the Obesity outpatient clinic at Haukeland University Hospital.

We hypothesize that the prevalence is similar to other European countries

b) To determine whether the SDS for the anthropometrical measurements WC, WHtR, and waist-to-sitting height-ratio (WSHR), in addition to BMI, predict cardiometabolic risk factors (insulin resistance, altered low density lipoprotein cholesterol (LDL), total cholesterol, triglycerides, high density lipoprotein cholesterol (HDL) and liver test (ASAT, ALAT, gamma-gt) or the MetS as defined by Cook et al. (50)) better than BMI SDS in obese children and adolescents at the Obesity outpatient clinic at Haukeland University Hospital.

We hypothesize that anthropometric measures can be a valuable predictor.

2 Materials and methods

2.1 Study design and population

This study has an observational cross-sectional design and has been approved by the Data Protection Official (Appendix I). As it can be considered a quality assurance of the treatment at the outpatient clinic of obesity, there was no need for approval from the Regional Committee of Ethics.

The cohort consists of 96 patients, of which 46 (47.9%) are boys, with an age range of 5-18 years. The patients have an IOTF BMI >35 kg/m^2 or >30 kg/m^2 with comorbidities listed in the introduction.

2.2 Recruitment, inclusion and exclusion criteria

The study participants were recruited from the Obesity outpatient clinic, Haukeland University Hospital, Bergen, Norway, by retrieving information from the medical records of the participants. All measurements retrieved were collected in the period August 2013 through November 2014.

When referred to the outpatient clinic of obesity, a broad informed consent for research is obtained which includes permission to retrieve information from the medical records in retrospect (Appendix II).

When including patients for participation, the first anthropometrical data assessment completed was obtained and combined with the biochemical data closest in time. If the time between anthropometric and biochemical assessment exceeded 3 months, the patients were excluded. If the biochemical collection lacked some of the components needed for assessment of the MetS, the patients were excluded. One participant was excluded because blood sample was likely to not be taken in the fasting state. The inclusion is illustrated in Figure 2.

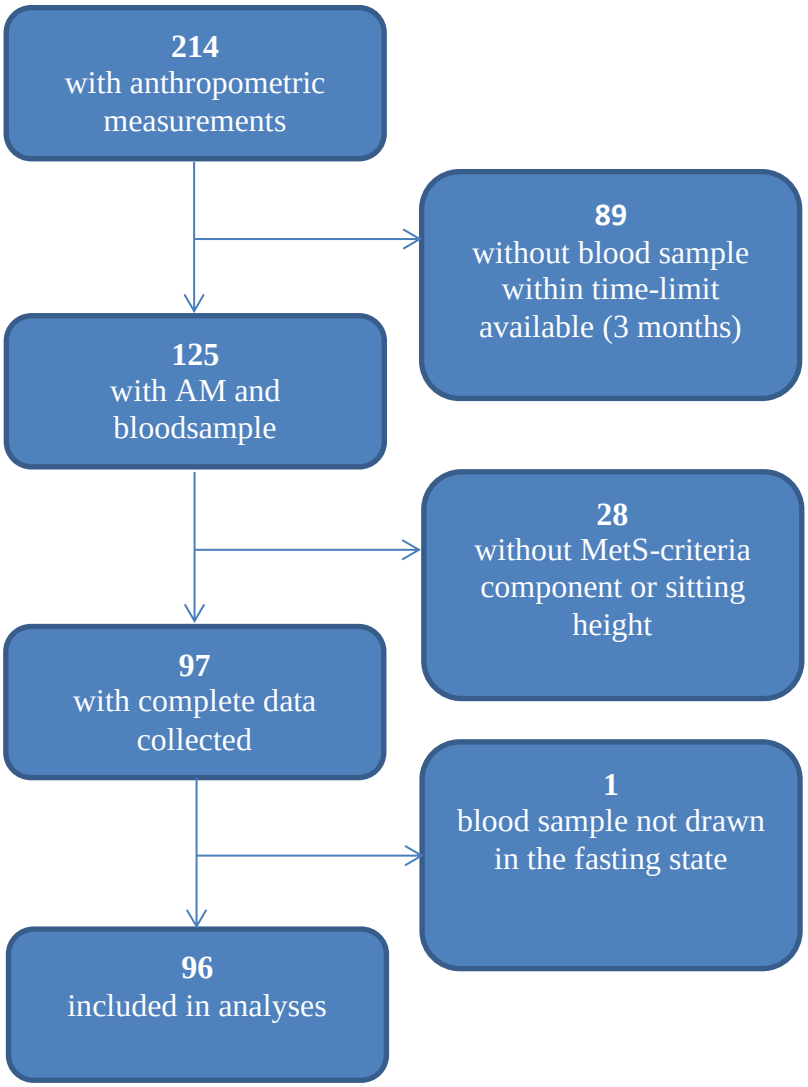

Figure 2 *Patient inclusion flowchart.*

Abbreviations: AM, Anthropometric measurements; MetS, Metabolic syndrome.

2.3 Assessment

At enrollment at the outpatient clinic the patients undergo a physical examination as part of the commencement of the treatment of obesity. The examination included the following assessments:

2.3.1 Assessment of anthropometric measurements

Height was measured to the nearest 1 mm with a stadiometer (Seca 240) with the participant standing with the feet together, and the heels, buttocks and shoulders touching the stadiometer. The participant should not wear shoes or socks, only light clothing. The head should be in a position with the lower edge of the eye socket in the same horizontal plane as the notch superior to the tragus of the ear.

Sitting height was also measured to the nearest 1 mm with a stadiometer, but with the participant sitting on a chair which is 72.1 cm high. This value was later subtracted from the outcome. The sacrum and shoulder should touch the stadiometer and the head should be in the same position as when measuring height.

WC was measured at the most narrow point between costae 10 and crista iliaca with a flexible non-elastic tape at the end of expiration.

Body weight was measured to the nearest 0.1 kg using a calibrated scale (InBody 720) with the participant ideally only wearing underwear; however, nine participants were weighed wearing clothes.

All measurements were done according to the recommended techniques described by Júlíusson et al. (74).

BMI was calculated using weight in kilograms divided by the square of the height in meters. WHtR and WSHR were calculated by dividing WC by height and sitting height, respectively.

2.3.2 Assessment of blood pressure and pulse

Blood pressure measurements and pulse were routinely assessed twice to be able to use the mean for analysis. When only one measurement was obtained this measurement was included with the means (two participants). Blood pressure measurements were in principle assessed by an automatic sphygmomanometer (Criticare 506 DN), but for three participants a manual control examination was assessed and the respective control data have been selected for analysis. Before measuring, the participant should be seated for at least five minutes, and an appropriate cuff size, covering about 2/3 of the upper arm, was used.

The definition of hypertension in children is following the Guidelines from the National High Blood Pressure Education Program Working group (75). Blood pressure was divided into the following four stages, after adjusting for age, height and gender (Appendix III):

Table 1 *Classification of hypertension.*

Systolic or diastolic blood pressure:	**Stage**	**Category**
<90th percentile	Normal blood pressure	0
90-<95th percentile or >120/80 (yet <95th percentile)	Prehypertension	1
95th – 5 mmHg above the 99th percentile	Stage 1 (moderate hypertension)	2
>99th percentile + 5 mmHg	Stage 2 (severe hypertension)	3

2.3.3 Assessment of laboratory measurements

At examination blood samples were requisitioned and the patients were encouraged to return for withdrawal of fasting blood samples at a later time. The following biochemical data were collected from fasting samples of serum, listed in the medical records: Glucose, HbA1c, CRP, ALAT, ASAT, gamma-GT, total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, insulin and insulin c-peptide.

HOMA-IR was calculated as HOMA-IR = [s-glc (mmol/L) x s-insulin (mU/L) /22.5] (76).

2.4 Defining the metabolic syndrome

The MetS was defined using the Cook's definition (50) with the following cut-offs:

- WC > 1.3 SDS,
- Fasting glucose ≥ 6.1 mmol/L,
- Triglycerides ≥ 1.24 mmol/L or HDL ≤ 1.03 mmol/L,
- SBP or DBP ≥ 90^{th} percentile, adjusted for height, age and gender.

The MetS is present if three or more abnormalities exist.

2.5 Statistical analyses and presentation of data

Descriptive and explorative statistics were run to check for normality. All variables were normally distributed, except for insulin, insulin c-peptide, HOMA-IR and triglycerides, which were skewed. The statistical analyses are therefore run with these assumptions, using Pearson correlation for the normally distributed data, and Spearman correlation for the skewed data. However, for comparing means, student t-test was used for all variables, and not Mann-Whitney as Mann-Whitney assumes equal distributions, and the student t-test is a very robust test, even for small samples.

SDS for the new variable WSHR were compiled, using R, based on Norwegian growth charts from the Bergen Growth Study (77).

All analyses were run using SDS for the anthropometric measurements as it makes the values comparable between age and gender.

The prevalence of the MetS was calculated using frequency statistics, and as the prevalence is a proportion, the 95% confidence interval (CI) was calculated using the central limit theorem for binomial distribution with the following formula:

$CI = \hat{p} \pm z \sqrt{(\hat{p}(1- \hat{p})/n)}$, where

$\hat{p}$ = prevalence

n = number of participants

z = 1.96.

Simple analyses of linear regression were performed to see how the anthropometric measurements were related to the cardiometabolic biomarkers. Linear regression models were then adjusted for age and gender. The reason why the analyses are run with and without

adjusting for age and gender although using SDS is that there may be different risks for age and gender beyond what the SDS can adjust for. For instance boys and girls with the same IOTF BMI and different age may have a different risk of developing the MetS.

Logistic regression models were performed when the outcomes were dichotomous, that is for the blood pressure levels (below or above the 90^{th} percentile) and liver transaminases as it would be irrelevant to see an association within the normal range for these parameters. Also for the presence of the MetS, logistic regression was used to see what anthropometric measurement predict the syndrome. The logistic regression models were run both with and without adjusting for age and gender. All descriptive data, correlations and regression models were performed using the Statistical Package for the Social Sciences (SPSS version 22 for Windows, Chicago, IL, USA).

Akaike weights were calculated from the Akaike Information Criteria (AIC) from a multinomial regression model, adjusted for age and gender, using R (version 3.1.3 for Windows).

Akaike weight is an alternative method for selecting the best approximating model in a set. When interpreting the AIC value, the absolute number is irrelevant; the important is the AIC values, in relation to each other and the difference between them. The best model will have the lowest AIC. The differences (Δ) between the top model and the other AIC values are calculated, and interpreted as follows: A model with a small difference (0-2) is plausible to have a substantial level of empirical support of the model, while a difference of 4-7 would have considerably less, and a difference of more than 10 would provide essentially no support (78). The relative likelihood is calculated as $\exp(-\Delta/2)$, and the Akaike weight is the relative likelihood divided by the sum of all relative likelihoods which can be interpreted as the probability of the model being the best.

The particular anthropometric measurement models were selected for Akaike information criteria because they theoretically should be able to contribute to the prediction of the MetS, the blood pressure values, and the transaminase values.

