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Graz, am 29.03.2023

Eidesstattliche Erklärung

Ich erkläre ehrenwörtlich, dass ich die vorliegende Arbeit selbstständig und ohne fremde Hilfe verfasst habe, andere als die angegebenen Quellen nicht verwendet habe und die den benutzten Quellen wörtlich oder inhaltlich entnommenen Stellen als solche kenntlich gemacht habe.

Graz, am 29.03.2023 *Natalie Bernadette Obernhumer eh.*

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Abbreviations

ACR	Albumin-Creatinine ratio
ADH	adiuretin (peptide hormone)
ADMA	Asymmetric Dimethylarginine
AIP	Atherogenic index of plasma
ANP	atrial natriuretic peptide
ATP	adenosine triphosphate
BMI	body-mass-index
BP	blood pressure
CHD	coronary heart disease
CI	confidence interval
CVD	cardiovascular diseases
DBP	diastolic blood pressure
FG	fasting glucose
GLP1	Glucagon-like peptide 1
GLUT-4	glucose transporter type 4
HDL	high-density lipoprotein
HDL-C	high-density lipoprotein cholesterol
HIV	human immunodeficiency virus
HOMA-IR	Homeostasis Model Assessment Index
HT	hypertensive
IGT	Impaired glucose tolerance
IDF	International Diabetes Federation
IR	insulin resistance
LDL	high low-density lipoprotein
MAP	mean arterial pressure
MetS	Metabolic Syndrome
NAFLD	non-alcoholic fatty liver disease
NCDs	non-communicable diseases
NCEP	National Cholesterol Education Program
NEFA	non-esterified fatty acid
NO	nitric oxides
O/O	overweight/obesity

OGTT	oral glucose tolerance test
OSAS	obstructive sleep apnea syndrome
PHT	pre-hypertensive
PWV	pulse wave velocity
RAAS	renin-angiotensin-aldosterone system
SD	standard deviation
SGLT2	Sodium-glucose Cotransporter-2
SBP	systolic blood pressure
SPSS	statistical package for social sciences
SSA	Sub-Saharan Africa
T2DM	diabetes mellitus type 2
TC	total cholesterol
TG	Triglycerides
VLDL	very-low-density lipoprotein
WC	waist circumference
WH-ratio	waist to hip ratio
WHO	World Health Organization
WHT	waist to height ratio
WSU	Walter Sisulu University

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Zusammenfassung

Hintergrund: Herz-Kreislauf- und Stoffwechselkrankheiten stellen weltweit eine große Herausforderung dar. Die Hauptursache für Morbidität und Mortalität in den entwickelten aber auch in den unterentwickelten Ländern sind inzwischen die so genannten nicht übertragbaren Krankheiten, betroffen hiervon neben Erwachsenen ebenso Kinder und Jugendliche. Das Metabolische Syndrom wird als Bündel von Risikofaktoren bezeichnet. Bei Personen mit Metabolischem Syndrom zeigt sich ein erhöhtes Risiko zur Entwicklung eines Typ-2-Diabetes mellitus und für kardiovaskuläre Ereignisse aufgrund vaskulärer Dysfunktion. Studien, die sich auf geschlechtsspezifische Unterschiede konzentrieren sind unterrepräsentiert, doch ist das Wissen um die geschlechtsspezifische Prävalenz notwendig, um individualisierte Präventionsmaßnahmen und Behandlungsoptionen zu entwickeln.

Zielsetzung: Wir untersuchten die Prävalenz von kardiovaskulären und metabolischen Risikofaktoren sowie das Vorhandensein eines Metabolischen Syndroms bei 13-16-jährigen Jugendlichen in Mthatha, Südafrika.

Methoden: An dieser Studie nahmen 244 Jugendliche teil. Es wurden anthropometrische Messungen vorgenommen und der Blutdruck gemessen, Blutproben entnommen und Nüchternglukose, Triglyzeride und High-Density-Lipoprotein-Cholesterin gemessen. Nach dem Ausschluss von zehn Probanden wurde die statistische Analyse für 234 Probanden durchgeführt. Für 98 Probanden (75 weibliche und 23 männliche) lagen alle nötigen Daten zur Risikobestimmung vor.

Ergebnisse: Ein erhöhter Blutdruck mit Werten über der 90. Perzentile wurde bei 37,8 % (37/98) der Studienteilnehmer*innen festgestellt. Zentrale Adipositas, gemessen am Taillenumfang >90. Perzentile, konnte bei 6,1 % (6/98) der Studienteilnehmer*innen festgestellt werden. 7,1 % (7/98) der Studienteilnehmer*innen erfüllten die Kriterien für ein Metabolisches Syndrom mit drei Risikofaktoren. Nach Geschlecht aufgeschlüsselt bedeutet dies, dass bei 8,0 % (6/75) der weiblichen Teilnehmerinnen und bei 4,3 % (1/23) der männlichen Teilnehmer ein Metabolisches Syndrom diagnostiziert werden kann. Es konnte keine statistisch signifikante Häufung des Auftretens eines Metabolischen Syndroms in Bezug auf das Geschlecht festgestellt werden.

Schlussfolgerung: Die Prävalenz von Übergewicht/Adipositas und erhöhtem Blutdruck ist bei südafrikanischen Jugendlichen hoch. Zu den damit verbundenen höheren Risiken für

diese Jugendlichen gehören das erhöhte Risiko von Herz-Kreislauf-Erkrankungen sowie ein höheres Risiko für die mögliche Entwicklung von Diabetes mellitus Typ 2 und des Metabolischen Syndroms. Die Forschung in diesem Bereich sollte fortgesetzt werden, zudem sind Längsschnittstudien erforderlich, um die Ätiologie der kardiometabolischen Risikofaktoren für diese Bevölkerungsgruppe zu untersuchen. Dies ist notwendig, um geeignete Präventionsmaßnahmen zu entwickeln und die Bevölkerung vor künftigen Komplikationen des Metabolischen Syndroms, wie Herz-Kreislauf-Erkrankungen zu schützen.

Abstract

Background: Cardiovascular and metabolic diseases represent a major challenge worldwide. The main cause of morbidity and mortality in developed but also underdeveloped countries are now so-called non-communicable diseases, affecting adults as well as children and adolescents. The metabolic syndrome is referred to as bundling of risk factors, those categorized with metabolic syndrome have an increased developing risk for type 2 diabetes mellitus and for cardiovascular events due to vascular dysfunction. Studies focusing on sex differences are underrepresented, but knowledge of sex-specific prevalence is necessary to develop individualized preventive interventions and treatment options.

Aims: We studied the prevalence of both cardiovascular and metabolic risk factors, as well as metabolic syndrome, among 13-16-year-old adolescents in Mthatha, South Africa.

Methods: This study included 244 adolescents. Anthropometric measurements were taken and blood pressure was obtained. Blood samples were obtained and fasting glucose, triglycerides, and high-density lipoprotein cholesterol were also measured. After the exclusion of ten subjects, statistical analysis was conducted for 234 subjects. For 98 subjects (75 female and 23 male) all necessary data for risk determination were available

Results: Elevated blood pressure with values above the 90th percentile was seen in 37.8% (37/98) of the study participants. Central obesity, as measured by waist circumference >90th percentile was evident in 6.1% (6/98) of the study participants. 7.1% (7/98) of the study population fulfilled the criteria for metabolic syndrome with three risk factors. By sex, this means that 8.0% (6/75) of the female participants and 4.3% (1/23) of the male participants can be diagnosed with metabolic syndrome. No statistically significant frequency of occurrence of a metabolic syndrome in relation to sex could be found.

Conclusions: There is a high prevalence of overweight/obesity and increased blood pressure in South African Adolescents. The associated higher risks for these adolescents include the risk of cardiovascular disease in addition to the possible development of type 2 diabetes mellitus and metabolic syndrome. Continued research is required and longitudinal studies are needed to investigate the etiology of cardiometabolic risk factors for this population. This is necessary for the development of appropriate preventive measures and to protect the population from future complications of metabolic syndrome such as cardiovascular diseases.

Angaben von bereits erfolgen Veröffentlichungen

Diese Diplomarbeit war Teil einer Studie, welche sich mit der Erkennung von kardiovaskulären Risiken bei Jugendlichen und jungen Erwachsenen in Mthatha, Südafrika befasste. Die Studie wurde im März 2021, in der Open-Access-Medizinzeitschrift BMJ Open publiziert:

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1 Introduction

Cardiovascular and metabolic diseases represent a major challenge worldwide. However, the fact that both groups of diseases are interrelated and occur together, thus also leading to mutual deterioration and progression, presents clinicians with a particular challenge. At this point, it is worth noting that cardiovascular diseases are particularly prevalent in countries with low- and middle-income. For example, in South Africa, there is growing evidence of obesity, hypertension, and other cardiovascular risk factors, among children of African descent (1-3).

1.1 Overweight and obesity

Nowadays, around 33% of the world's population can be classified as overweight or obese, and prevalence has doubled in the last 40 years. In general, prevalence is higher among women and older people, and regardless of socioeconomic status, geographic location, and ethnicity, obesity, and overweight rates have increased in both sexes and all age groups (4, 5).

1.1.1 Definition

Medically, the terms overweight and obesity are similar but not the same. When body weight exceeds a certain level (normal weight), it is called overweight. Obesity describes an excessive accumulation of body fat tissue and it leads to disease when important organ functions are negatively affected (6).

Various methods are available to determine body composition and to classify the nourishing condition into underweight, normal weight, pre-obesity/ overweight and obesity. A good method to measure the nutritional status of a person is to use the body mass index (BMI), but to estimate the health risk, other methods are necessary, such as measuring body fat distribution. There are several methods for measuring body fat distribution, such as skin-fold thickness measurement, bioelectrical impedance, or waist circumference (WC) measurement (6-8).

1.1.1.1 Adult criteria

The body-mass-index (BMI) is a popular marker for measuring the nutritional status of a person and is applied easily since body weight and height are the only two parameters needed to calculate the BMI. This marker is calculated by dividing a person's body weight in kilograms by the square of their height in meters (9, 10). The BMI categories were determined by the World Health Organization (WHO) as shown in **Table 1**.

Table 1 BMI Categories according to WHO (4)

Categories	**BMI (kg/m2)**
Underweight	< 18.5
Normal weight	18.5-24.9
Pre-obesity	25.0-29.9
Class I obesity	30.0-34.9
Class II obesity	35.0-39.9
Class III obesity	≥40.0

Central obesity is a major determinant of risk in the development of cardiovascular diseases (CVD) and other metabolic diseases. Waist circumference (WC) is a good tool for measuring central obesity (8). It is important to use ethnic-specific WC values as seen in **Table 2** below:

Table 2 Ethic-specific WC adapted from *Alberti et.al. (The Lancet 2005)* (8)

Ethnic group	**Waist circumference (WC)**	
	Men	**Women**
USA	≥102 cm	≥88 cm
Ethnic South and Central Americans	≥90 cm	≥80 cm
Europids	≥94 cm	≥80 cm
Sub-Saharan Africans	≥94 cm	≥80 cm
Chinese and South-Asians	≥90 cm	≥80 cm
Japanese	≥85 cm	≥90 cm
Eastern Mediterranean and the Middle East (Arab)	≥94 cm	≥80 cm

1.1.1.2 Children and Adolescent criteria

There are age- and sex-specific parameters integrated into the calculation of the BMI for children and adolescents, resulting in reference values presented by guidelines of the *"Deutsche Adipositas Gesellschaft*" as percentiles (11), as represented in **Table 3** below.