3 Results

All of the included participants had all anthropometric measurements and the parameters required for defining the MetS available. However, for some of the metabolic parameters, a smaller sample was used (i.e. s-insulin, n=87; insulin c-peptide, n=85; total cholesterol, n=95; LDL, n=95; gGT, n=83; ALAT, n=89).

The results include the presentation of descriptive statistics, prevalence of the MetS, correlation and regression models, and Akaike weights.

3.1 Descriptive statistics

Sample size, mean, standard deviation and range for age and the anthropometric measurements are presented in Table 2. Independent samples t-test indicated boys were significantly heavier, taller and had a higher sitting height than girls (all p-values <0.02), however no significant differences were found between the respective SDS. Boys had a significantly smaller WC SDS and WHtR SDS (p-value <0.01) than girls.

Sample size, mean, standard deviation, median, 25^{th}-75^{th} percentile and range for the biomarkers are presented in Table 5. Independent samples t-test indicated boys had significantly higher ALAT-levels than girls.

Table 2 *Descriptive data on age and anthropometric measurements.*

	Total (n=96)		**Boys** (n=46)		**Girls** (n=50)		
Variables	**Mean±SD**	**Min-Max**	**Mean±SD**	**Min-Max**	**Mean±SD**	**Min-Max**	**p-value***
Age (years)	12.98±3.26	5.89-18.20	13.07±2.89	5.97-17.91	12.89±3.59	5.89-18.20	
Weight (kg)	87.5±27.1	29.4-137.3	94.7±27.3	36.1-137.3	80.9±25.5	29.4-129.0	0.010
Weight SDS	3.17±0.81	-0.21-5.40	3.24±0.59	1.71-4.56	3.11±0.98	-0.20-5.40	
Height (cm)	159.6±16.9	115.3-186.6	165.1±17.2	117.0-186.6	154.6±15.0	115.0-179.0	<0.001
Height SDS	0.48±1.25	-3.62-4.47	0.71±1.17	-2.20-4.47	0.26±1.30	-3.60-4.20	
Sitting height (cm)	84.8±8.1	66.0-101.5	86.9±8.3	66.0-101.5	83.0±7.5	66.1-94.7	0.020
Sitting height SDS	0.81±1.07	-1.93-4.13	0.99±1.05	-1.73-4.13	0.64±1.08	-1.90-3.47	
WC (cm)	103.9±15.6	60.1-137.8	105.4±14.1	66.4-130.8	102.5±17.0	60.1-138.0	
WC SDS	3.12±0.58	1.68-4.74	2.85±0.31	1.79-3.47	3.36±0.67	1.68-4.74	<0.001
BMI (kg/m2)	33.3±5.4	21.8-45.6	33.9±5.1	21.8-45.6	32.8±5.6	22.1-43.1	
BMI SDS	3.09±0.55	1.76-4.56	3.05±0.40	2.19-4.17	3.13±0.67	1.76-4.56	
WHtR	0.649±0.064	0.516-0.808	0.638±0.056	0.516-0.784	0.660±0.067	0.520-0.808	
WHtR SDS	3.06±0.41	1.82-3.96	2.95±0.35	1.96-3.54	3.16±0.45	1.82-3.96	0.010
WSHR SDS	2.95±0.41	1.50-4.00	2.91±0.36	1.76-3.44	2.98±0.45	1.50-4.00	

*Differences between boys and girls, students t-test.

Abbreviations: WC, waist circumference; BMI, Body Mass Index; WHtR, Waist-to-height-Ratio; WSHR, Waist-to-sitting height-Ratio

Descriptive data for the blood pressure values are shown in Table 3. Boys had a significantly higher SBP than girls, but for DBP there was no significant difference.

Table 3 *Descriptive data on blood pressure.*

Variables	Total (n=96)		Boys (n=46)		Girls (n=50)	
	Mean±SD	Min-Max	Mean±SD	Min-Max	Mean±SD	Min-Max
SBP(mmHg)	125.4±13.7	90-163	128.4±14.1	93-163	122.6±12.9	90-151*
DBP(mmHg)	73.8±9.6	57-99.5	74.6±9.2	57.5-98.5	73.1±10.1	57-99.5

* Significant difference between boys and girls, students t-test (p=0.040)
Abbreviations: SBP, Systolic blood pressure; DBP, Diastolic blood pressure

When adjusted for age, height and gender, most boys had SBP in the second category, between the 95th and 99th percentile, while most girls were in the first category, below the 90th percentile. For DBP, both boys and girls, most participants were in the first category, below the 90th percentile.

Table 4 *Prevalence in the different blood pressure categories.*

Blood pressure category	Total (n=96)		Boys (n=46)		Girls (n=50)	
	SBP (%)	DBP (%)	SBP (%)	DBP (%)	SBP (%)	DBP (%)
0 (<90th percentile)	29.2	66.7	23.9	60.9	34.0	72.0
1 (90-95th percentile)	26.0	16.7	28.3	21.7	24.0	12.0
2 (95-99th percentile)	31.3	13.5	34.8	15.2	28.0	12.0
3 (>90th percentile)	13.5	3.1	13.0	2.2	14.0	4.0

Abbreviations: SBP, Systolic blood pressure; DBP, Diastolic blood pressure

Table 5 *Descriptive data on the biomarkers.*

	Total					Boys					Girls				
Variables	n	Mean ±SD	Min-Max	Median	25-75 percentile	n	Mean ±SD	Min-Max	Median	25-75p	n	Mean ±SD	Min-Max	Median	25-75 percentile
Glucose (mmol/L)	96	5.0 ±0.5	4.1-7.1	5.0	4.6-5.2	46	5.0 ±0.4	4.1-6.2	5.0	4.8-5.2	50	4.9 ±0.5	4.2-7.1	4.9	4.6-5.2
Insulin (mU/L)[δ]	87	18.4 ±13.6	2.0-73.7	15.4	10.4-21.2	46	18.8 ±13.9	2.0-73.7	15.7	10.2-22.1	41	17.9 ±13.4	2.0-66.8	15.4	10.4-20.4
Insulin c-peptid (nmol/L)[δ]	85	1.0 ±0.6	0.3-3.0	0.87	0.7-1.2	44	1.1 ±0.6	0.3-3.0	0.9	0.6-1.3	41	1.0 ±0.5	0.3-2.9	0.8	0.7-1.0
HOMA-IR[δ]	87	4.2 ±3.4	0.4-17.6	3.31	2.1-4.6	46	4.2 ±3.2	0.4-16.4	3.3	2.1-5.0	41	4.1 ±3.6	0.4-17.6	3.5	2.2-4.6
TG (mmol/L)[δ]	96	1.2 ±0.6	0.3-2.6	1.05	0.8-1.6	46	1.3 ±0.5	0.5-2.6	1.2	0.9-1.2	50	1.1 ±0.6	0.3-2.4	0.9	0.7-1.5
Tchol (mmol/L)	95	4.3 ±0.9	2.3-6.6	4.3	3.7-4.8	45	4.3 ±0.8	2.3-6.4	4.2	3.7-4.8	50	4.3 ±0.9	2.5-6.6	4.3	3.7-4.8
HDL-C (mmol/L)	96	1.2 ±0.3	0.6-2.4	1.2	1.1-1.3	46	1.2 ±0.3	0.6-1.9	1.2	1.0-1.3	50	1.3 ±0.3	0.8-2.4	1.2	1.2-1.3
LDL-C (mmol/L)	95	2.8 ±0.8	0.6-5.2	2.8	2.3-3.3	46	2.8 ±0.8	0.6-5.2	2.8	2.3-3.3	49	2.8 ±0.8	1.2-4.9	2.8	2.3-3.3
gammaGT (U/L)	83	20.9 ±10.7	5.0-50.0	17.0	14.0-27.0	44	25.7 ±11.5	8.0-50.0	23.5	16.3-32.8	39	15.5 ±6.4	5.0-39.0	14.0	12.0-16.0
ALAT (U/L)	89	30.6 ±22.5	8.0-131	23.0	17.0-34.5	45	39.1 ±27.0	11.0-131	27.0	20.0-56.5	44	21.8 ±11.8	8.0-75.0	20.0	15.3-27.0*

[δ]The shaded variables were not normally distributed.

*Difference between boys and girls, students t-test ($p<0.001$).

Abbreviations: HOMA-IR, Homeostatic model assessment of insulin resistance; TG, Triglycerides; Tchol, Total cholesterol; HDL-C, High-Density Lipoprotein cholesterol; LDL-C, Low-Density Lipoprotein Cholesterol; gammaGT, gamma-Glutamyl-Transferase; ALAT, Alanine Aminotransferase

3.2 Prevalence

The prevalence of the MetS among obese children and adolescents in this sample as defined by Cook et al. (50) was 39.6% and the 95 % confidence interval was 29.8%-49.4%.

Chi squared test revealed that there was no significant difference between the prevalence in boys (45.7%) and girls (34.0%) (χ^2(1, N=96 =1.36, p=0.244).

A figure presenting the prevalece of the number of components of the MetS for all participants, and for boys and girls seperately is described below. None of the participants had zero components.

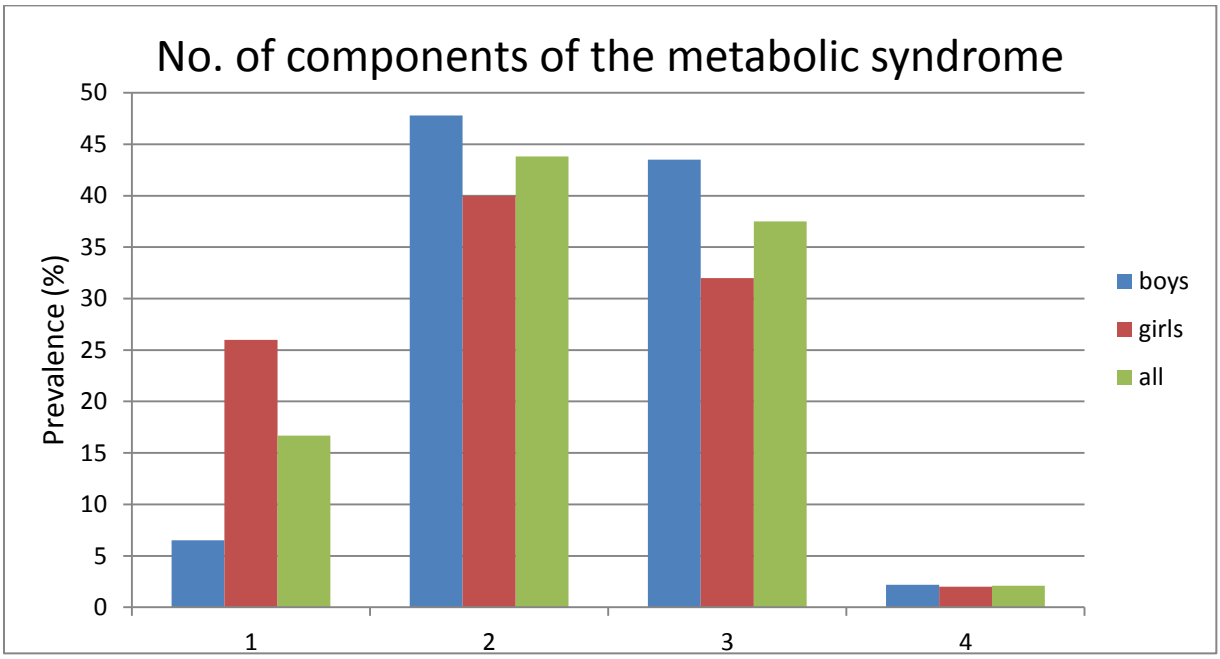

Figure 3 *Subjects grouped according to the number of components of the metabolic syndrome they present with.*

Frequency statistics for the determinants used to define the MetS showed that all of the participants had a WC SDS greater than 1.3, 77.1% had increased blood pressure, 45.8% had decreased HDL-cholesterol or increased triglyceride levels, and 2.1% had increased glucose-levels as shown in the figure below:

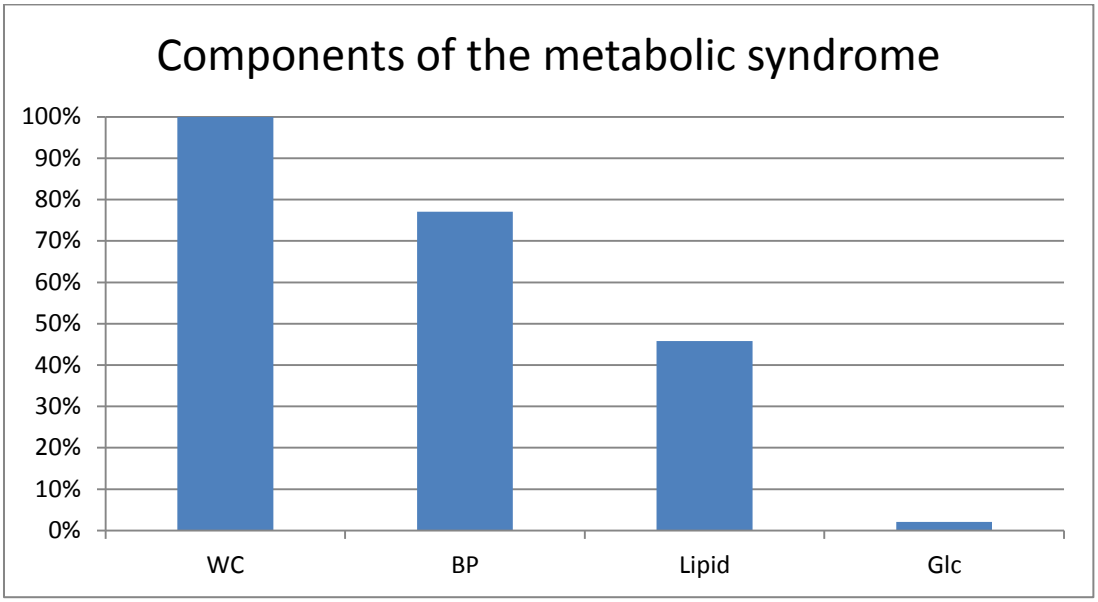

Figure 4 *Prevalence of the different components of the metabolic syndrome.*

Abbreviations: WC, waist circumference; BP, blood pressure; Lipid, decreased HDL or increased triglycerides; Glc, fasting serum glucose

3.3 Correlations

All anthropometric measurements were highly correlated with each other:

Table 6 *Pearson correlations for anthropometric measurements.*

		Pearson Correlations			
		BMI SDS	WC SDS	WHtR SDS	WSHR SDS
BMI SDS	r sig.	1			
WC SDS	r sig.	0.776* <0.001	1		
WHtR SDS	r sig.	0.779* <0.001	0.883* <0.001	1	
WSHR SDS	r sig.	0.684* <0.001	0.817* <0.001	0.916* <0.001	1

*p-value<0.001

Abbreviations: BMI, Body Mass Index; WC, waist circumference; WHtR, Waist-to-height-Ratio; WSHR, Waist-to-sitting height-Ratio

WSHR SDS was correlated with the highest amount of biomarkers and was the only model significantly correlated to gGT. BMI SDS was correlated strongest to the blood pressure-values. Age was also significantly correlated with several of the examined biomarkers, as shown in Table 7.

Table 7 *Pearson and Spearman correlations for anthropometric measurements and blood pressure and biomarkers.*

		Correlations										
		SBP	DBP	glucose	insulin$^{\delta}$	c-peptide$^{\delta}$	HOMA-IR$^{\delta}$	triglycerides$^{\delta}$	cholesterol	HDL	LDL	gGT
Age	r	0.299**	0.285**	0.188	0.416***	0.485***	0.410***	0.257*	0.161	-0.223*	0.164	0.433***
	sig	0.003	0.005	0.067	<0.001	<0.001	<0.001	0.012	0.119	0.029	0.113	<0.001
Gender	r	0.073	0.064	0.090	0.044	0.065	0.051	0.201	-0.032	-0.233*	0.013	0.477***
	sig	0.482	0.539	0.383	0.683	0.556	0.637	0.050	0.755	0.022	0.898	<0.001
BMI SDS	r	0.347**	0.306**	0.163	0.319**	0.314**	0.316**	0.122	0.053	-0.141	0.044	0.165
	sig	0.001	0.002	0.112	0.003	0.003	0.003	0.236	0.607	0.170	0.675	0.136
WC SDS	r	0.257*	0.288**	0.094	0.191	0.252*	0.189	0.004	0.074	-0.082	0.061	0.054
	sig	0.012	0.005	0.362	0.076	0.020	0.079	0.965	0.478	0.425	0.557	0.627
WHtR SDS	r	0.289**	0.262**	0.057	0.156	0.188	0.151	0.014	0.035	-0.061	0.018	0.093
	sig	0.004	0.010	0.583	0.149	0.085	0.163	0.896	0.738	0.554	0.860	0.401
WSHR SDS	r	0.253*	0.256*	0.072	0.218*	0.244*	0.213*	-0.006	0.023	-0.127	0.030	0.273*
	sig	0.013	0.012	0.487	0.042	0.025	0.048	0.956	0.823	0.216	0.776	0.012

$^{\delta}$Spearman correlations

*p<0.05
**p<0.01
***p<0.001

Abbreviations: BMI, Body Mass Index; WC, waist circumference; WHtR, Waist-to-height-Ratio; WSHR, Waist-to-sitting height-Ratio; SBP, systolic blood pressure; DBP, Diastolic blood pressure; c-peptide, insulin-c-peptide; HOMA-IR, Homeostatic model assessment of insulin resistance; HDL, High-Density Lipoprotein cholesterol; LDL, Low-Density Lipoprotein Cholesterol; gGT, gamma-Glutamyltransferase

3.4 Regression

Simple linear regression models on raw data showed that BMI SDS was significantly associated with serum insulin, insulin c-peptide, HOMA-IR (all p<0.01) and triglycerides (p=0.024). WC SDS and WHtR SDS were not associated with the selected biomarkers. WSHR SDS was significantly associated with c-peptide (p=0.039) and with gamma-gt (p=0.012). P-values below 0.050 are presented in bold.

Table 8 *Unadjusted linear regression for BMI SDS and biomarkers.*

	BMI SDS					
	b	SE	95% c.i. lower	95% c.i. upper	R^2	p-value
Glucose	0.20	0.12	-0.48	0.45	0.027	0.112
Insulin	0.01	0.00	0.01	0.02	0.084	**0.006**
HbA1c	0.14	0.18	-0.22	0.51	0.006	0.447
HOMA-IR	0.05	0.02	0.02	0.08	0.098	**0.003**
C-peptide	0.25	0.09	0.07	0.44	0.081	**0.008**
TC	0.04	0.07	-0.10	0.17	0.003	0.607
HDL	-0.29	0.21	-0.71	0.13	0.020	0.170
LDL	0.03	0.07	-0.11	0.17	0.002	0.675
TG	0.22	0.10	0.03	0.42	0.053	**0.024**
GammaGT	0.01	0.01	-0.01	0.02	0.027	0.136

Abbreviations: HbA1c, Hemoglobin A1c; HOMA-IR, Homeostatic model assessment of insulin resistance; c-peptide, serum-insulin c-peptide; TC, Total cholesterol; HDL, High-Density Lipoprotein cholesterol; LDL, Low-Density Lipoprotein Cholesterol; TG, triglyceride; GammaGT, Gamma-Glutamyltransferase

Table 9 *Unadjusted linear regression for WC SDS and biomarkers.*

	WC SDS					
	b	SE	95% c.i. lower	95% c.i. upper	R^2	p-value
Glucose	0.12	0.13	-0.14	0.38	0.009	0.362
Insulin	0.01	0.00	-0.00	0.02	0.031	0.100
HbA1c	0.01	0.19	-0.37	0.40	0.000	0.949
HOMA-IR	0.03	0.02	-0.00	0.06	0.038	0.070
C-peptide	0.19	0.10	-0.00	0.39	0.044	0.053
TC	0.05	0.07	-0.09	0.19	0.005	0.478
HDL	-0.18	0.22	-0.63	0.27	0.007	0.425
LDL	0.04	0.07	-0.10	0.19	0.004	0.557
TG	0.14	0.11	-0.07	0.34	0.017	0.203
GammaGT	0.01	0.01	-0.01	0.02	0.003	0.627

Abbreviations: HbA1c, Hemoglobin A1c; HOMA-IR, Homeostatic model assessment of insulin resistance; c-peptide, serum-insulin c-peptide; TC, Total cholesterol; HDL, High-Density Lipoprotein cholesterol; LDL, Low-Density Lipoprotein Cholesterol; TG, triglyceride; GammaGT, Gamma-Glutamyltransferase

Table 10 *Unadjusted linear regression for WHtR SDS and biomarkers.*

	WHtR SDS					
	b	SE	95% c.i. lower	95% c.i. upper	R^2	p-value
Glucose	0.05	0.09	-0.14	0.24	0.003	0.583
Insulin	0.00	0.00	-0.00	0.01	0.023	0.159
HbA1c	0.12	0.14	-0.16	0.39	0.008	0.404
HOMA-IR	0.02	0.01	-0.01	0.04	0.024	0.149
C-peptide	0.12	0.07	-0.03	0.26	0.031	0.108
TC	0.02	0.05	-0.08	0.12	0.001	0.738
HDL	-0.10	0.16	-0.41	0.22	0.004	0.554
LDL	0.01	0.05	-0.09	0.11	0.000	0.860
TG	0.07	0.08	-0.08	0.22	0.010	0.338
GammaGT	0.00	0.00	-0.01	0.01	0.009	0.401

Abbreviations: HbA1c, Hemoglobin A1c; HOMA-IR, Homeostatic model assessment of insulin resistance; c-peptide, serum-insulin c-peptide; TC, Total cholesterol; HDL, High-Density Lipoprotein cholesterol; LDL, Low-Density Lipoprotein Cholesterol; TG, triglyceride; GammaGT, Gamma-Glutamyltransferase