Table 3 BMI Categories for children and adolescents obtained from AGA (9)

Classification	**BMI percentile**
Underweight	< 10th
Normal weight	10th – 90th
Overweight	> 90th – 97th
Obesity	> 97th – 99,5th
Massive obesity	> 99,5th

The WHO defines overweight in children and adolescents using the BMI-Z score, a standard deviation (SD) score that uses the standard deviation and median to compare the BMI distribution pattern with a reference population (10). In this context, overweight is defined as *"BMI for age greater than one standard deviation above the reference median"* (10) for an age group of 5-19-year-olds, and *"BMI for age greater than two standard deviations above the median"* (10) represents obesity.

For a more detailed evaluation of the risk of developing CVD in children and adolescents, it is recommended that WC be added to the usual measures of body fat content, such as BMI and skinfold thickness. To be able to determine age- and sex-specific risk criteria in children and adolescents, similar to BMI, WC data from specific reference populations are used (12, 13).

1.1.2 Physiology and Pathophysiology

A balanced energy level is necessary to maintain various functions of the body such as thermoregulation, organ functions and various biochemical processes. The energy stored in the body increases when there is an imbalance between the supply and consumption of energy. The resulting energy balance is a positive one and leads to weight gain over a prolonged period (14, 15).

The reason why this weight gain does not occur immediately is due to the body's effort to resist both a decrease and an increase via various homeostatic mechanisms. For example, small movements in everyday life account for about 2/3 of the energy consumption as compensation. Energy consumption also varies at the cellular level. So-called "uncoupling proteins" in the mitochondrial membrane transport protons through the membrane as part of oxidative adenosine triphosphate (ATP) phosphorylation, but do not use them for molecule production and thus lead to energy consumption in the form of heat (16).

Contrary to what was previously thought, obesity cannot be explained solely by an imbalance in the supply and expenditure of energy (nutrition), but rather concerning multifactorial factors such as environmental, psychological, and behavioral factors, as well as genetic and metabolic factors that lead to overweight and obesity (17).

The body defends itself against weight loss in further consequence with neuro-hormonal factors, therefore a decrease is just as prevented as a renewed increase and/or a relapse established. About certain metabolic adaptations of the body react to with weight loss, with specific adaptations around this to counteract. These adaptations range from the reduction of the metabolic rate (energy consumption decreases) and the increase of hunger-promoting hormones such as ghrelin, to the decrease or disturbance of the effect of satiety hormones such as insulin and leptin (15).

To avoid weight loss, for example, the peripheral concentration of thyroid hormones drops during weight loss, which means that the basal metabolic rate can also be reduced by up to 40% during weight loss. Conversely, an obese person who loses weight must consume fewer calories than a person who has always had this weight. In addition, the counter-regulation of gastrointestinal hormones leads to an increasing feeling of hunger, which

means that by down-regulating the basal metabolic rate, the initial weight can even be exceeded by a renewed increase in caloric intake compared to the beginning of the diet (16).

A central role in developing systemic inflammatory reactions plays adipose tissue, this happens via the secretion of cytokines by the macrophages in the adipose tissue, but the function of an operating endocrine organ is also an influential factor in the progression of the associated symptoms. The fat distribution type is nevertheless a decisive factor here, for example, the conversion of androgens into estrogens takes place in the central adipose tissue via the aromatase, which subsequently explains gynecomastia in male patients (18).

1.2 Hyperglycemia

1.2.1 Definition Insulin resistance

The complete absence of the effect of insulin or a strong reduction of it is called insulin resistance (IR) (19).

1.2.2 Assessment

Chronic hyperglycemia and insufficient insulin effect can lead to various diseases. One group of these diseases, which can be classified according to pathogenesis, is called diabetes mellitus (DM). Several forms of diabetes are known, including autoimmune diabetes type I, type 2 diabetes mellitus (T2DM), gestational diabetes, and other rarer forms. The most common form is T2DM (19).

Prediabetes and DM can be diagnosed by detecting elevated plasma glucose levels and other variables as seen in **Table 4** . Cutoff values vary depending on the test performed. It is possible to measure fasting glucose (FG), glycated hemoglobin A1C (HbA1c), an indicator of plasma glucose levels over the past few months, or the levels after an oral glucose tolerance test (OGTT). The definitions of prediabetes and diabetes for children and adolescents are identical to those for adults (19).

Table 4 Criteria for the Screening and Diagnosis of Prediabetes and Diabetes obtained from *the American Diabetes Association (Diabetes Care 2021)* (19)

Classification	Prediabetes	Diabetes
HbA1c	5.7–6.4% (39–47 mmol/mol)	≥6.5% (48 mmol/mol)
Fasting plasma Glucose	100–125 mg/dL (5.6–6.9 mmol/L)	≥126 mg/dL (7.0 mmol/L)
2-hour plasma glucose during 75g OGTT	140–199 mg/dL (7.8–11.0 mmol/L)	≥200 mg/dL (11.1 mmol/L)
Random plasma glucose	-	≥200 mg/dL (11.1 mmol/L)

1.2.3 Physiology and Pathophysiology

The uptake of glucose in certain tissues (except glucose-independent erythrocytes and the brain) is dependent on insulin. This is an in the pancreas produced peptide hormone, formed as precursor cells, called proinsulin, by the β-cells of the islets of Langerhans. An insulin molecule and a C-peptide are subsequently released in equal proportions. To determine whether the body is still producing enough insulin, this C-peptide can be measured in the blood (9). The hormone glucagon, the so-called antagonist of insulin, is produced in the alpha cells of the pancreas and promotes the formation and release of stored sugar reserves in the liver, for example, thus leading to elevated blood sugar levels. In the state of insulin resistance, the blood sugar can only be insufficiently absorbed by the cells, this state leads to an elevated production of insulin in the pancreas to compensate for the increased blood sugar level (9). Glucose is transported into the respective cells via certain transporters, for example, glucose transporter type 4 (GLUT-4) for adipose tissue and skeletal muscle cells, to lower the glucose level in the blood. As an antagonist of the hormone glucagon, Insulin decreases gluconeogenesis in the liver and it stimulates the formation and storage of glycogen in the muscles and liver, which can later be cleaved back into glucose in the catabolic state of metabolism. When glucose stores are full, the excess glucose is converted into fatty acids, and in this process, insulin stimulates uptake into fat cells to form fat deposits (9, 20).

1.3 Dyslipidemia

1.3.1 Definition

This is a disorder of lipid metabolism in which there is a change in the composition of blood fats (apolipoproteins or lipids). A change or shift in these leads, for example, to a lipoprotein disorder (e.g. low high-density lipoprotein [HDL] or high low-density lipoprotein [LDL]) with normal triglyceride and cholesterol levels, an increase in triglycerides (hypertriglyceridemia), plasma cholesterol (hypercholesterolemia) or an increase in cholesterol and triglycerides (combined hyperlipidemia) (21).

1.3.2 Physiology and Pathophysiology

Lipoproteins are complexes of proteins (apolipoproteins), cholesterol, triglycerides, and phospholipids. They are responsible for the transport of water-insoluble lipids in plasma and serve to transport hydrophobic lipids in the blood (9).

Lipoproteins present in serum are subdivided according to their density into chylomicrons, VLDL (very-low-density lipoprotein), LDL (low-density lipoprotein), and HDL (high-density lipoprotein). Triglycerides are deposited in the fatty tissue and represent the organism's largest energy store (21).

These are either taken up with food, the resulting chylomicrons or VLDL remnants are bound with the help of apoprotein E via receptors of the liver cells, absorbed and degraded there (transport as chylomicrons) or via endogenous synthesis (VLDL), here LDL and HDL cholesterol particles are formed. This means that after food intake and enzymatic cleavage (lipolysis), free fatty acids (energy suppliers) and glycerol (link to glucose metabolism, a substrate of gluconeogenesis) is formed. Fatty acid degradation occurs predominantly via β-oxidation to acetyl-CoA. Fatty acid biosynthesis also occurs starting from acetyl-CoA (9).

1.3.2.1 Primary dyslipidemias

This genetically caused form of dyslipidemia, for example at the LDL receptor, can occur either as homozygotes or heterozygotes (the most common form of congenital metabolic disorder). The homozygote variant can lead to cardiovascular events like myocardial infarction even in very young patients due to the extreme elevation in cholesterol and LDL cholesterol concentration and the resulting damage to the vessels. The heterozygote variant is one of the most common inborn errors of metabolism, the cholesterol levels and LDL cholesterol levels are not as elevated in this case as in the homozygote variant, yet they also lead to premature cardiovascular events. Other examples of primary dyslipidemias include combined hyperlipidemia and familial hypertriglyceridemia (9).

1.3.2.2 Secondary dyslipidemias

These dyslipidemias are so-called acquired or secondary lipid metabolism disorders that have developed due to another underlying disease. These underlying diseases are, for example, endocrinological, such as thyroid disorders or diabetes mellitus, and can also be triggered by liver pathologies, such as hepatitis and liver dysfunction caused by medication or alcohol. Kidney diseases such as nephrotic syndrome can also lead to this type of lipid metabolism disorder, as can systemic diseases such as lupus erythematosus. Diseases like HIV can lead to secondary lipometabolic disorders as well as storage diseases like Cushing's syndrome, obesity, etc. As with primary dyslipidemias, the consequences of these disorders are an increased risk of cardiovascular events, so it is not surprising that they can also be promoted by lifestyle (little exercise, poor diet, alcohol, medication, etc.) (9, 21).

1.4 Hypertension

1.4.1 Definition

Hypertension is defined as the increase in arterial pressure above a certain level (22, 23). According to WHO (22), it is "*a major cause of premature death worldwide, with upwards of 1 in 4 men and 1 in 5 women – over a billion people"* who are suffering from chronically raised blood pressure.

1.4.1.1 Adult Criteria

Hypertension in adults can be classified into different categories depending on the severity as shown in **Table 5**. (23). Blood pressure is measured by using a cuff and two values are used to indicate the blood pressure. The first value is also called the systolic value or systolic blood pressure (SBP) and is representative of the pressure in the blood vessels that occurs when the heart beats or contracts. The second value is called the diastolic value or diastolic blood pressure (DBP) and represents the pressure in the blood vessels when the heart is at rest (22).

According to WHO (22): *"Hypertension is diagnosed when, when measured on two different days, the systolic blood pressure value on both days is ≥140 mmHg and/or the diastolic blood pressure value on both days is ≥90 mmHg"*

Table 5 Blood pressure Classification obtained from *2018 ESC/ESH Guidelines for the management of arterial hypertension (European Heart Journal (2018)* (23)

Systolic (mmHg)	Diastolic (mmHg)	**Category**
<120	<80	Optimal
120–129	80–84	Normal
130–139	85–89	High normal
140–159	90–99	Grade 1 hypertension
160–179	100–109	Grade 2 hypertension
≥180	≥110	Grade 3 hypertension
≥140	<90	Isolated systolic hypertension (ISH)

1.4.1.2 Children and Adolescent criteria

Like BMI, blood pressure in children and adolescents will be expressed by percentiles that capture age, sex, and height and compare them to the reference population (24), the Classification of Hypertension in Children and Adolescents is displayed in **Table 6** below.