Table 11 *Unadjusted linear regression for WSHR SDS and biomarkers.*

	WSHR SDS					
	b	SE	95% c.i. lower	95% c.i. upper	R^2	p-value
Glucose	0.07	0.09	-0.12	0.25	0.005	0.487
Insulin	0.01	0.00	0.00	0.01	0.040	0.063
HbA1c	0.16	0.14	-0.11	0.43	0.015	0.239
HOMA-IR	0.02	0.01	-0.00	0.04	0.038	0.072
C-peptide	0.15	0.07	0.01	0.29	0.050	**0.039**
TC	0.01	0.05	-0.09	0.11	0.001	0.823
HDL	-0.20	0.16	-0.51	0.12	0.016	0.216
LDL	0.02	0.05	-0.09	0.12	0.001	0.776
TG	0.08	0.07	-0.07	0.23	0.012	0.298
GammaGT	0.01	0.00	0.00	0.02	0.075	**0.012**

Abbreviations: HbA1c, Hemoglobin A1c; HOMA-IR, Homeostatic model assessment of insulin resistance; c-peptide, serum-insulin c-peptide; TC, Total cholesterol; HDL, High-Density Lipoprotein cholesterol; LDL, Low-Density Lipoprotein Cholesterol; TG, triglyceride; GammaGT, Gamma-Glutamyltransferase

Scatter diagrams illustrating the significant results from unadjusted linear regression models are presented below:

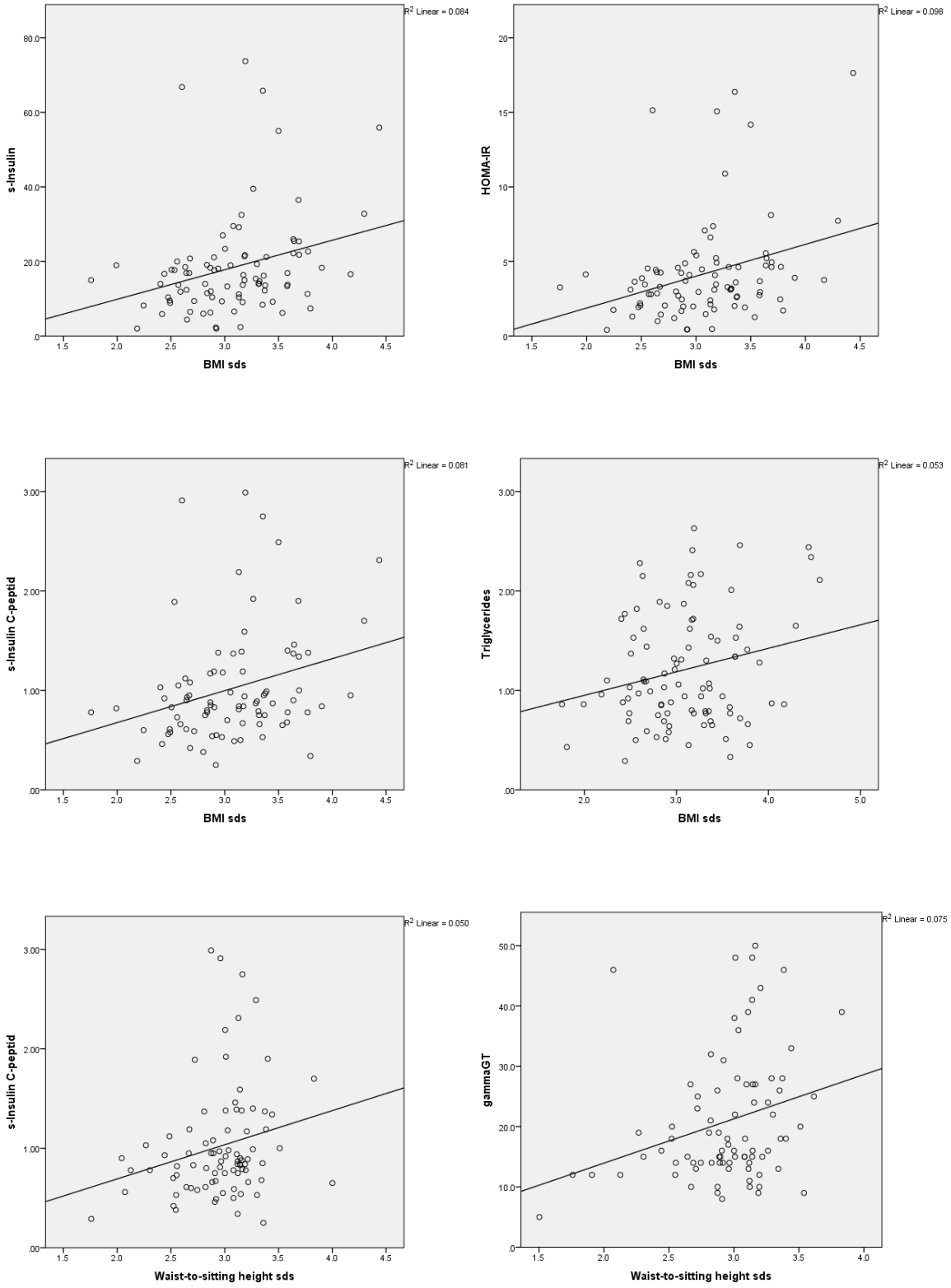

Figure 5 *Scatterplots for linear regression models with p<0.05.*

When adjusted for age and gender, linear regression models showed no significant association between the anthropometrics and the biomarkers from the blood samples (All p>0.05).

Table 12 *Linear regression for BMI SDS and biomarkers, adjusted for age and gender.*

BMI SDS						
	b	SE	95% c.i. lower	95% c.i. upper	R^2	p-value
Glucose	0.09	0.09	-0.10	0.27	0.051	0.358
Insulin	5.10	3.07	-1.02	11.20	0.138	0.101
HbA1c	0.72	0.07	-0.06	0.20	0.047	0.273
HOMA-IR	1.41	0.76	-0.10	2.92	0.153	0.066
C-peptide	0.18	0.13	-0.07	0.44	0.162	0.152
TC	-0.05	0.18	-0.40	0.31	0.028	0.789
HDL	-0.04	0.05	-0.14	0.07	0.105	0.519
LDL	-0.06	0.18	-0.40	0.29	0.028	0.753
TG	0.15	0.11	-0.07	0.38	0.118	0.181
GammaGT	-0.05	1.98	-3.99	3.88	0.401	0.979

Abbreviations: BMI, Body Mass Index; HbA1c, Hemoglobin A1c; HOMA-IR, Homeostatic model assessment of insulin resistance; c-peptide, serum-insulin c-peptide; TC, Total cholesterol; HDL, High-Density Lipoprotein cholesterol; LDL, Low-Density Lipoprotein Cholesterol; TG, triglyceride; GammaGT, Gamma-Glutamyltransferase

Table 13 *Linear regression for WC SDS and biomarkers, adjusted for age and gender.*

WC SDS						
	b	SE	95% c.i. lower	95% c.i. upper	R^2	p-value
Glucose	0.06	0.10	-0.14	0.27	0.047	0.533
Insulin	2.75	3.55	-4.32	9.82	0.116	0.441
HbA1c	0.08	0.07	-0.06	0.22	0.049	0.243
HOMA-IR	0.73	0.88	-1.02	2.48	0.125	0.410
C-peptide	0.18	0.15	-0.11	0.47	0.156	0.225
TC	-0.03	0.19	-0.41	0.35	0.028	0.865
HDL	-0.07	0.06	-0.18	0.05	0.113	0.260
LDL	-0.01	0.19	-0.38	0.36	0.027	0.947
TG	0.13	0.12	-0.11	0.08	0.112	0.280
GammaGT	1.79	2.09	-2.36	5.95	0.407	0.393

Abbreviations: HbA1c, Hemoglobin A1c; HOMA-IR, Homeostatic model assessment of insulin resistance; c-peptide, serum-insulin c-peptide; TC, Total cholesterol; HDL, High-Density Lipoprotein cholesterol; LDL, Low-Density Lipoprotein Cholesterol; TG, triglyceride; GammaGT, Gamma-Glutamyltransferase

Table 14 *Linear regression for WHtR SDS and biomarkers, adjusted for age and gender.*

WHtR SDS						
	b	SE	95% c.i. lower	95% c.i. upper	R^2	p-value
Glucose	0.01	0.13	-0.24	0.26	0.043	0.944
Insulin	2.59	4.19	-5.74	10.92	0.113	0.538
HbA1c	0.14	0.87	-0.04	0.31	0.060	0.123
HOMA-IR	0.58	1.04	-1.48	2.65	0.121	0.576
C-peptide	0.14	0.17	-0.20	0.48	0.148	0.410
TC	-0.10	0.24	-0.57	0.38	0.029	0.687
HDL	-0.03	0.07	-0.17	0.12	0.102	0.688
LDL	-0.10	0.23	-0.56	0.10	0.029	0.660
TG	0.06	0.15	-0.24	0.37	0.102	0.685
GammaGT	0.95	2.67	-4.36	6.27	0.402	0.722

Abbreviations: WHtR, Waist-to-Height-Ratio; HbA1c, Hemoglobin A1c; HOMA-IR, Homeostatic model assessment of insulin resistance; c-peptide, serum-insulin c-peptide; TC, Total cholesterol; HDL, High-Density Lipoprotein cholesterol; LDL, Low-Density Lipoprotein Cholesterol; TG, triglyceride; GammaGT, Gamma-Glutamyltransferase

Table 15 *Linear regression for WSHR SDS and biomarkers, adjusted for age and gender.*

WSHR SDS						
	b	SE	95% c.i. lower	95% c.i. upper	R^2	p-value
Glucose	0.02	0.12	-0.22	0.26	0.042	0.871
Insulin	4.45	4.02	-3.55	12.45	0.122	0.272
HbA1c	0.12	0.08	-0.04	0.29	0.058	0.141
HOMA-IR	0.99	1.00	-1.00	2.97	0.128	0.326
C-peptide	0.22	0.17	-0.11	0.54	0.158	0.197
TC	-0.08	0.23	-0.54	0.37	0.029	0.723
HDL	-0.06	0.07	-0.19	0.08	0.107	0.429
LDL	-0.05	0.22	-0.49	0.38	0.027	0.808
TG	0.05	0.15	-0.24	0.34	0.102	0.752
GammaGT	4.32	2.58	-0.82	9.46	0.422	0.098

Abbreviations: WSHR, Waist-to-sitting height-Ratio; HbA1c, Hemoglobin A1c; HOMA-IR, Homeostatic model assessment of insulin resistance; c-peptide, serum-insulin c-peptide; TC, Total cholesterol; HDL, High-Density Lipoprotein cholesterol; LDL, Low-Density Lipoprotein Cholesterol; TG, triglyceride; GammaGT, Gamma-Glutamyltransferase

Unadjusted binary logistic regression models showed BMI SDS was the only model to significantly predict the MetS, with an OR of 3.62.

Table 16 *Unadjusted logistic regression for BMI SDS.*

	BMI SDS					
	OR	b (SE)	95% c.i. lower	95% c.i. upper	Nagelkerke R^2	p-value
ALAT	0.91	-0.09 (0.50)	0.34	2.43	0.001	0.854
SBP	5.21	1.65 (0.53)	1.86	14.59	0.173	**0.002**
DBP	2.63	0.97 (0.42)	1.15	6.02	0.079	**0.023**
MetS	3.62	1.29 (0.44)	1.53	8.60	0.133	**0.004**

Abbreviations: BMI, Body Mass Index; ALAT, Alanine Aminotransferase; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; MetS, Metabolic syndrome.