Table 6 Blood pressure Classification for Children and Adolescents obtained from *2016 European Society of Hypertension guidelines (Journal of Hypertension 2016)* (24)

Age 0-15 years SBP and/or DBP percentile	**Age 16 and older SBP and/or DBP values (mmHg)**	**Category**
<90th	<130/85	Normal
90th to <95th	130–139/85–89	High normal
≥95th	≥140/90	Hypertension
≥95th ≤99th+ 5 mmHg	140–159/90–99	Grade 1 hypertension
>99th + 5 mmHg	160–179/100–109	Grade 2 hypertension
SBP ≥95th and DBP <90th	≥140/<90	ISH

1.4.2 Physiology and Pathophysiology

Arterial blood pressure is physically affected by the volume of blood in the vascular system, the vascular resistance of the arteries (diameter), and cardiac output. To ensure a steady supply to all organs, the blood flow must be kept at a steady niveau (9, 24).

The regulation of this blood flow can happen in a short time, within seconds, this happens in the case via so-called baroreceptors (pressoreceptors) in the blood vessel wall. They are located in the layer between media and adventitia of vessels in arteries (A. carotis communis), sinus caroticus, and aortic arch and measure the so-called mean arterial pressure (MAP) (9).

The signals are further transmitted to medulla oblongata via nerves (N.vagus, N. glossopharyngeus) and then to Nucleus tractus solitarii in the brain stem, causing the so-called inhibition of the sympathetic nervous system, which causes relaxation of the vessels, a decrease of the frequency of the heart and of the stroke volume (9, 25).

The mean arterial pressure is calculated as follows:

$$MAP \approx (SBP+(2xDBP))/3$$

It is important to know here that this is lower in so-called arteries far from the heart than in vessels close to the heart. If there is a permanent change in this mean arterial pressure, the base pressure changes (9).

Medium-term and long-term regulation occur via the renin-angiotensin-aldosterone-system (RAAS). The regulation works through many mechanisms, one mechanism is for example the release of certain proteins such as aldosterone and their effect on the sodium balance via the retention of sodium and excretion of potassium. Excessive blood pressure results in decreased secretion of the peptide hormone adiuretin (ADH) by the pituitary gland and atrial natriuretic peptide (ANP, antagonist of aldosterone) by the atria, leading to increased diuresis and thus volume depletion (26).

However, it should be noted that certain factors can influence blood pressure. These are, for example, the so-called circadian rhythm (blood pressure peaks in the early morning and late afternoon and lows during nighttime sleep), the influence of sleeping and waking phases and orthostatic influencing factors (lying down, sitting, standing). Physical conditions such as pain, mental states of emergency, physical influence (lack of oxygen at altitude, noise), chemical influences such as carbon dioxide, carbon monoxide) to name but a few (9).

Hypertension can be classified according to the cause, the so-called primary hypertension (90% of cases) is not caused by a disease but by other causes such as higher age, smoking, excess weight, high salt consumption, lack of exercise and genetic factors (22, 23).

Secondary hypertension is due to a disease or other cause, this can include many things from taking certain medications to endocrine, renovascular and cardiovascular diseases (22).

1.5 Metabolic syndrome

1.5.1 History and Definitions

Historically, the first definition of metabolic syndrome (MetS), was formed in 1988 by American physician *Gerald Reaven* (27). He used the term *Syndrome X*, which described a discovered correlation in obese adults between enhanced blood glucose levels, insulin resistance, accelerated blood pressure, dyslipidemia, and an associated risk of atherosclerotic and cardiovascular disease (27). While he completely disregarded obesity, especially visceral obesity (ethnic-specific high waist circumference) as an essential component in his definition, it is now considered by many to be an exceedingly influential risk factor for the progression of MetS and, consequently, for the onset of CVD and T2DM (8).

At this point, the most common definition for MetS is, that it occurs when three of five different risk factors are combined, consisting of the following (**Figure 1**): central obesity, elevated fasting glucose blood levels, elevated blood pressure, and dyslipidemia (elevated triglycerides (TG), low HDL cholesterol) (28, 29).

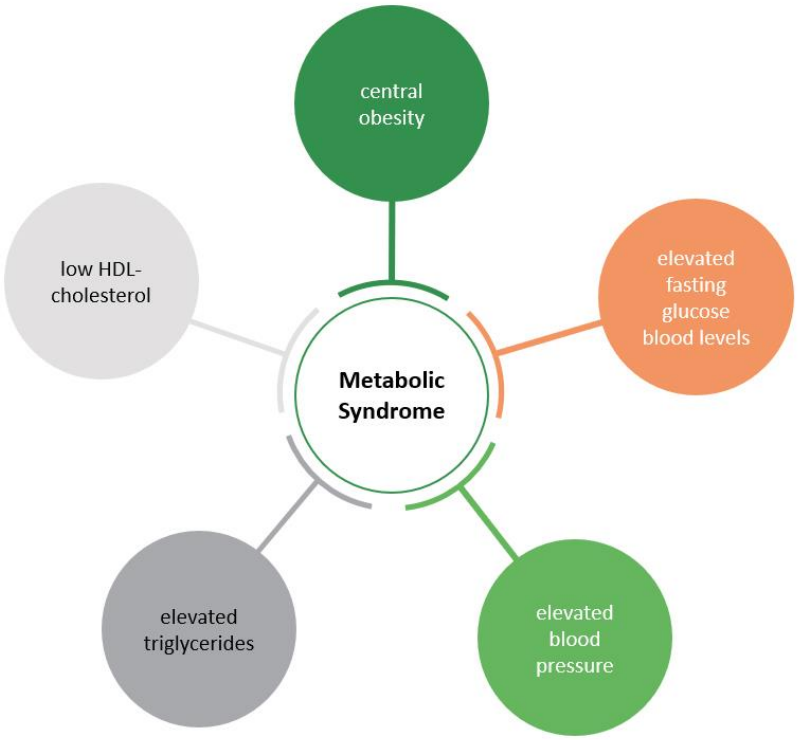

Figure 1 Risk factors for MetS. Adapted from the Criteria of clinical diagnosis from *R.H. Eckel et al. (The Lancet, 2010)* (29)

1.5.1.1 Adult criteria

An attempt was launched by certain significant scientific societies in the year 2009, to develop a standardized clinical tool for the diagnosis of the MetS, which includes the most important cut points of the risk factors displayed in **Figure 1.** This led to the development of the consensus definition for the clinical diagnosis of the MetS as listed below in **Table 7.**

Table 7 Adult criteria for clinical diagnosis of MetS adapted from *R.H. Eckel et.al.* (The Lancet 2010) (29)

Parameter	Control variable
Central obesity (elevated waist circumference)	Population- and Country specific variables
Hyperglycemia (or the drug treatment of it)	> 100 mg/dL (5,5 mmol/L)
Hypertension (or the drug treatment of it)	Systolic ≥130 and/or diastolic ≥85 mmHg
Dyslipidemia (or drug treatment for increased TG)	≥150 mg/dL (1·7mmol/L)
Dyslipidemia (or drug treatment for low HDL-cholesterol)	<40 mg/dL (1·0 mmol/L) in men <50 mg/dL (1·3 mmol/L) in women

1.5.1.2 Pediatric criteria

There has been no clear consensus on adult criteria for decades, although there have been attempts to reach a consensus, which have been shown in **Table 7** (28).

It is therefore unsurprising that the pediatric criteria are even more ambiguously defined. In a 2009 published literature review by *Ford et. al.,* they found 46 existing definitions for MetS in children and adolescents in 27 different articles (30), this was also described by Reisinger et al. as shown in **Table 8** (31).

Table 8 Different criteria for children and Adolescents obtained from *C. Reisinger et. al. (International Journal of Obesity 2021)* (31)

	Criteria for diagnosis	Central obesity	Fasting glucose	Hyper-tension	Dys-lipidemia (TG↑)	Dys-lipidemia (HDL↓)
IDF (32)	WC↑+2/4	*10–15 y* WC ≥ 90th percentile *>15 years of age* WC ≥94 cm (♂) WC≥ 80 cm (♀)	≥100 mg/dl OR diagnosis of T2D	Systolic BP ≥ 130 mmHg OR diastolic BP ≥ 85 mmHg OR Specific treatment	≥150 mg/dl OR Specific treatment	< 40 mg/dl (♂) <50 mg/dl (♀)
Cook et al. (33)	3/5	≥ 90th percentile	≥110 mg/dl	≥ 90th percentile	≥ 110 mg/dl	≤ 40 mg/dl
Ford et al. (34)	3/5	≥ 90th percentile	≥110 mg/dl additional analysis with ≥100 mg/dl	≥ 90th percentile	≥ 110 mg/dl	≤ 40 mg/dl
De Ferranti et al. (35)	3/5	≥ 75th percentile	≥110 mg/dl	≥ 90th percentile	≥ 100 mg/dl	≤ 50 mg/dl

1.5.2 Prevalence

A look at the several findings in the literature over the last few years shows, that MetS is found in a large number of adult people worldwide and is therefore more widespread than assumed. For example, there is just over one fourth of the population in the United States of America and well over a third of South African inhabitants affected by MetS (36).

Based on the application of different criteria, there are no worldwide or country-specific absolute figures on the prevalence of MetS in children and adolescents, but it is expected to be rather low. Nevertheless, the problem should by no means be underestimated, as the number of children with a minimum of one risk factor or metabolic pathology is increased (31, 37).

As described by *C.Reisinger et al*. in their literature review (31), depending on the definition applied, the following prevalence for MetS in children and adolescents resulted:

The prevalence for MetS in Europe, based on criteria of the International Diabetes Federation (IDF), shows a minimum of 0,4% and a maximum of 2,7% whereas the data based on modified criteria of the National Cholesterol Education Program (NCEP) by *Cook et al*. (33), *Ford et al.* (34) and *Ferranti et al*. (35) show a range between 1,4% and 3,5% (31).
In the United States, a higher prevalence is seen in both, IDF criteria with a range of 3,1-4,5%, and modified NCEP criteria with a prevalence of 10,1% (31).
In South Africa, the occurrence of MetS in children and adolescents differs greatly based on the criteria which have been used. For the IDF criteria, we have a prevalence of 1.9%, while for the modified criteria there is a range between 3.1% and 6.0% (31).

1.5.3 Pathogenesis of Metabolic Syndrome

Over the decades, different mechanisms for the development of the MetS have been researched. According to the current state of knowledge, a key role in this development is played by so-called central obesity (characterized by high waist circumference), which, through the release of certain chemokines via visceral fat cells, leads to macrophage infiltration and thus to cytokine release and the development of systemic inflammation. (38-40). Another characteristic is the increase in the release of free fatty acids and the impaired ability of adipocytes to produce, to prevent insulin resistance, adiponectin (41, 42).