Table 17 *Unadjusted logistic regression for WC SDS.*

	WC SDS					
	OR	b (SE)	95% c.i. lower	95% c.i. upper	Nagelkerke R^2	p-value
ALAT	0.63	-0.47 (0.49)	0.24	1.64	0.010	0.341
SBP	2.92	1.07 (0.45)	1.21	7.08	0.093	**0.018**
DBP	2.33	0.85 (0.40)	1.07	5.09	0.069	**0.033**
MetS	1.92	0.65 (0.38)	0.92	4.02	0.044	0.083

Abbreviations: WC, Waist circumference; ALAT, Alanine Aminotransferase; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; MetS, Metabolic syndrome.

Table 18 *Unadjusted logistic regression for WHtR SDS.*

	WHtR SDS					
	OR	b (SE)	95% c.i. lower	95% c.i. upper	Nagelkerke R^2	p-value
ALAT	0.61	-0.49 (0.65)	0.17	2.21	0.010	0.455
SBP	5.47	1.70 (0.61)	1.66	18.03	0.126	**0.005**
DBP	3.00	1.10 (0.58)	0.96	9.30	0.055	0.058
MetS	2.39	0.87 (0.54)	0.83	6.88	0.038	0.107

Abbreviations: WHtR, Waist-to-Height-Ratio; ALAT, Alanine Aminotransferase; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; MetS, Metabolic syndrome.

Table 19 *Unadjusted logistic regression for WSHR SDS.*

WSHR SDS						
	OR	b (SE)	95% c.i. lower	95% c.i. upper	Nagelkerke R^2	p-value
ALAT	1.57	0.45 (0.71)	0.39	6.29	0.007	0.526
SBP	5.48	1.70 (0.61)	1.66	18.11	0.127	**0.005**
DBP	3.46	1.24 (0.63)	1.02	11.77	0.064	**0.047**
MetS	2.11	0.75 (0.55)	0.72	6.18	0.028	0.174

Abbreviations: WSHR, Waist-to-sitting height-Ratio; ALAT, Alanine Aminotransferase; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; MetS, Metabolic syndrome.

Binary logistic regression adjusted for age and gender also showed that BMI SDS was the only model significantly related to the MetS (p=0.03), with an OR of 2.96. BMI SDS, WHtR SDS and WSHR SDS were significantly associated with SBP, while WC SDS had a p-value of 0.054. WC SDS was the only model significantly associated with DBP (p=0.031).

Table 20 *Logistic regression for BMI SDS, adjusted for age and gender.*

BMI SDS						
	OR	b (SE)	95% c.i. lower	95% c.i. upper	Nagelkerke R^2	p-value
ALAT	0.54	-0.62 (0.74)	0.13	2.30	0.357	0.405
SBP	3.37	1.22 (0.55)	1.15	9.86	0.24	**0.026**
DBP	2.13	0.76 (0.49)	0.82	5.56	0.139	0.123
MetS	2.96	1.08 (0.05)	1.11	7.86	0.193	**0.030**

Abbreviations: BMI, Body Mass Index; ALAT, Alanine Aminotransferase; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; MetS, Metabolic syndrome.

Table 21 *Logistic regression for WC SDS, adjusted for age and gender.*

WC SDS						
	OR	b (SE)	95% c.i. lower	95% c.i. upper	Nagelkerke R^2	p-value
ALAT	0.73	-0.32 (0.87)	0.13	4.02	0.349	0.716
SBP	2.89	1.06 (0.55)	0.98	8.50	0.222	**0.054**
DBP	4.07	1.40 (0.65)	1.14	14.57	0.178	**0.031**
MetS	2.15	0.77 (0.55)	0.73	6.33	0.155	0.166

Abbreviations: WC, Waist circumference; ALAT, Alanine Aminotransferase; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; MetS, Metabolic syndrome.

Table 22 *Logistic regression for WHtR SDS, adjusted for age and gender.*

WHtR SDS						
	OR	b (SE)	95% c.i. lower	95% c.i. upper	Nagelkerke R^2	p-value
ALAT	0.56	-0.59 (0.96)	0.08	3.66	0.353	0.541
SBP	4.38	1.48 (0.67)	1.18	16.28	0.236	**0.027**
DBP	3.02	1.11 (0.70)	0.77	11.78	0.142	0.112
MetS	1.99	0.69 (0.64)	0.56	7.00	0.144	0.286

Abbreviations: WHtR, Waist-to-Height-Ratio; ALAT, Alanine Aminotransferase; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; MetS, Metabolic syndrome.

Table 23 *Logistic regression for WSHR SDS, adjusted for age and gender.*

WSHR SDS						
	OR	b (SE)	95% c.i. lower	95% c.i. upper	Nagelkerke R^2	p-value
ALAT	1.01	0.01 (0.98)	0.15	6.81	0.347	0.993
SBP	4.04	1.40 (0.64)	1.15	14.17	0.235	**0.029**
DBP	2.75	1.01 (0.68)	0.73	10.37	0.138	0.136
MetS	1.44	0.36 (0.61)	0.43	4.76	0.133	0.555

Abbreviations: WSHR, Waist-to-sitting height-Ratio; ALAT, Alanine Aminotransferase; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; MetS, Metabolic syndrome.

3.5 Akaike Information Criteria

Akaike information criteria used to compare the models selected for predicting the MetS showed by Akaike weights that BMI SDS has the highest probability of being the best model (69.5%). The differences in AIC between BMI SDS and the other models show that WC SDS was somewhat less likely to provide a similar level of empirical support of the model, and the WHtR SDS and WSHR SDS were considerably less likely to provide a similar level of empirical support of the model.

Table 24 *Model fit for predicting the metabolic syndrome.*

Model	AIC	Δ	Relative likelihood	Akaike weight
BMI SDS	122.12	0	1	0.695
WC SDS	125.2	3.08	0.214	0.149
WHtR SDS	126.12	4.00	0.135	0.094
WSHR SDS	126.94	4.82	0.090	0.062

Abbreviations: WC, waist circumference; BMI, Body Mass Index; WHtR, Waist-to-height-Ratio; WSHR, Waist-to-sitting height-Ratio; AIC, Akaike's information criterion.

For the prediction of SBP, the differences in AIC values were below two, which tells us all measurements were plausible to have a substantial level of empirical support of the model.

Table 25 *Model fit for predicting elevated systolic blood pressure.*

Model	AIC	Δ	Relative likelihood	Akaike weight
BMI SDS	106.22	0	1	0.317
WHtR SDS	106.54	0.32	0.852	0.270
WSHR SDS	106.62	0.40	0.819	0.260
WC SDS	107.69	1.47	0.480	0.152

Abbreviations: WC, waist circumference; BMI, Body Mass Index; WHtR, Waist-to-height-Ratio; WSHR, Waist-to-sitting height-Ratio; AIC, Akaike's information criterion.

For the prediction of DBP, WC SDS had the highest probability of being the best model (60.4%), and the other anthropometric measurements were somewhat less likely to provide a similar level of empirical support.

Table 26 *Model fit for predicting elevated diastolic blood pressure.*

Model	AIC	Δ	Relative likelihood	Akaike weight
WC SDS	117.01	0	1	0.604
WHtR SDS	119.89	2.88	0.237	0.143
BMI SDS	120.08	3.07	0.215	0.130
WSHR SDS	120.19	3.18	0.204	0.123

Abbreviations: WC, waist circumference; BMI, Body Mass Index; WHtR, Waist-to-height-Ratio; WSHR, Waist-to-sitting height-Ratio; AIC, Akaike's information criterion.

4 Discussion

4.1 Discussion of the results

The first aim of this thesis was to determine the prevalence of the MetS among obese children and adolescents at the Obesity outpatient clinic at Haukeland University Hospital.

The second aim was to determine whether the SDS for the anthropometrical measurements WC, WHtR, and WSHR predict cardiometabolic risk factors (insulin resistance, altered low density lipoprotein cholesterol, total cholesterol, triglycerides, high density lipoprotein cholesterol, and liver test (ALAT, gGT) or the MetS as defined by Cook et al. (50)) better than BMI SDS in overweight and obese children and adolescents at the Obesity outpatient clinic at Haukeland University Hospital.

First I will discuss the results regarding the prevalence of the MetS, and then the different ways of assessing associations between anthropometric measurements and cardiometabolic risk factors. Further I will consider methodological strengths and limitations of this study, followed by the conclusions and implications for further research.

4.1.1 Prevalence

The prevalence of the MetS in this group of obese children and adolescents was 39.6 %.

It seems there is little similarity among other Western reports: Cook et al. (50) found a prevalence of the MetS of 28.7% in adolescents with a BMI $\geq 95^{th}$ percentile in the United States. A Spanish study (79), using the same definition on children and adolescents with an IOTF BMI >30 kg/m^2 reported a prevalence of the MetS of 29.9%, and a Finnish study (80) on 17-year olds with an IOTF BMI >30 kg/m^2 found the prevalence of the MetS based on ATP III criteria to be 36.7 % and 30.3% for boys and girls, respectively.

An article from the 'Oslo Adiposity Intervention Study' (81) investigated the prevalence of the MetS in Norwegian children and adolescents compared with immigrants, all with an IOTF BMI>30 kg/m^2, also using the Cook's definition. They found the prevalence to be 30.0% in those with a Norwegian origin, and 50.0% for those with Middle Eastern and South Asian Origin.

Another study conducted by laFortuna et al. (82) on adolescents with a BMI $\geq 97^{th}$ percentile found a prevalence of the MetS of 23.3% among Italian adolescents and 40.4% among German adolescents, using the criteria proposed by the International Diabetes Federation

(IDF) (83). A Danish study (84) on adolescents with an IOTF BMI > 30 kg/m^2 also applied the IDF criteria and found a prevalence of 14.0%.

The varying results in the studies substantiate a perception that there is little consensus on the prevalence of the MetS among Western countries. It is likely that the use of different criteria for defining the MetS, as well as different inclusion criteria will lead to different prevalences, as the prevalence of the MetS has been proposed to depend strongly on the parameters chosen and their respective cut-off points (85), and as the risk of cardiometabolic alterations increase with an increasing BMI (86). However, there can also be other causes of variation, for instance methodological differences.

The majority of the studies used for comparison have a lower prevalence than the one presented in this thesis. It is likely that this is due to the fact that several of the studies include children and adolescents with a lower BMI than ours, as the inclusion criteria for the Obesity outpatient clinic is having an IOTF BMI above 35 kg/m^2. Also, for the report from the US, data from the NHANES survey in 1988-1994 was used, and it is likely that the prevalence in this age-group would be higher today as secular trends suggest an increase in obesity and DMT2 over the last years (50).

Of the presented studies, the Spanish is the only one to include children younger than 12 years of age. As the presence of the MetS is highly correlated with age, different age-ranges in the studies make comparison somewhat difficult. Less is known of the prevalence of the MetS in younger children. It is also a drawback that the Danish study only included 51 participants.

Another reason why our results are difficult to compare with other studies is the lack of assessment of ethnicity. It is probable that a quite large proportion of our study sample has an ethnicity other than Norwegian, as the 'Oslo Adiposity Intervention Study' which has a similar mission as the Obesity outpatient clinic in Bergen reported only 40.4% of their treated patients to be Norwegian. And as the MetS seems to be more frequent in immigrants than Norwegians (81) this can also explain the high prevalence in our study.

While the prevalence of hypertension, altered lipid concentrations, and increased WC SDS are all quite high, the results of this thesis present a relatively low prevalence of hyperglycemia, measured by fasting glucose. This has been reported in other studies as well (79, 82), and hyperglycemia seems to be a less common component of the MetS in children compared with adults. This is strange as the insulin resistance is thought to be a significant contributor to the

development of the metabolic phenotype (54). However, a possible explanation can be that the insulin resistance has not manifested yet as the participants are rather young, or due to the fact that fasting insulin and glucose poorly describes the insulin-resistant state in children, compared with an oral glucose tolerance test which is considered the gold standard, although it has limitations for screening large-scale populations (87).

4.1.2 Predictive value of anthropometric measurements

Although some associations were significant in the correlation and unadjusted linear regression models, none were significant after adjusting for age and gender. Further, logistic regression showed the MetS was significantly related to BMI SDS, SBP was significantly related to all anthropometric measurements, and DBP was significantly related to BMI SDS, WC SDS and WSHR SDS when unadjusted, but only with WC SDS when adjusted for age and gender. BMI SDS was the best prediction model for the MetS and SBP, and WC SDS was the best for DBP, as they had the highest Akaike weights.

It is of great importance to take into consideration that even though some of the correlations were statistically significant, they do not substantiate any causality, meaning that these results are not able to report any cause-and-effect relationship and we are therefore not able to imply whether an increased BMI SDS or WSHR SDS will cause altered transaminase-levels or cardiovascular risk.

In the unadjusted linear regression models, the associations that are statistically significant all have a low r^2 that vary between 0.05-0.10. This tells us none of the associations are particularly tight, and that a rather small proportion of the variance in the biomarkers is explained by the anthropometric models.

The adjusted linear regression models showed no significant relation between the biomarkers and the anthropometric measurements. It has previously been described that anthropometric measurements are not associated with fasting plasma glucose (88, 89), however, the respective studies showed associations with insulin and HOMA-IR, which is different from the presented results. Other studies are further in disagreement with the result of this thesis: Androutsos et al. found several cardiovascular risk factors to be associated with BMI, WC and WHtR (90). BMI and WHtR has also been reported to detect cardiometabolic disturbances in the Bogalusa Heart Study (91), and, in Australian children, Denney-Wilson et al. found associations between BMI and WHtR and insulin levels (92). Also in German

children anthropometrics are considered to be valuable for cardiovascular risk assessment (93).

A drawback for using the presented studies as comparison is that all have investigated the associations in children with a broad range of BMI, whilst our study sample only include obese children. However, Bluher et al. (94) also found several cardiovascular risk factors (HDL, HOMA-IR, ALAT, and gGT) to be significantly correlated with BMI, WC, and WHtR in a group of overweight children, which contradict our results.

The fact that this study group represents a marginal segment of the weight range is likely to be the reason why both correlation and regression analyses shows no association between WC and the cardiometabolic risk factors. This finding is particularly surprising, as other researchers have concluded that there is substantial evidence that WC is significantly associated with obesity-related morbidity, based on similar biomarkers as the ones presented in this thesis, and that WC should be used to identify children at risk (95). As a small variance in weight will make correlations hard to assess, it is plausible to believe that stronger associations would be present for several measurements if the study sample included children of all weight categories. This is further supported by Morandi et al. who also investigated associations between anthropometrical measurements and metabolic impairments in obese children, and concluded that anthropometrical measurements should not be used as a screening tool in the clinical setting to assess metabolic risk, as the predictive value is not satisfactory (96).

The logistic regression analyses show that an increase of one standard deviation in BMI SDS gives 3.62 higher odds of having the MetS. However, the Nagelkerke squared r was 0.13, and again this underpins the fact that the MetS is accounted for by anthropometric measurements in a small degree. Also, the precise odds ratio is not of great importance as the confidence intervals are rather wide. The Akaike table nevertheless shows there was a 69.5% probability that BMI SDS was the best predictor for the MetS among the selected models. The fact that the other anthropometric models were less likely to provide a similar level of empirical support of the model is in accordance with the results from the logistic regression models, as BMI SDS was the only measurement significantly associated with the MetS. However, a low Akaike weight does not imply the model has no support in the data, only that the other models have more support.

For the SBP, the Nagelkerke squared r is ranging from 0.22-0.24 which implies that a greater degree of variation in blood pressure can be explained by the variation in anthropometric measurements. This is supported by other researchers who have found that anthropometric measurements are associated with and can predict SBP (90, 94, 97, 98). Also, for the prediction of SBP, the Akaike weights are more similar, ranging between 15-32%. BMI SDS was the best prediction model, and WC SDS the worst, but there was little difference between all. This is also in accordance with the results from the logistic regression models, as all anthropometric measurements were significantly associated with SBP except for WC SDS, which was borderline significant (p=0.054).

Regarding DBP, WC SDS was more clearly a better predictor with an Akaike weight of 60.4%. The AIC difference substantiates the other models are somewhat less likely to provide a similar level of support of the model. Again, the results from the Akaike weight are congruent with the result from the logistic regression as WC SDS was the only measurement significantly associated with the DBP. The findings on DBP are in accordance with what other researchers have found (90, 94, 97).

Because WC previously has been shown to be a good predictor, other researchers have considered the question of whether it would be beneficial to combine BMI and WC. This is supported by Katzmanzyk et al. (98), and by Janssen et al. (97), and has been recommended in the clinical setting, as a high WC gives a higher health risk than a low WC across the same BMI category in adults (99). On the other hand, as the investigated anthropometric measurements in this thesis are so highly correlated with each other, as shown in Table 3, the effect of multicollinearity is reason to not pair the variables in statistical analyses for adjustment. Also, as the measurements based on WC SDS seem to contribute to such a small extent in this thesis, there is little reason to recommend WC as a complimentary measurement to BMI for predicting cardiometabolic risk. This account only for this group of obese children and adolescents, of course, as other ranges of BMI may provide different results.

4.2 Methodological strengths and limitations

Due to the retrospective collection method and the fact that the aim of this thesis not was ready when the assessment of data was conducted, the following methodological limitations were not predicted.

Pubertal stage has not been assessed or been accounted for in the medical records. As anthropometrics are influenced by pubertal stage in terms of that body composition changes dramatically during puberty, both level of body fatness and fat distribution may be stronger related to pubertal stage, rather than age. Therefore, the lack of this variable is a major setback.

Although the patients are told to do the blood sampling in the fasting state, there is no control of whether they actually do so. As a blood sample of triglycerides will be dramatically higher if not taken in the fasting state, this may lead to a higher prevalence of the MetS than what is the actual case. This can also give misleading results regarding correlations and regression models, if the patients assumed to have increased insulin-, glucose-, or triglyceride levels are actually within the normal range, but have altered values because they have eaten before blood sampling.

Another factor very likely to affect both body composition and biomarkers is ethnicity, which neither was assessed in a sufficient number of patients to be able to use for the analyses. As shown previously, ethnicity may affect cardiometabolic alterations investigated in this thesis, and can be a reason why the prevalence for the MetS is high.

Nine of the participants were weighed with clothes on, and in retrospect we were not able to adjust for this because the collection method did not assess how much clothes they wore or how much weight should be subtracted.

Moreover, blood samples of C-reactive protein were not assessed in enough patients to use the variable for statistics. It would be informative to collect these data, as acute phase proteins such as CRP reflect an inflammatory state which is thought to affect the development of the MetS (100).

A positive feature regarding the assessment is that the documentation in the medical records at the Obesity outpatient clinic now is systematized in a better fashion as a result of this, which will make future research based on pre-collected data easier.

The age range in this group can be considered a strength, as it is one of few studies that has included children below the age of ten years. On the other hand, including the youngest patients makes it hard to implement the IDF criteria for the MetS, which leads to some difficulties in comparing the prevalence of the MetS with other studies.

Another strength of this study is that it is one of few to investigate the predictive value of anthropometrical measurements in obese children and adolescents.

Furthermore, there are some general drawbacks with anthropometric measurements affecting precision and accuracy, such as a non-standardized methodology and measurement discrepancies between methods (101). Despite the fact that the clinic uses guidelines for assessment, other studies may use other guidelines and direct comparisons are perhaps not based on the exact same measurement. Also, some interpersonal variation can be expected for measurements carried out at the clinic.

As all anthropometric measurements have been converted to SDS, blood pressure measurements are adjusted for height, age and gender, and the MetS is defined using cutoffs based on percentiles in order to make comparison across age possible, these variables are already adjusted, and adjusting again in the regression models can be considered an "over-adjustment". The biomarkers on the other hand, are not adjusted, which makes a second adjustment necessary. It is also plausible that a second adjustment is necessary to correct for associations with age and gender which are not accounted for by the SDS.

4.3 Conclusions

4.3.1 Prevalence

We hypothesized that the prevalence of the MetS would be similar to other European countries. Based on the presented literature, a prevalence of the MetS close to 40% in our sample is relatively high compared with what others have found, although one must take in to consideration that comparison is difficult without standardized international criteria.

The high prevalence nevertheless underlines the importance of screening for cardiometabolic risk factors and providing good treatment for this group of patients with severe obesity.

Moreover, the disputed literature on prevalence in different countries underlines the need for consensus on an international definition of the MetS in children, which also has been proposed by Ford et al. (52).

4.3.2 Predictive value of anthropometric measurements

We hypothesized that anthropometric measures can be a valuable predictor for the cardiometabolic risk factors.

Anthropometric measurements are probably not the main factor affecting the presence of the cardiovascular risk factors in this group of obese children and adolescents, except for the prediction of SBP, which is associated with several anthropometric measurements, and probably best explained by BMI SDS.

One can hypothesize that because all of our participants are obese, other factors, such as a genetic predisposition, or other underlying causes, constitute who develops the MetS and who does not, and that there is a distinction between normal and overweight children and adolescents and those who are obese for the predictive value of anthropometric measurements. This thesis argues that for obese children, anthropometrical measurements have a rather low predictive value.

Nevertheless, it is possible that the tendencies in the unadjusted analyses can be explained by differences in age and gender, and that the adjusted results therefore would become clearer with a greater dataset.

The results showed that BMI SDS is the best predictor among the models selected as it had the lowest AIC, and it remains a valuable predictor for SBP.

4.4 Further research

For determining the prevalence of the MetS in obese children and adolescents further studies including assessment of ethnicity are needed.

Although we did not find the WSHR SDS to improve the prediction of cardiometabolic disturbances beyond BMI SDS, there may still be other indexes including sitting height which can have a better predictive value. For instance it would be very interesting to investigate the weight-to-sitting height-ratio, or weight/(sitting height)^2 as they would be more similar to the BMI.

It would also be interesting to look for the predictive value of the anthropometric measurements in a sample of participants with a broader weight range, including normal weight children and adolescents, as it seems rather few of the articles used for comparison are based on a study sample with the inclusion criteria of an IOTF BMI >35 kg/m^2. This thesis does not uncover whether the WSHR has a predictive value of metabolic changes in a sample with a wider weight range.