The increase in oxidative stress as a result of the excessive release of free fatty acids and triglycerides, as well as their effect on mitochondrial function in peripheral tissues, in turn, leads to resistance to insulin-stimulated glucose uptake. This decreased ability of insulin leads to increased insulin release via the pancreas to a level at which insulin resistance surpasses the ability of the pancreas to secrete adequate amounts of insulin (38, 39). One consequence of this is the increase in glucose levels and the increased risk of developing T2DM, in addition, there is now an increased risk of cardiovascular disease with additional effects such as decreased HDL levels and increased blood pressure (38).

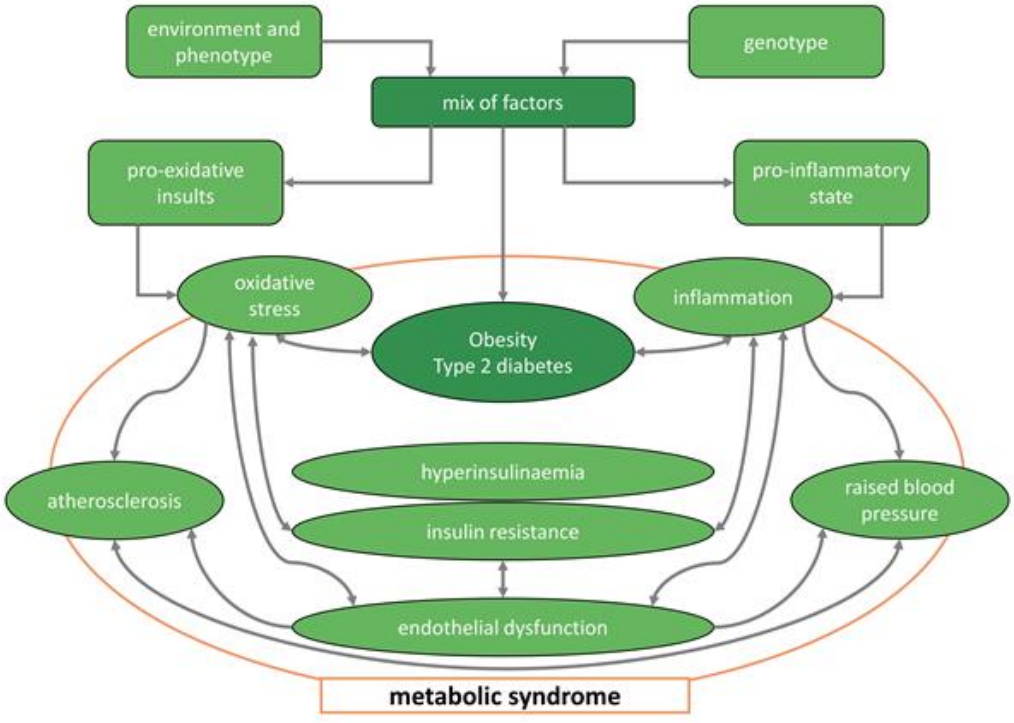

Figure 2 The Pathophysiology of MetS. Modified from *R.Kumari et al. (Diabetes&Metabolic Syndrome 2019)* (36)

1.5.4 Predisposing factors for metabolic syndrome

Numerous predisposing factors for MetS have been identified in studies over the years. Most prevalent, however, were genetic influences, as well as environmental factors with the greatest impact on the individual risk of developing MetS. (42).

1.5.4.1 Prenatal risk factors

Genetic influences that occur before or during pregnancy such as hormonal imbalances, negative influences such as stress, reduced physical activity, maternal weight and gestational diabetes. In addition, there is a higher individual risk for the development of MetS if one parent was already diagnosed with early coronary artery disease (42, 43).

1.5.4.2 Risk factors in childhood/adolescence

These include individual and social aspects of environmental influences.
Individual factors include birth weight, lifestyle risk factors like unhealthy eating habits, previous dieting experiences and recurrent obesity and hormonal and metabolic dysfunctions. Minimal levels of physical activeness are linked to an increased risk of developing MetS, so the level of activity is also playing an important role (43). Smoking is another risk factor. However, social factors must not be disregarded here under any circumstances; those who were exposed to passive smoking at a young age by caregivers, such as parents, have a higher probability of becoming smokers themselves later on (44).

In general, there is a range of different factors that can influence the progression to MetS. also poor sleeping habits and sleeping quality but also medications that influence the metabolism. This mechanism can usually be explained by the side effects of specific drugs, such as psychopharmaceuticals but the psychiatric disease itself can also be a risk factor that can lead to the development of MetS (43, 45).

1.5.5 Consequences and Comorbidities

The complications and consequences of untreated MetS are manifold. The individual effects of the predisposing risk factors add up in this symptom complex and therefore lead to an accumulation of complications. Some of them combine to form a vicious circle.

Central obesity, as the sole risk factor, already shows serious effects on metabolism. Among these are the negative effects on lipid metabolism with hyper-/dyslipidemia (LDL↑, HDL↓), effects on sugar metabolism via impaired glucose tolerance, and insulin resistance. Effects on blood pressure regulation via interference with the RAAS system via increases in renin-angiotensin-aldosterone, increases in sympathetic nerve activity, and sodium retention. Other effects of central obesity include liver dysfunction resulting in fatty liver (NAFLD) and hyperuricemia (6, 26).

Also, effects on coagulability and endothelial function which in combination with the systemic inflammation caused by the chemokine release and macrophage proliferation of visceral adipocytes, an increase of acute phase proteins and procoagulant states as macrovascular changes can lead to vascular dysfunction and stiffness of the arteries and cause one of the most important complications, namely atherosclerosis. A manifest T2DM intensifies the problem for the large vessels and additionally causes microangiopathies. (26, 40, 46) In addition, some patients with visceral obesity have restrictive ventilatory dysfunction due to compression caused by adipose tissue as other numerous effects by obesity that can cause respiratory impairment and are therefore at increased risk for the development of obstructive sleep apnea syndrome (OSAS), which then lead to poor sleeping quality and increased sympathetic nerve activity (47).

The consequences of MetS affect multiple organ systems such as the cardiovascular system with atherosclerosis, stroke, left ventricular hypertrophy and myocardial infarction, and other CDV and coronary heart disease (CHD). Effects of impaired metabolism on pancreas and liver (NFLD) to name a few consequences (40, 42, 46).

1.5.6 Sex differences

A 2006 publishes article by *Regitz-Zagrosek et al*. suggested, that there might be pathophysiological diversities in MetS that are sex-related, for example in puberty and adolescence girls show a higher insulin resistance than boys (48). In their study, published in 2020, *Calcaterra et al*. (49) mentioned, that pathologically elevated blood pressure was the only significant sex difference, which was higher in male participants (p=0.02).

In contrast, regarding the consequences, in a longitudinal cohort study, *Ramezankhani et al.* found that for the MetS group, there was a significantly enhanced risk for the development of CVD and CHD in female participants due to high blood pressure, than in male participants (50). So, there might be no significant difference between sex and developing MetS, but there seems an increased risk of developing CVD and CHD in women with diagnosed MetS.

1.5.7 Therapeutic possibilities

As, described in the 2019 published article by *Weihe et al*, the major determinant of risk in the treatment or prevention of MetS, is obesity in children and adolescents, as it has the strongest association with cardiometabolic comorbidities (51).

1.5.7.1 Conventional treatment options

The "gold-standard" and most effective way in the treatment of MetS is a versatile lifestyle change (52). One of these therapy options is for example to encourage the increase of physical activity, adjust dietary habits by taking advantage of a Mediterranean diet versus a typical Western diet, as well as behavioral therapy to sufficiently implement the new lifestyle habits, since the psychological aspect must not be disregarded under any circumstances (51, 53, 54).

1.5.7.2 Medical therapy options

In an article published in 2017, *Rask et al.* recommend substances that are targeted to the renin-angiotensin-aldosterone system, statins for dyslipidemia, metformin, inhibitors for sodium-glucose transporter 2 (SGLT2), Glucagon-like peptide-1 (GLP-1) agonists for impaired glucose tolerance (IGT) as first-line therapy in MetS patients for the treatment of

hypertension. As additional secondary prevention to optimize the risk of developing cardiovascular events, patients at high risk are advised to take antiplatelet agents (55).
It should be noted here that the only approved pharmacologic therapy for children, in this case, is metformin, which has effects on IGT. The medicinal product is licensed for children ten years of age and older, yet the first-line therapy in children is lifestyle modification (51, 54).

1.5.7.3 Surgical therapy options

For adult patients with aggravated obesity and those for whom conventional treatment methods are unsuccessful, surgical procedures such as gastric bypass or sleeve gastrectomy are an option. These surgical procedures show great success in weight loss, cardiovascular health with improvements in hypertension and dyslipidemia, and regaining quality of life (56). However, bariatric surgery in children is a treatment option for only a minority of patients with morbid (extreme) obesity and comorbidities when conservative treatments have failed (54).

1.6 Aims and Objectives

The main cause of morbidity and mortality in developed but also underdeveloped countries are now so-called non-communicable diseases (NCDs), affecting adults as well as children and adolescents (3, 54). Certain childhood diseases such as obesity are strongly associated with serious health complications that persist into adulthood, such as insulin resistance, non-alcoholic fatty liver disease and T2DM and hypertension, as well as their consequences such as CVD (1, 57). Therefore, an important factor in reducing cardiovascular risk is the early identification of risk factors in young patients. Cardiovascular disease is particularly disproportionate in low- and lower-income countries (1). In countries such as South Africa, slightly more than 40% of adults suffer from overweight/obesity (O/O), and an increase in obesity among children and adolescents has also been noted (1, 3).

Studies on the sex-specific assessment of cardiovascular risk factors in children and adolescents from low-income and low-socioeconomic-status areas are quite modest. In recent years, several studies have been conducted by researchers at Walter Sisulu University (WSU) in Mthatha to determine, among other things, the prevalence of cardiometabolic risk factors for this age group of children, these have been able to detect an increase in these risk factors, yet little attention has been paid to sex differences in the results (1, 58, 59).

The aim of this study on adolescents in secondary schools from Mthatha was to determine the prevalence of cardiometabolic risk factors and MetS. Measurement of anthropometric data was performed, as well as the collection of laboratory parameters to determine and assess a disturbance in fasting blood glucose levels and detect dyslipidemia and measurement of blood pressure. It was hypothesized that there would be a significant sex difference in terms of cardiovascular risk factors and, therefore, in the outcomes of who among the two groups had already developed a metabolic syndrome. Based on the existing literature, it was anticipated that sex differences in the distribution of cardiovascular risk factors will be seen.

2 Materials and Methods

2.1 Study design

This work was part of a study that focused on the detection of cardiovascular risk in adolescents and young adults in Sub-Saharan Africa. The study itself was of a cross-sectional cohort design. 244 pupils aged 13 to 16 years from low socioeconomic families in rural areas were recruited from four secondary schools in Mthatha, Eastern Cape Province, South Africa. Recruitment was a collaborative effort between Walter Sisulu University (WSU), teachers, and participants' parents or guardians.

2.2 Criteria of Inclusion and Exclusion

In an initial screening, exclusion criteria were used for filtering. These exclusion criteria included individuals with T2DM, renal, pulmonary, cardiovascular, or orthopedic diseases. Pregnant or lactating subjects were excluded, as were subjects with endocrine disorders, physical or mental limitations, patients taking antihypertensive medications, and endurance athletes.

Of the 800 eligible subjects, 552 did not provide written informed consent, and an additional four subjects were excluded from the age group because they were either too young or too old.

The sample was drawn from 244 healthy female and male adolescents of African descent, aged 13 to 16 years, who met the inclusion criteria.

2.3 Ethics

The study followed the principles of the Declaration of Helsinki (revised version, 2008) and South African regulations. The WSU ethics committee gave its approval (reference number: 014/2014). The study procedure and protocol, as well as the measurements, were explained and communicated in writing to the adolescents and their legal guardians. Written consent was obtained from the youth and their legal guardians. Anonymization of participant data was performed using codes prior to the start of data collection.

2.4 Data Collection and anthropometric measurements

Trained fieldworkers (medical students from the Medical University of Graz and physiology students from WSU) recorded demographic data such as age, sex, height, weight, and anthropometric measurements, which were then entered into data sheets. Measurements on female participants were taken by female fieldworkers, and measurements on male participants were taken by male fieldworkers.

A scale (Tanita Body Composition Scale) was used to measure the weight of the study participants. The scale automatically calculated body fat percentage and BMI. Age- and sex-specific percentile curves from the International Obesity Task Force (60) were used to classify BMI. The classification was as follows: Underweight: < 5th percentile, Normal weight: >5th < 85th percentile, Overweight: ≥ 85th < 95th percentile, and obesity: ≥ 95th percentile.Measurements were taken wearing light clothing and no shoes. During measurements, participants stood straight, had their feet together, and let their arms hang at the sides of their bodies. Body height was accurately recorded to the nearest 0.1 cm with a wall-mounted Harpenden stadiometer. Circumferences (e.g., the circumference of waist, etc.) were measured with an anthropometric tape measure.

2.5 Blood pressure measurements

As part of the briefing on the study procedure, all participants were asked not to take caffeine or other stimulants for 24 hours before the measurements and to avoid physical activity for 48 hours beforehand. For blood pressure measurements, appropriately sized cuffs were placed on participants' upper arms, and three measurements were taken in a quiet room, at two-minute intervals using an automatic oscillometric blood pressure monitor (HBP-1100; Omron Healthcare Co. Ltd.) after a five-minute rest period. In accordance with the blood pressure percentile guidelines for children (Centre for Disease Control and Prevention-National Health and Nutrition Examination Survey (61)), the average of three measurements was then extrapolated into percentiles for age, sex, and height. Hypertensive was described as SBP and/or DBP ≥ 95th percentile, pre-hypertensive SBP and DBP > 90th < 95th percentile or SBP/DBP ≥120/80 mm Hg and normotensive described as systolic BP (SBP) and diastolic BP (DBP) < 90th percentile (61).

2.6 Blood collection and biochemical analysis

After an overnight fasting period, a trained nurse drew the blood samples. Following centrifugation, plasma was collected, and fasting glucose (FG), triglycerides (TG), total cholesterol (TC), and high-density lipoprotein cholesterol (HDL-c) were then analyzed.

2.7 Definition of MetS

The classification of Cook et al. (33) was used to diagnose metabolic syndrome. As soon as three of the five parameters mentioned, WC (≥90th percentile), FG (≥110 mg/dl, 6.1 mmol/l), TGs (≥110 mg/dl, ≥1.24 mmol/l), HDL-C (≤40 mg/dl, ≤1.03 mmol/l), and BP (≥90th percentile), were above the reference value, one was referred to as having MetS.

2.8 Statistical analysis

For data analysis, the statistical package for social sciences (SPSS) Version 27.0 (IBM Corp. Armonk, NY, USA) was used. Descriptive statistics were calculated for sex, age, BMI, anthropometric data, blood pressure, and blood parameters and expressed as mean ± SD. Data were tested for normality using the Shapiro-Wilks test. Depending on the normality of the data, Student's t-test was used to show differences between groups. For categorical data, a chi-square test was performed and the significance level was set at $p < 0.05$.

3 Results

3.1 Baseline characteristics

After meeting the inclusion criteria for the study, 244 adolescents (188 females and 56 males) with an average age of 14.4 +/- 1 years (min./max.: 13-16 years), were recruited. From further analyses excluded were 10 children who were categorized as underweight (BMI <5th percentile).

In **Table 9** you can see the mean values listed including the standard deviation and the 95% confidence interval of the total cohort.

There were some sex differences that stood out more significantly with p=0.001.
In terms of anthropometric data, these were height in cm, for females the mean height in cm was 157.0 (95% CI[156-158.1]) for women and 164.4 (95% CI[161.9-166.9]) for males. The mean neck circumference in cm was 29.9 (95% CI[29.6-30.0]) for females and 164.4 (95% CI[161.9-166.9]) for males. Other examples are the mean waist-to-hip ratio of 0.78 (95% CI[0.77-0.79]) for females and 0.82 (95% CI[0.80-0.83]) for males, further examples of a significant difference include body fat % of 26.8% (95% CI[25.6-28.0]) for females and 14.4% (95% CI[12.3-16.6]) for males.

Among the hemodynamic parameters, the heart rate in beats per minute (bpm) was 87.2 bpm (95% CI[86.0 -88.3]) for females and 76.2 bpm (95% CI[72.9-79.5]) for males.

There were significant sex differences in blood levels for the total cholesterol value in mmol/L of 3.8 mmol/L (95% CI[3.7 -4.0]) for females and 3.4 mmol/L (95% CI[3.2-3.6]) for males and fasting glucose levels in mmol/L of 4.73 mmol/L (95% CI[4.7-4.8]) for females and 5.0 mmol/L (95% CI[4.8-5.2]) for males.

Table 9: Study participants` characteristics

	Females			Males		
	n	Mean (SD)	95% CI	*n*	Mean (SD)	95% CI
Age (years)	180	14.2 (0.96)	14.1-14.4	54	14.8 (1.0)	14.5-15.0
Anthropometric data						
Weight (kg)	180	54.6 (12.1)	52.8-56.4	54	56.8 (15.1)	52.7-61.0
Height (cm)**	180	157.0 (7.3)	156-158.1	54	164.4 (9.3)	161.9-166.9
BMI (kg/m^2)	180	22.0 (4.5)	21.3-22.7	54	20.9 (4.6)	19.6-22.2
Neck circumference**	180	29.9 (2.0)	29.6-30.0	54	31.7 (2.5)	31.0-32.4
Waist (cm)	178	71.7 (9.6)	70.3-73.1	54	72.6 (10.6)	69.7-75.5
Hip (cm)*	178	92.6 (11.3)	90.9-94.3	54	89.0 (11.4)	85.9-92.1
WH ratio**	178	0.78 (.07)	0.77-0.79	54	0.82 (.06)	0.80-0.83
WHT ratio	178	0.46 (.06)	0.45-0.47	54	0.44 (.06)	0.42-0.46
Fat (%)**	178	26.8 (8.0)	25.6-28.0	54	14.4 (7.9)	12.3-16.6
Hemodynamic parameters						
SBP (mmHg)	180	114.4 (11.4)	112.8-116.1	54	116.9 (11.4)	113.8-120.0
DBP (mmHg)*	180	73.5 (7.8)	72.4-74.7	54	70.5 (8.7)	68.1-72.9
MAP (mmHg)	180	87.2 (7.9)	86.0 -88.3	54	86.0 (8.4)	83.6-88.3
HR (Hz)**	180	87.2 (12.9)	85.3-89.1	54	76.2 (12.1)	72.9-79.5
PWV (m/s)*	180	6.3 (.75)	6.1-6.4	54	6.6 (1.1)	6.3-6.9
Plasma parameters						
TC (mmol/L)**	143	3.8 (0.76)	3.7 -4.0	41	3.4 (0.63)	3.2-3.6
HDL-c (mmol/L)	72	1.30 (0.60)	1.2-1.4	19	1.13 (0.56)	0.9-1.4
nonHDL-c (mmol/L)	66	2.56 (0.95)	2.3-2.8	19	2.19 (0.75)	1.8-2.5
TG (mmol/L)	143	0.83 (0.28)	0.78-0.88	41	0.78 (0.22)	0.71-0.85
FG (mmol/L)**	146	4.73 (0.48)	4.7-4.8	41	5.0 (0.59)	4.8-5.2
Insulin (lU/L)	102	25.0 (24.2)	20.3-29.8	21	24.5 (25.1)	13.0-35.9
ACR	126	0.83 (.78)	0.70-0.97	39	0.86 (.91)	0.56-1.15
ADMA*	106	1.49 (0.29)	1.43-1.55	21	1.35 (0.38)	1.18-1.52
NEFA	70	33.3 (19.3)	28.7-37.9	17	31.1 (18.8)	21.4-40.8
NO	76	2.70 (1.1)	2.44-2.95	20	2.88 (1.3)	2.27-3.48
AIP	66	-0.16 (.25)	-0.22- -0.10	19	-0.14 (.24)	-0.25- -0.02
HOMA-IR	83	2.22 (1.4)	1.92-2.53	18	2.36 (1.5)	1.63-3.09

Note: **P<.01, *P<.05 flag significant sex differences. Abbreviations: BMI: body mass index; WH ratio: waist to hip ratio; WHT: waist to height ratio; SBP: systolic blood pressure; DBP: diastolic blood pressure; MAP: mean arterial blood pressure; PWV: Pulse wave velocity; TC: Total cholesterol; TG: Triglycerides; (non) HDL-c: (non) High-density lipoprotein cholesterol; FG: Fasting glucose; ACR: Albumin-Creatinine ratio; ADMA: Asymmetric Dimethylarginine; NEFA: non-esterified fatty acid; NO: nitric oxides; AIP: Atherogenic index of plasma; HOMA-IR: Homeostasis Model Assessment Index.

3.1.1 Extracted cohort description

For better comparability, another description was completed with a subgroup n=98 (75 women and 23 men) from whom all required data including blood parameters were available as shown in **Table 10** below:

Table 10: Description of the extracted cohort at baseline

Description	Females	Males	Statistics	
	Mean (SD)	Mean (SD)	t	p
Age	13.95 (0.914)	14.83 (0.984)	-3.966	0.000
Waist circumference	70.136 (9.411)	72.674 (9.100)	-1.140	0.257
BMI Percentile	57.172 (29.5184)	47.657 (32.1090)	1.325	0.188
Fasting Glucose (mmol/L)	4.779 (0.5391)	5.022 (0.5351)	-1.895	0.061
Total cholesterol (mmol/L)	3.8269 (0.85524)	3.1761 (0.75431)	3.277	0.001
TG (mmol/L)	0.9232 (0.44587)	0.7552 (0.24277)	1.726	0.088
HDL-C (mmol/L)	1.3309 (0.86152)	1.1189 (0.49204)	1.123	0.264
Systolic Blood Pressure	113.02 (10.900)	118.64 (10.645)	-2.173	0.032

There was a statistically significant difference between sex and age $t(96) = -3.966$, $p = 0.000$, and other various parameters such as sex and systolic blood pressure $t(96) = -2.173$, $p = .032$ and between sex and total cholesterol (mmol/L) $t(96) = 3.277$, $p = 0.001$.