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6 Appendices

6.1 Appendix I: Data Protection Official

6.2 Appendix II: Informed consent

6.3 Appendix III: Blood pressure tables

6.1 Appendix I: Data Protection Official

HELSE BERGEN
Haukeland universitetssjukehus

Personvernombudet

Petur Benedikt Juliusson
Haukeland universitetssjukehus
Barneklinikken
petur.benedikt.juliusson@helse-bergen.no

Deres ref:	Vår ref:	Saksbehandler	BERGEN,
	2014/21567	Øystein Svindland, tlf. 55975558	06.11.2014

Kvalitetssikring: *«Beyond BMI»* - tilråding

Viser til innsendt melding om behandling av personopplysninger / helseopplysninger. Det følgende er en formell tilråding fra personvernombudet. Forutsetningene nedenfor må være oppfylt før innsamlingen av opplysningene / databehandlingen kan begynne.

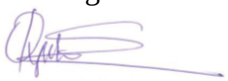
Prosjektet utgår fra Medisinsk avdeling og vil også bli benyttet i en mastergradsoppgave. Personvernombudet har vurdert det til at den planlagte databehandlingen faller inn under helsepersonelloven § 26: *Den som yter helsehjelp, kan gi opplysninger til virksomhetens ledelse når dette er nødvendig for å kunne gi helsehjelp, eller for internkontroll og kvalitetssikring av tjenesten. Opplysningene skal så langt det er mulig, gis uten individualiserende kjennetegn.*

Personvernombudet tilrår at kvalitetsprosjektet gjennomføres under forutsetning av følgende:

1. Behandling av helse- og personopplysningene skjer i samsvar med og innenfor det formål som er oppgitt i meldingen.
2. Tilgangen til registeret skjer i overensstemmelse med taushetspliktbestemmelsene. Evt. prosjektmedarbeidere som ikke er ansatt i Helse Bergen HF må underskrive en såkalt ikke-ansatt-avtale (se mal i forskningsrutinene) samt underskrive taushetsplikterklæring før de kan få tilgang til personopplysninger / helseopplysninger.
3. Personidentifiserende data lagres avidentifisert utelukkende på helseforetakets Kvalitetsserver. For å få tildelt plass på Kvalitetsserveren må saksnummer på denne godkjenningen (under Vår ref) fylles ut i søknadsskjemaet og selve tilrådingsbrevet må også legges ved.
Søknadsskjema finnes på:
Helse Bergen Innsiden –Personvernombudet for Helse Bergen
Annen elektronisk lagringsform forutsetter gjennomføring av en risikovurdering som må godkjennes av personvernombudet.
4. Kryssliste som kobler avidentifiserte data med personopplysninger lagres enten elektronisk på tildelt område på Kvalitetsserveren eller nedlåst på prosjektleders kontor.
5. Data slettes eller anonymiseres (ved at krysslisten slettes) 31.05.2020. Når formålet med registeret er oppfylt sendes melding om bekreftet sletting til personvernombudet

6. Dersom det senere blir aktuelt å forske på det innsamlede materialet, må det søkes om godkjenning fra REK før forskningen starter.
7. Dersom formålet eller databehandlingen endres må personvernombudet informeres om dette.

Vennlig hilsen



Øystein Svindland
Personvernombud

Kopi til:
Lars Birger Nesje

6.2 Appendix II: Informed consent

Forespørsel om samtykke til forskning innen: ”Til normal vekt” – Behandlingsopplegg for sykelig overvekt, Barneklinikken, Haukeland Universitetssykehus

Bakgrunn og hensikt

Forskning på helseopplysninger relatert til pasienters diagnose, behandling og prognose er avgjørende for å sikre befolkningen en høy kvalitet på helsetjenestetilbudet. Ved Helse Bergen HF/Haukeland universitetssykehus arbeider vi kontinuerlig med å oppnå ny kunnskap om barneovervekt. For å kunne utføre denne forskningen, er vi avhengig av pasientenes samtykke.

Samtykkets omfang og dine rettigheter

Ved å signere samtykkeerklæringen aksepterer du at opplysninger og eventuelt prøvemateriale kan benyttes til forskning innen barneovervekt. I tillegg kan du bli spurt om å besvare spørreskjemaer og delta på oppfølgingstiltak for å samle inn ytterligere opplysninger. Vi vil også innhente relevante opplysninger om deg fra andre offentlige helseregistre ved behov.

Eventuelle prøver og informasjonen som registreres om deg, vil bli behandlet konfidensielt og bli brukt til forskning på barneovervekt. Alle opplysningene vil bli behandlet uten navn og fødselsnummer eller andre direkte gjenkjennende opplysninger. En kode knytter deg til dine opplysninger og prøver gjennom en navneliste. Det vil ikke være mulig å identifisere deg i forskningsresultatene når disse publiseres.

Du kan til enhver tid få innsyn i hvilke opplysninger som er registrert om deg. Du har videre rett til å få korrigert eventuelle feil i de opplysningene vi har registrert. Dersom du trekker tilbake samtykket, kan du kreve å få slettet innsamlede prøver og opplysninger, med mindre opplysningene allerede er inngått i analyser eller brukt i vitenskapelige publikasjoner.

Vi gjør oppmerksom på at opplysninger kan utleveres til samarbeidende forskere ved foretakene i Helse Vest og Universitetet i Bergen. Enhver utlevering av opplysninger til samarbeidende forskere vil bli lagt frem for Regional Etisk Komité (REK).

Ytterligere informasjon

Har du spørsmål tilknyttet forskningsvirksomheten, kontakt Pétur B. Júlíusson, Barneklinikken, Haukeland Universitetssykehus, petur.juliusson@med.uib.no, telefon 55975200.

Skjema for samtykke til forskning (Skannes til DIPS)

- Voksne over 16 år

Forskningsområde	Prosjektnummer
”Til normal vekt” – Behandlingsopplegg for sykelig overvekt, Barneklinikken, Haukeland Universitetssykehus	177286

Prosjektleders navn	Klinikk/avdeling
Pétur B. Júlíusson	Barneklinikken, Haukeland Universitetssykehus

All forskningsdeltakelse er frivillig. Dersom du ønsker å delta, undertegner du denne samtykkeerklæringen. Om du nå sier ja til å delta, kan du senere når som helst og uten å oppgi noen grunn, trekke tilbake ditt samtykke uten at det påvirker din øvrige behandling. Dersom du senere ønsker å trekke deg eller har spørsmål om forskningen, kan du kontakte prosjektleder.

Jeg er villig til at prøver og opplysninger om meg brukes i forskning på barneovervekt

Navn med blokkbokstaver	Fødselsnummer (11 siffer)

Dato	Underskrift

Fylles ut av representant for forskningsområdet

Jeg bekrefter å ha gitt informasjon om forskningsområdet:

Dato	Underskrift	Brukerkode (4-tegnskode)
Eventuelle kommentarer:		

Skjema for samtykke til forskning (Skannes til DIPS)
- Ungdom mellom 12 og 16 år

Forskningsområde	Prosjektnummer
”Til normal vekt” – Behandlingsopplegg for sykelig overvekt, Barneklinikken, Haukeland Universitetssykehus	177286

Prosjektleders navn	Klinikk/avdeling
Pétur B. Júlíusson	Barneklinikken, Haukeland Universitetssykehus

All forskningsdeltakelse er frivillig. Dersom du ønsker å delta, undertegner du denne samtykkeerklæringen. Om du nå sier ja til å delta, kan du senere når som helst og uten å oppgi noen grunn, trekke tilbake ditt samtykke uten at det påvirker din øvrige behandling. Dersom du senere ønsker å trekke deg eller har spørsmål om forskningen, kan du kontakte prosjektleder.

Jeg er villig til at prøver og opplysninger om meg brukes i forskning innen på barneovervekt

Navn med blokkbokstaver	Fødselsnummer (11 siffer)

Dato	Underskrift

Helse Bergen ønsker at foresatte skal være informert og samtykke til deltakelse i forskning for ungdom over 12 år, med mindre pasienten av forhold som bør respekteres ønsker noe annet.

Dato	Underskrift	Rolle (mor/far/verge)

Fylles ut av representant for forskningsområdet		
Jeg bekrefter å ha gitt informasjon om forskningsområdet:		
Dato	Underskrift	Brukerkode (4-tegnskode)
Eventuelle kommentarer:		

Skjema for samtykke til forskning (Skannes til DIPS)
- Barn under 12 år

Forskningsområde	Prosjektnummer
”Til normal vekt” – Behandlingsopplegg for sykelig overvekt, Barneklinikken, Haukeland Universitetssykehus	177286

Prosjektleders navn	Klinikk/avdeling
Pétur B. Júlíusson	Barneklinikken, Haukeland Universitetssykehus

All forskningsdeltakelse er frivillig. Dersom du på vegne av barnet sier ja til å delta, undertegner du denne samtykkeerklæringen. Om du nå sier ja til å delta, kan du senere når som helst og uten å oppgi noen grunn, trekke tilbake ditt samtykke uten at det påvirker barnets øvrige behandling. Dersom du eller barnet senere ønsker å trekke tilbake samtykket eller har spørsmål om forskningen, kan du kontakte prosjektleder.

Jeg sier på vegne av barnet ja til at prøver og opplysninger om barnet brukes i forskning innen på barneovervekt

Barnets navn med blokkbokstaver	Barnets fødselsnummer (11 siffer)

Dato	Foresattes underskrift	Rolle (mor/far/verge)

Fylles ut av representant for forskningsområdet

Jeg bekrefter å ha gitt informasjon om forskningsområdet:

Dato	Underskrift	Brukerkode (4-tegnskode)
Eventuelle kommentarer:		