3.2 Anthropometric measures and weight status

The results of these parameters were calculated with the subgroup as shown in **Table 11** below:

Table 11: Anthropometric measures

Description	Females	Males	Statistics	
	Mean (SD)	Mean (SD)	t	p
Waist circumference	70.136 (9.4117)	72.674 (9.100)	-1.140	0.257
BMI Percentile	57.172 (29.5184)	47.657 (32.1090)	1.325	0.188

The results of the waist circumference showed that 93.3% (70/75) of female study participants and 95.7% (22/23) of male study participants are within the normal range. In terms of risk factors, 6.7% (5/75) of female study participants and 4.3% (1/23) of male study participants are above the 90th percentile.

A χ^2-test for association was conducted to find a possible difference between female and male participants and the frequency of occurrence of a waist circumference >90th percentile, this test showed no statistically significant relationship, $\chi^2(1) = .0.165$, p = 0.685.

A t-test for independent samples was performed with BMI percentile results. There was no statistically significant relationship between sex and BMI percentiles t(96) = 1.325, p = 0.188

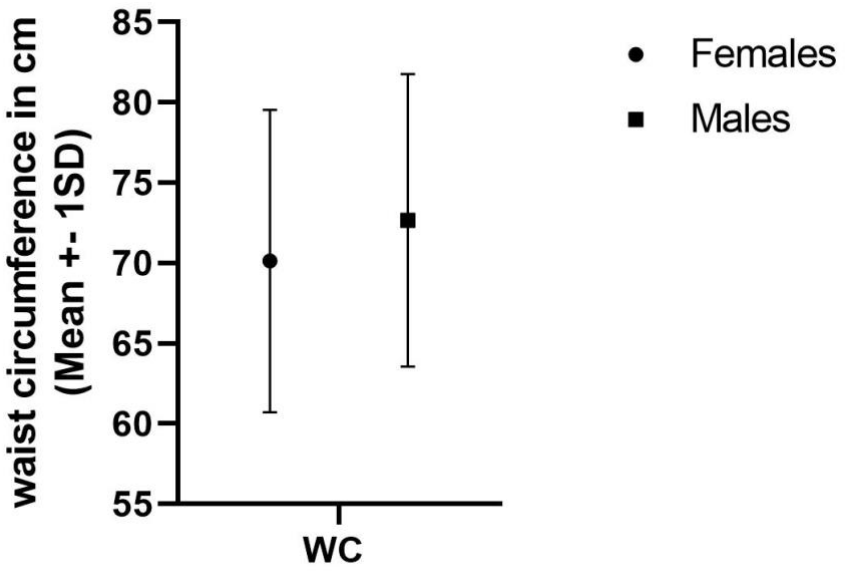

Figure 3 Mean values and standard deviation of waist circumference split into sex: In the graph, you can see the representation of the mean values including the standard deviation of the waist circumference for females and males in cm. The dot represents the mean value of the waist circumference for females, the square represents the mean value of the waist circumference for males. SD, standard deviation; WC, waist circumference

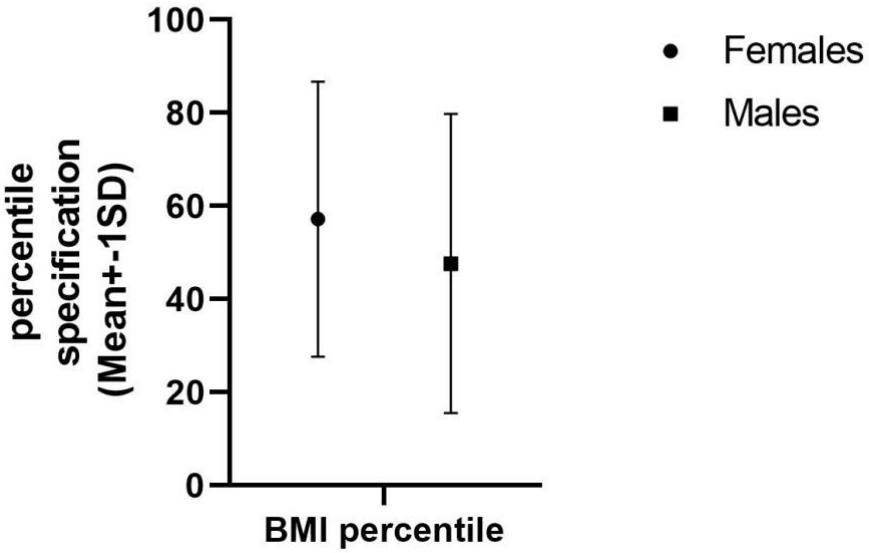

Figure 4 Mean values and standard deviation of BMI percentiles split into sex: In the graph, you can see the representation of the mean values including the standard deviation of the BMI percentiles for females and males. The dot represents the mean value of the BMI percentile for females, the square represents the mean value of the BMI percentile for males. SD, standard deviation; BMI, body mass index

3.3 Blood pressure

The results of blood pressure status in study participants showed, after categorization into percentiles, which showed in **Table 12** that 61.5% (111/180) of female study participants and 66.7% (36/54) of male study participants were in the normotensive range. A pre-hypertensive status was seen in 15.0% (27/180) of female study participants and 14.8% (8/54) of male study participants. Hypertensive blood pressure above the 95th percentile was evident in 23.5% (42/180) of female and 18.5% (10/54) of male study participants.

Table 12: Classification of blood pressure based on sex

Arterial blood pressure	Females			Males		
		SBP	DBP		SBP	DBP
(mmHg)	*n (%)*	Mean (SD)	Mean (SD)	*n(%)*	Mean (SD)	95% CI
Normal	111 (61.5)	109 (8.8)	70 (5.2)	36 (66.7)	112 (7.7)	67 (6.7)
Pre-Hypertensive (≥ 90 <95 pc)	27 (15.0)	117 (6.7)	77 (3.9)	8 (14.8)	124 (6.3)	75 (4.0)
Hypertensive (≥ 95 pc)	42 (23.5)	127 (9.1)	82 (7.7)	10 (18.5)	130 (11.7)	81 (8.1)

Abbreviations: SBP: systolic blood pressure; DBP: diastolic blood pressure; grouping based on percentiles of mean systolic and diastolic blood pressure.

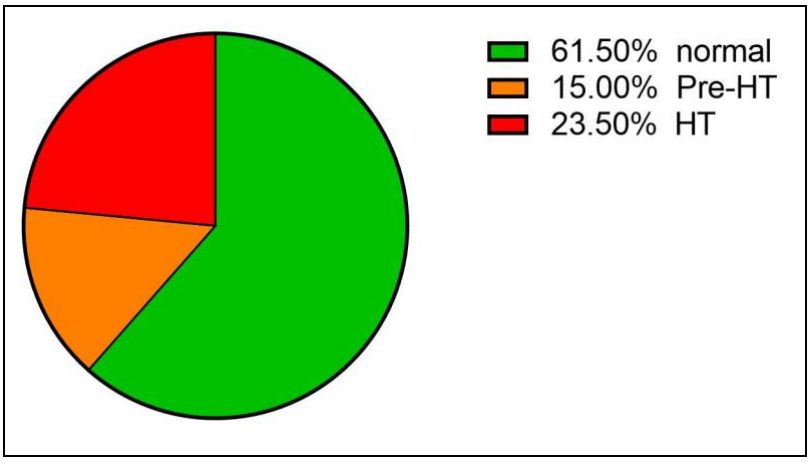

Figure 5: Classification of BP-status from female participants: This graph is about the classification of blood pressure in the female study participants. For better understanding, we decipher the corresponding color representation: green= normotensive, orange= pre-hypertensive and red= hypertensive. As can be seen in the graph, 61.5% of the female study participants' measured blood pressure is within the normal range. 15.0% of the participants were classified as pre-hypertensive and 23.5% of the participants had a blood pressure above the 95th percentile and were therefore classified as Hypertensive. Pre-HT, Pre-Hypertension; HT, Hypertension

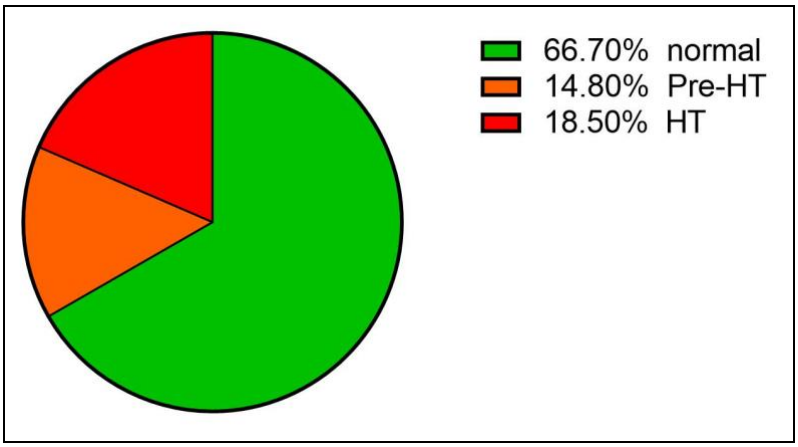

Figure 6: Classification of BP-status from male participants: Here we see the graphical representation of the classification of blood pressure in the male study participants. For better understanding, we decipher the corresponding color representation: green= normotensive, orange= pre-hypertensive and red= hypertensive. 66.7% of the male study participants are within the normal range with their measured blood pressure. Pre-hypertensive 14.8% and classified as hypertensive 18.5% of the participants, whose blood pressure is above the 95th percentile.

The results of the blood pressure status were then correlated with the weight status of the study participants, which can be seen in **Table 13**. The table shows that both subjects who were classified as lean and those who were classified as O/O had a prevalence of pre-HT/HT. In the female study participants, the prevalence was 38.3% (69/180), and in the male study participants 33.3% (18/54). Those subjects with O/O showed an even higher prevalence for pre-HT/HT. This showed that 38.6% (22/57) of the female subjects and 46.2% (7/13) of the male subjects already had hypertension.

Table 13: Comparison of weight status and BP-status

	Female				**Male**			
	NT (%)	PHT (%)	HT (%)	total	NT (%)	PHT (%)	HT (%)	total
lean	87 (70.7)	16 (13.0)	20 (16.3)	123 (100%)	32 (78.0)	5 (12.2)	4 (9.8)	41 (100%)
O/O	24 (42.1)	11 (19.3)	22 (38.6)	57 (100%)	4 (30.8)	3 (23.1)	7 (46.2)	13 (100%)
total	111 (61.7)	27 (15.0)	42 (23.3)	180 (100%)	36 (66.7)	8 (14.8)	10 (18.5)	54 (100%)
		69 (38.3)				18 (33.3)		

Abbreviations: O/O: overweight/obese; NT: normotensive, PHT: pre-hypertensive, HT: hypertensive; classification based on percentiles of mean systolic and diastolic blood pressure.

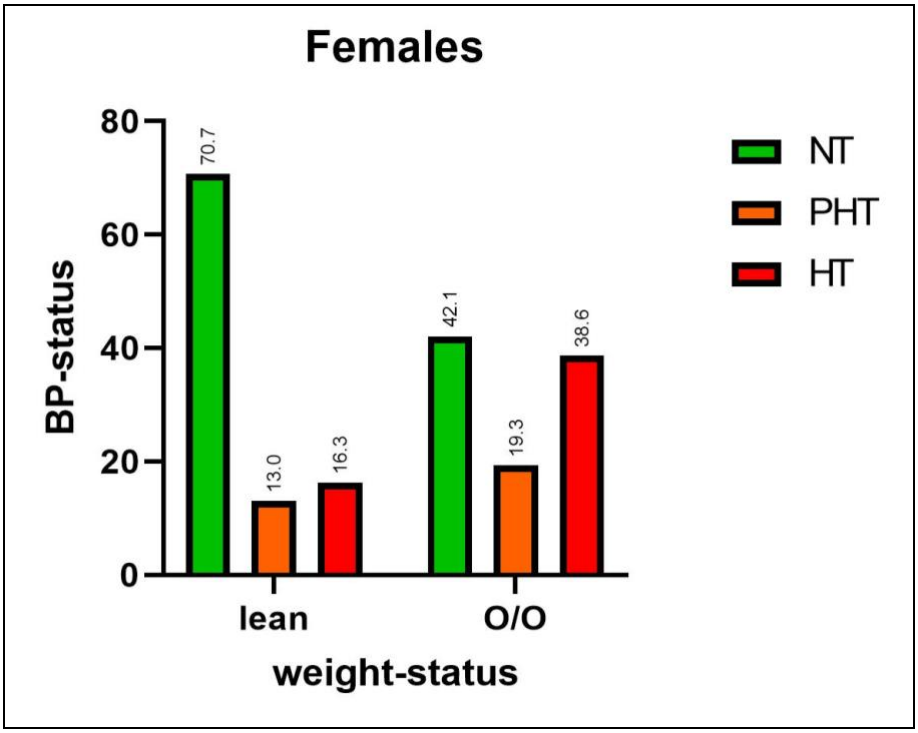

Figure 7: Comparison of female weight status and BP-status: The graph compares the percentage of participants in the corresponding classification of blood pressure status with the weight status of the female study participants. The group of lean females is n=123 and the group of overweight/obese females is n=57. The blood pressure status was presented in the form of different colored columns, each group has three columns. The green column represents normotensive values, the orange column represents pre-hypertensive values and the red column represents hypertensive blood pressure values. In the lean female study participants, a higher proportion of individuals with normotensive values can be seen at 70.7% (87/123), compared to the female overweight/obese group, whose proportion of normotensive females is 42.1% (24/57), also it must be noted, that normotensive values are dominant in both groups. The percentage of females with hypertensive values is 38.6% (22/57) in the O/O group and 16.3% (20/123) in the lean group. This means that hypertension is more prevalent in the O/O group, but also that lean females already have elevated blood pressure.

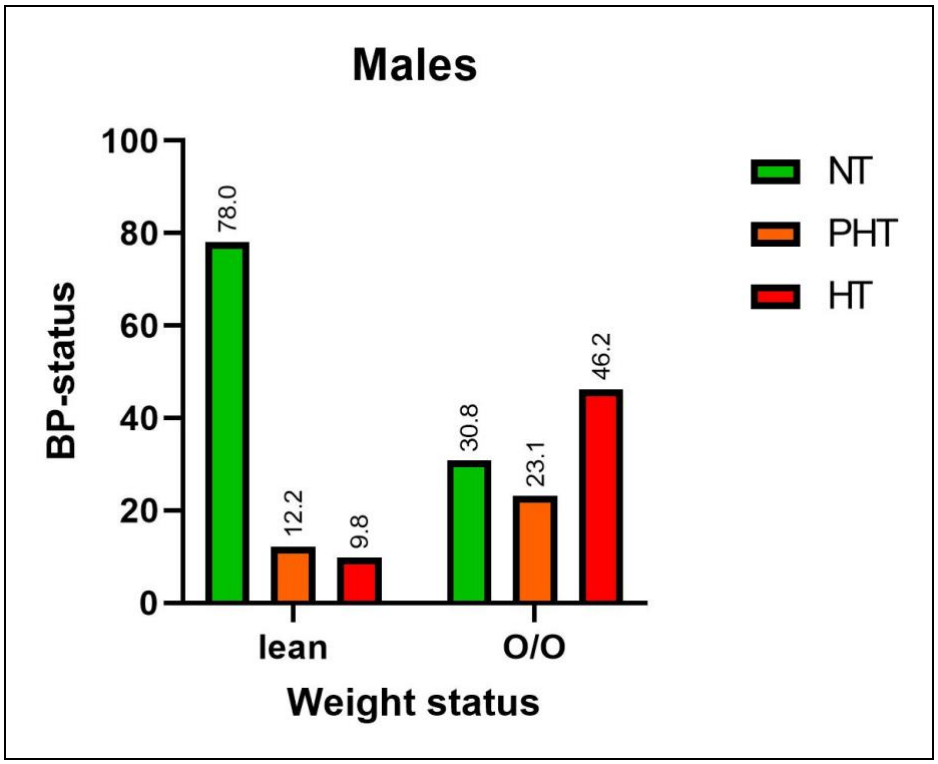

Figure 8: Comparison of male weight status and BP-status: The graph compares the percentage of participants in the corresponding classification of blood pressure status with the weight status of the male study participants. The group of lean males is n=41 and the group of overweight/obese males is n=13. The blood pressure status was presented in the form of different colored columns, each group has three columns. Green= normotensive values, orange= pre-hypertensive values and red= hypertensive blood pressure values. In males, it was observed that in the O/O group, the hypertensive proportion was more dominant at 46.2% (7/13) than the normotensive proportion at 30.8% (4/13). In the lean male study participants, the normotensive proportion was more dominant at 78.0% (32/41) compared with the hypertensive proportion at 9.8% (4/41).

For better comparability to other risk factors, another description was completed with the subgroup from whom all required data was available. The results showed that the blood pressure in 36.0% (27/75) of the female participants and 43.5% (10/23) of the male participants is above the 90th percentile.

A χ^2-test for association was conducted to show a possible difference between female and male participants and the frequency of occurrence of a blood pressure status >90th percentile, this test showed no statistically significant relationship, $\chi^2(1) = .0.419$, $p = 0.517$.

3.4 Blood parameters

The data from the subgroup were used for statistics as shown in **Table 14**. The only statistically significant difference in sex was shown in total cholesterol (mmol/L) t(96) = 3.277, p = 0.001. The other blood parameters were of no statistical significance.

Table 14: Blood parameters

Description	Females	Males	Statistics	
	Mean (SD)	Mean (SD)	T	p
Fasting Glucose (mmol/L)	4.779 (0.5391)	5.022 (0.5351)	-1.895	0.061
Total cholesterol (mmol/L)	3.8269 (0.85524)	3.1761 (0.75431)	3.277	0.001
TG (mmol/L)	0.9232 (0.44587)	0.7552 (0.24277)	1.726	0.088
HDL-C (mmol/L)	1.3309 (0.86152)	1.1189 (0.49204)	1.123	0.264

Fasting glucose results showed that 6.1% (6/98) of the study participants had a fasting glucose value above 110mg/dL. Broken down by sex, there were 5.3% (4/75) of the female participants and 8.7% (2/23) of the male participants with higher fasting glucose levels, indicating a risk factor for metabolic syndrome.

A χ^2-test for association was conducted to show a possible difference between female and male participants and the frequency of occurrence of a fasting glucose level >110mg/dL, this test showed no statistically significant relationship, $\chi^2(1) = .0.346$, p = 0.556.

The results of blood lipid values showed that 10.2% (10/98) of the study participants had a TG level above 110mg/dl. There were 12.0% (9/75) of the female participants and 4.3% (1/23) of the male participants with higher TG levels, indicating a risk factor for metabolic syndrome. For the HDL levels it was shown, that 55.1% (54/98) of the total study population had decreased HDL-blood levels.
A χ^2-test for association was conducted to show a possible difference between female and male participants and the frequency of occurrence of a HDL-c level <40 mg/dL, this test showed no statistically significant relationship, $\chi^2(1) = 3.009$, p = 0.078.

3.5 Metabolic syndrome

In the subgroup all required data for the MetS components were available. As shown in **Table 15**, 6.1% (6/98) of the study participants have a waist circumference above the 90th percentile, which is 6.7% (5/75) of the girls and 4.3% (1/23) of the boys.

Elevated blood pressure with values above the 90th percentile was seen in 37.8% (37/98) of the study participants, 36.8% (27/75) of the girls, and 43.5% (10/23) of the boys showed elevated blood pressure. Hence, it was found that more than 1/3 of the subjects in the study were affected by elevated blood pressure.

Regarding the blood samples, fasting glucose levels showed an elevation above 100mg/dL in 6.0% (6/98), affecting 5.3% (4/75) of the girls and 8.7% (2/23) of the boys. For the criteria for possible dyslipidemia, triglyceride levels were elevated above 110mg/dL in 10.2% (10/98) and HDL levels were decreased to below 40mg/dL in 55.1% (54/98), corresponding to 60.0% (45/75) of the girls and 39.1% (9/23) of the boys.

Table 15: Metabolic Syndrome Criteria split by sex

Criteria	Female	male	n
Central obesity			
WC >90th pc	5 (5.1%)	1 (1.0%)	98
Elevated blood pressure			
BP >90th pc	27 (27.6%)	10 (10.2%)	98
Hyperglycaemia			
FG > 110 mg/dL	4 (4.1%)	2 (2.0%)	98
Dyslipidaemia (TG)			
TG > 110 mg/dL	9 (9.2%)	1 (1.0%)	98
Dyslipidaemia (HDL)			
HDL ≤ 40 mg/dL	45 (45.9%)	9 (9.2%)	98