6.3 Appendix III: Blood pressure tables

TABLE 3. BP Levels for Boys by Age and Height Percentile

Age, y	BP Percentile	SBP, mm Hg							DBP, mm Hg						
		Percentile of Height							Percentile of Height						
		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
1	50th	80	81	83	85	87	88	89	34	35	36	37	38	39	39
	90th	94	95	97	99	100	102	103	49	50	51	52	53	53	54
	95th	98	99	101	103	104	106	106	54	54	55	56	57	58	58
	99th	105	106	108	110	112	113	114	61	62	63	64	65	66	66
2	50th	84	85	87	88	90	92	92	39	40	41	42	43	44	44
	90th	97	99	100	102	104	105	106	54	55	56	57	58	58	59
	95th	101	102	104	106	108	109	110	59	59	60	61	62	63	63
	99th	109	110	111	113	115	117	117	66	67	68	69	70	71	71
3	50th	86	87	89	91	93	94	95	44	44	45	46	47	48	48
	90th	100	101	103	105	107	108	109	59	59	60	61	62	63	63
	95th	104	105	107	109	110	112	113	63	63	64	65	66	67	67
	99th	111	112	114	116	118	119	120	71	71	72	73	74	75	75
4	50th	88	89	91	93	95	96	97	47	48	49	50	51	51	52
	90th	102	103	105	107	109	110	111	62	63	64	65	66	66	67
	95th	106	107	109	111	112	114	115	66	67	68	69	70	71	71
	99th	113	114	116	118	120	121	122	74	75	76	77	78	78	79
5	50th	90	91	93	95	96	98	98	50	51	52	53	54	55	55
	90th	104	105	106	108	110	111	112	65	66	67	68	69	69	70
	95th	108	109	110	112	114	115	116	69	70	71	72	73	74	74
	99th	115	116	118	120	121	123	123	77	78	79	80	81	81	82
6	50th	91	92	94	96	98	99	100	53	53	54	55	56	57	57
	90th	105	106	108	110	111	113	113	68	68	69	70	71	72	72
	95th	109	110	112	114	115	117	117	72	72	73	74	75	76	76
	99th	116	117	119	121	123	124	125	80	80	81	82	83	84	84
7	50th	92	94	95	97	99	100	101	55	55	56	57	58	59	59
	90th	106	107	109	111	113	114	115	70	70	71	72	73	74	74
	95th	110	111	113	115	117	118	119	74	74	75	76	77	78	78
	99th	117	118	120	122	124	125	126	82	82	83	84	85	86	86
8	50th	94	95	97	99	100	102	102	56	57	58	59	60	60	61
	90th	107	109	110	112	114	115	116	71	72	72	73	74	75	76
	95th	111	112	114	116	118	119	120	75	76	77	78	79	79	80
	99th	119	120	122	123	125	127	127	83	84	85	86	87	87	88
9	50th	95	96	98	100	102	103	104	57	58	59	60	61	61	62
	90th	109	110	112	114	115	117	118	72	73	74	75	76	76	77
	95th	113	114	116	118	119	121	121	76	77	78	79	80	81	81
	99th	120	121	123	125	127	128	129	84	85	86	87	88	88	89
10	50th	97	98	100	102	103	105	106	58	59	60	61	61	62	63
	90th	111	112	114	115	117	119	119	73	73	74	75	76	77	78
	95th	115	116	117	119	121	122	123	77	78	79	80	81	81	82
	99th	122	123	125	127	128	130	130	85	86	86	88	88	89	90
11	50th	99	100	102	104	105	107	107	59	59	60	61	62	63	63
	90th	113	114	115	117	119	120	121	74	74	75	76	77	78	78
	95th	117	118	119	121	123	124	125	78	78	79	80	81	82	82
	99th	124	125	127	129	130	132	132	86	86	87	88	89	90	90
12	50th	101	102	104	106	108	109	110	59	60	61	62	63	63	64
	90th	115	116	118	120	121	123	123	74	75	75	76	77	78	79
	95th	119	120	122	123	125	127	127	78	79	80	81	82	82	83
	99th	126	127	129	131	133	134	135	86	87	88	89	90	90	91
13	50th	104	105	106	108	110	111	112	60	60	61	62	63	64	64
	90th	117	118	120	122	124	125	126	75	75	76	77	78	79	79
	95th	121	122	124	126	128	129	130	79	79	80	81	82	83	83
	99th	128	130	131	133	135	136	137	87	87	88	89	90	91	91
14	50th	106	107	109	111	113	114	115	60	61	62	63	64	65	65
	90th	120	121	123	125	126	128	128	75	76	77	78	79	79	80
	95th	124	125	127	128	130	132	132	80	80	81	82	83	84	84
	99th	131	132	134	136	138	139	140	87	88	89	90	91	92	92
15	50th	109	110	112	113	115	117	117	61	62	63	64	65	66	66
	90th	122	124	125	127	129	130	131	76	77	78	79	80	80	81
	95th	126	127	129	131	133	134	135	81	81	82	83	84	85	85
	99th	134	135	136	138	140	142	142	88	89	90	91	92	93	93
16	50th	111	112	114	116	118	119	120	63	63	64	65	66	67	67
	90th	125	126	128	130	131	133	134	78	78	79	80	81	82	82
	95th	129	130	132	134	135	137	137	82	83	83	84	85	86	87
	99th	136	137	139	141	143	144	145	90	90	91	92	93	94	94
17	50th	114	115	116	118	120	121	122	65	66	66	67	68	69	70
	90th	127	128	130	132	134	135	136	80	80	81	82	83	84	84
	95th	131	132	134	136	138	139	140	84	85	86	87	87	88	89
	99th	139	140	141	143	145	146	147	92	93	93	94	95	96	97

The 90th percentile is 1.28 SD, the 95th percentile is 1.645 SD, and the 99th percentile is 2.326 SD over the mean.
For research purposes, the SDs in Table B1 allow one to compute BP Z scores and percentiles for boys with height percentiles given in Table 3 (ie, the 5th, 10th, 25th, 50th, 75th, 90th, and 95th percentiles). These height percentiles must be converted to height Z scores given by: 5% = −1.645; 10% = −1.28; 25% = −0.68; 50% = 0; 75% = 0.68; 90% = 1.28; and 95% = 1.645, and then computed according to the methodology in steps 2 through 4 described in Appendix B. For children with height percentiles other than these, follow steps 1 through 4 as described in Appendix B.

TABLE 4. BP Levels for Girls by Age and Height Percentile

Age, y	BP Percentile	SBP, mm Hg							DBP, mm Hg						
		Percentile of Height							Percentile of Height						
		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
1	50th	83	84	85	86	88	89	90	38	39	39	40	41	41	42
	90th	97	97	98	100	101	102	103	52	53	53	54	55	55	56
	95th	100	101	102	104	105	106	107	56	57	57	58	59	59	60
	99th	108	108	109	111	112	113	114	64	64	65	65	66	67	67
2	50th	85	85	87	88	89	91	91	43	44	44	45	46	46	47
	90th	98	99	100	101	103	104	105	57	58	58	59	60	61	61
	95th	102	103	104	105	107	108	109	61	62	62	63	64	65	65
	99th	109	110	111	112	114	115	116	69	69	70	70	71	72	72
3	50th	86	87	88	89	91	92	93	47	48	48	49	50	50	51
	90th	100	100	102	103	104	106	106	61	62	62	63	64	64	65
	95th	104	104	105	107	108	109	110	65	66	66	67	68	68	69
	99th	111	111	113	114	115	116	117	73	73	74	74	75	76	76
4	50th	88	88	90	91	92	94	94	50	50	51	52	52	53	54
	90th	101	102	103	104	106	107	108	64	64	65	66	67	67	68
	95th	105	106	107	108	110	111	112	68	68	69	70	71	71	72
	99th	112	113	114	115	117	118	119	76	76	76	77	78	79	79
5	50th	89	90	91	93	94	95	96	52	53	53	54	55	55	56
	90th	103	103	105	106	107	109	109	66	67	67	68	69	69	70
	95th	107	107	108	110	111	112	113	70	71	71	72	73	73	74
	99th	114	114	116	117	118	120	120	78	78	79	79	80	81	81
6	50th	91	92	93	94	96	97	98	54	54	55	56	56	57	58
	90th	104	105	106	108	109	110	111	68	68	69	70	70	71	72
	95th	108	109	110	111	113	114	115	72	72	73	74	74	75	76
	99th	115	116	117	119	120	121	122	80	80	80	81	82	83	83
7	50th	93	93	95	96	97	99	99	55	56	56	57	58	58	59
	90th	106	107	108	109	111	112	113	69	70	70	71	72	72	73
	95th	110	111	112	113	115	116	116	73	74	74	75	76	76	77
	99th	117	118	119	120	122	123	124	81	81	82	82	83	84	84
8	50th	95	95	96	98	99	100	101	57	57	57	58	59	60	60
	90th	108	109	110	111	113	114	114	71	71	71	72	73	74	74
	95th	112	112	114	115	116	118	118	75	75	75	76	77	78	78
	99th	119	120	121	122	123	125	125	82	82	83	83	84	85	86
9	50th	96	97	98	100	101	102	103	58	58	58	59	60	61	61
	90th	110	110	112	113	114	116	116	72	72	72	73	74	75	75
	95th	114	114	115	117	118	119	120	76	76	76	77	78	79	79
	99th	121	121	123	124	125	127	127	83	83	84	84	85	86	87
10	50th	98	99	100	102	103	104	105	59	59	59	60	61	62	62
	90th	112	112	114	115	116	118	118	73	73	73	74	75	76	76
	95th	116	116	117	119	120	121	122	77	77	77	78	79	80	80
	99th	123	123	125	126	127	129	129	84	84	85	86	86	87	88
11	50th	100	101	102	103	105	106	107	60	60	60	61	62	63	63
	90th	114	114	116	117	118	119	120	74	74	74	75	76	77	77
	95th	118	118	119	121	122	123	124	78	78	78	79	80	81	81
	99th	125	125	126	128	129	130	131	85	85	86	87	87	88	89
12	50th	102	103	104	105	107	108	109	61	61	61	62	63	64	64
	90th	116	116	117	119	120	121	122	75	75	75	76	77	78	78
	95th	119	120	121	123	124	125	126	79	79	79	80	81	82	82
	99th	127	127	128	130	131	132	133	86	86	87	88	88	89	90
13	50th	104	105	106	107	109	110	110	62	62	62	63	64	65	65
	90th	117	118	119	121	122	123	124	76	76	76	77	78	79	79
	95th	121	122	123	124	126	127	128	80	80	80	81	82	83	83
	99th	128	129	130	132	133	134	135	87	87	88	89	89	90	91
14	50th	106	106	107	109	110	111	112	63	63	63	64	65	66	66
	90th	119	120	121	122	124	125	125	77	77	77	78	79	80	80
	95th	123	123	125	126	127	129	129	81	81	81	82	83	84	84
	99th	130	131	132	133	135	136	136	88	88	89	90	90	91	92
15	50th	107	108	109	110	111	113	113	64	64	64	65	66	67	67
	90th	120	121	122	123	125	126	127	78	78	78	79	80	81	81
	95th	124	125	126	127	129	130	131	82	82	82	83	84	85	85
	99th	131	132	133	134	136	137	138	89	89	90	91	91	92	93
16	50th	108	108	110	111	112	114	114	64	64	65	66	66	67	68
	90th	121	122	123	124	126	127	128	78	78	79	80	81	81	82
	95th	125	126	127	128	130	131	132	82	82	83	84	85	85	86
	99th	132	133	134	135	137	138	139	90	90	90	91	92	93	93
17	50th	108	109	110	111	113	114	115	64	65	65	66	67	67	68
	90th	122	122	123	125	126	127	128	78	79	79	80	81	81	82
	95th	125	126	127	129	130	131	132	82	83	83	84	85	85	86
	99th	133	133	134	136	137	138	139	90	90	91	91	92	93	93

* The 90th percentile is 1.28 SD, the 95th percentile is 1.645 SD, and the 99th percentile is 2.326 SD over the mean.
For research purposes, the SDs in Table B1 allow one to compute BP Z scores and percentiles for girls with height percentiles given in Table 4 (ie, the 5th, 10th, 25th, 50th, 75th, 90th, and 95th percentiles). These height percentiles must be converted to height Z scores given by: 5% = −1.645; 10% = −1.28; 25% = −0.68; 50% = 0; 75% = 0.68; 90% = 1.28; and 95% = 1.645 and then computed according to the methodology in steps 2 through 4 described in Appendix B. For children with height percentiles other than these, follow steps 1 through 4 as described in Appendix B.