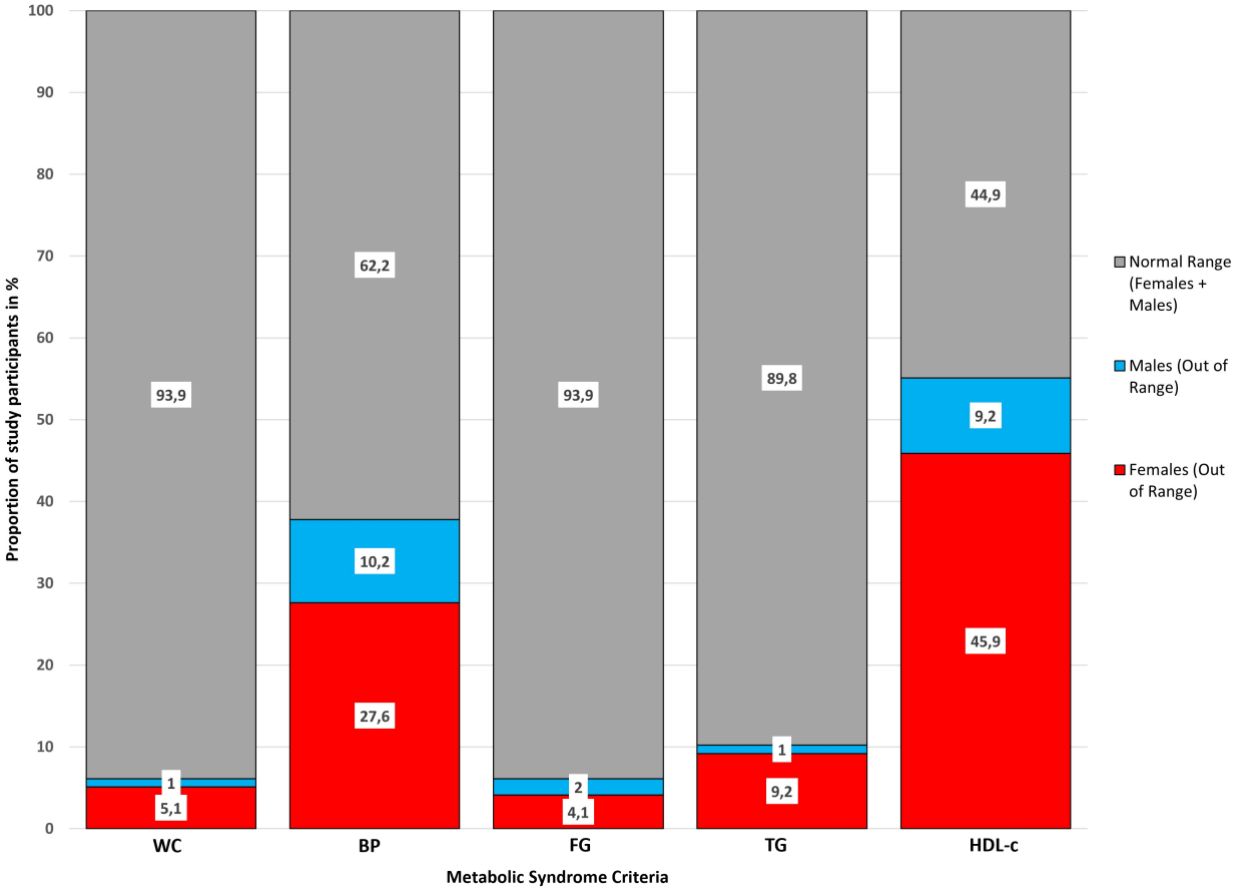

Figure 9 Metabolic Syndrome Criteria: In this graph, the individual risk factors of metabolic syndrome were graphically represented, and the respective groups were divided into segments. The red segment represents the females who show an increase/decrease in the respective risk factor, the blue represents the males who show deviations, and the gray represents the remaining study participants who are in the normal range. This graphical representation clearly shows that the risk factor of a low HDL-c is so strongly represented that more than 50% of the study participants have a low HDL-c value. It can also be seen that the segments of the participants with normal values are more prominent, except for the HDL-c values. WC, waist circumference; BP, blood pressure; FG, fasting glucose; TG, triglycerides; HDL-c, high-density lipoprotein cholesterol.

For ease of comparison, **Table 16** shows the number of metabolic risk factors starting with no risk factor for the MetS to four out of five risk factors. As shown in the table, 24.5% (24/98) of the study participants showed no risk factor for MetS, this represented 22.7% (17/75) of the women and 30.4% (7/75) of the men who showed no risk factor. Whereas 7.1% (7/98) of the study population fulfilled the criteria for MetS with 3 risk factors. By sex, this means that 8.0% (6/75) of the female participants and 4.3% (1/23) of the male participants can be diagnosed with MetS. There was even one female participant who showed four of five risk factors. At least one risk factor was shown by 44.9% (44/98) of the participants, divided into sex 45.3% (34/75) of the female participants, and 43.5% (10/23) of the male participants showed at least one risk factor for MetS. It has been shown that there are more participants with one risk factor than participants without a risk factor for the MetS. In addition, a χ^2-test for association was conducted to find a possible difference between female and male participants and the frequency of occurrence of a MetS, this test showed no statistically significant relationship, $\chi^2(1) = .0.584$, $p = 0.445$.

Table 16: Metabolic risk factors split by sex

risk factors		**Sex**		**Total**
		Female	**Male**	
0	count	17	7	24
	% within sex	22.7%	30.4%	24.5%
	% within group	17.3%	7.1%	24.5%
1	Count	34	10	44
	% within sex	45.3%	43.5%	44.9%
	% within group	34.7%	10.2%	44.9%
2	Count	17	5	22
	% within sex	22.7%	21.7%	22.4%
	% within group	17.3%	5.1%	22.4%
3	Count	6	1	7
	% within sex	8.0%	4.3%	7.1%
	% within group	6.1%	1.0%	7.1%
4	Count	1	0	1
	% within sex	1.3%	0.0%	1.0%
	% within group	1.0%	0.0%	1.0%
	Total	**75**	**23**	**98**

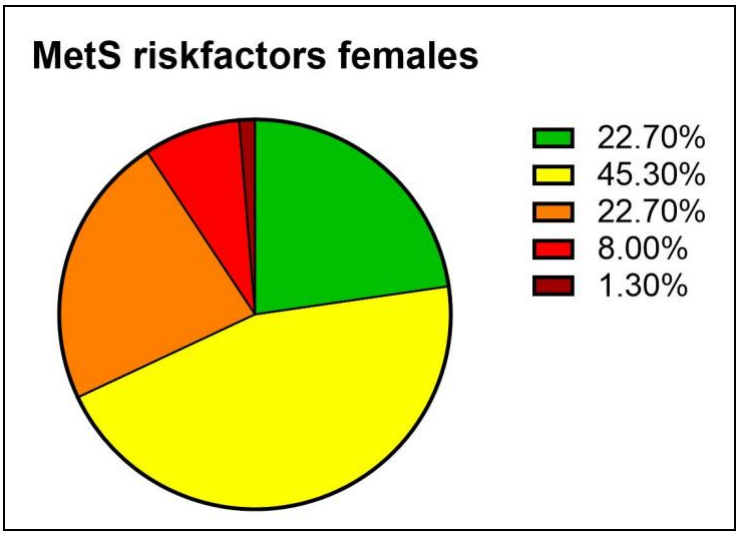

Figure 10: MetS risk factors of female participants. This graph is specifically about the clustering of risk factors in the female study participants. For better understanding, we decipher the associated color representation: green=zero risk factors, yellow=one risk factor, orange=two risk factors, red=three risk factors, dark red=four risk factors. As can be seen in the pie chart, female participants with one risk factor are more representative at 45.30%, while the percentage of participants with none and two risk factors is identical at 22.70%. A full 8% of female participants have three of five risk factors and may receive a diagnosis of metabolic syndrome for this reason.

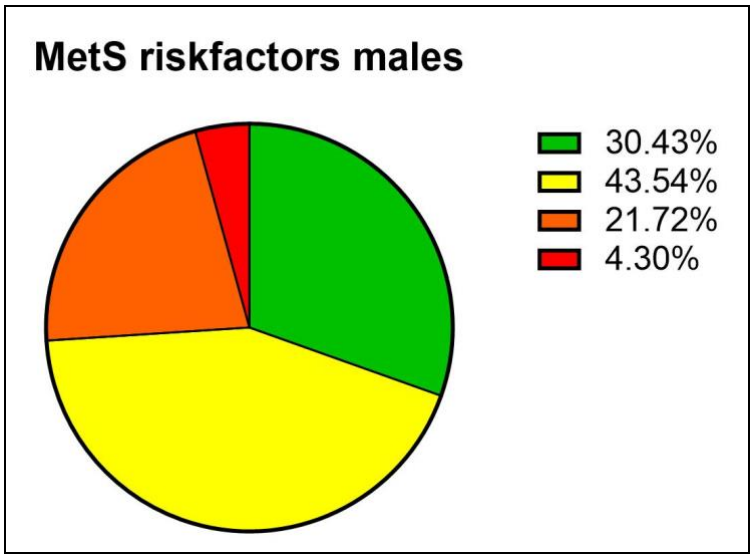

Figure 11: MetS risk factors of male participants. This graph is about the clustering of risk factors in the male study participants. For better understanding, we decipher the associated color representation: green=zero risk factors, yellow=one risk factor, orange=two risk factors, red=three risk factors, dark red=four risk factors. As can be seen in the pie chart, male participants with one risk factor are more representative at 43.54%, while the proportion of participants with no risk factor is second at 30.43%. The next Great proportion is 21.72% of male participants with two risk factors and 4.3% of male participants have three out of five risk factors and can be diagnosed with metabolic syndrome for this reason.

4 Discussion

This study examined the prevalence of metabolic syndrome (MetS) and cardiovascular risk factors among adolescents aged 13 to 16 years from four secondary schools in Mthatha. After correlating blood pressure status with weight status, it was observed that participants who were classified as overweight/obese (O/O), as well as those who were classified as lean, had a prevalence of pre-hypertensive and hypertensive blood pressure.

In the female study participants, the prevalence was 38.3% (69/180), and in the male study participants 33.3% (18/54). Moreover, in the male O/O group, the proportion of hypertensives 46.2% (7/13) was greater than the proportion of normotensives 30.8% (4/13). In the female O/O group, the proportion of normotensive females was 42.1% (24/57), compared with 38.6% (22/57) of hypertensive females. These results are consistent with the findings of previous studies on adolescents in Mthatha, although it should be noted that compared with the study by *Sekokotla et al* (1) where the proportion of pre-HT/HT in females was 32.6% our result was 38.6% and therefore slightly higher. Of course, this could be due to the fact that the number of study participants (255 females/127 males) was significantly higher than our number of study participants (180 females/54 males). For this reason, further investigation would be advised regarding the development/etiology of hypertension in this population with a representative number of participants. In previous studies, exposure to air pollution, in addition to IR, was suspected as a cause of elevated blood pressure in the lean population (62, 63).

In a study conducted in elementary schools of Mthatha, which was published by *Matjuda et al.* in 2020, it was shown that the prevalence of pre-HT/HT is already very high at 24.18% (74/129) in females and 19.97% (55/129) in males (59). These results might be lower than the results in our study, but it should be kept in mind that this is an age group of 6–9-year-old children and that already in this group of young individuals there is an increased prevalence for pre-HT/HT. Of course, effects such as so-called white coat hypertension and an increase in blood pressure due to the unusual situation, especially in a study group with children, should not be disregarded. The fact that high blood pressure, along with other cardiovascular risk factors such as O/O, is already present in young South African residents should lead to a rethinking of the prevention of these very diseases. Here

it would be necessary that children of preschool age, even those who are in kindergarten, learn positive behaviors about healthy and balanced eating as well as exercise and sports activities so that these experiences can become habits for the children. Some studies in South Africa, such as the KaziBantu Study by *Müller et al.* that tested interventions for school children (KaziKidz) and their teachers (KaziHealth) in disadvantaged communities in Port Elizabeth have already begun to address this issue (64). Based on the results of this study, it would be important to start such projects also in Mthatha.

Regarding cardiometabolic risk factors, after applying the criteria for MetS by *Cook et. al.* (33), we found a high overall prevalence in the study participants. In the extracted cohort (75 females and 23 males), in which all parameters were available, we found 8.1% (8/98) showed three or more risk factors, which can be diagnosed as MetS. Less than a quarter of the study participants showed no risk factor 24.5% (24/98) and at least one risk factor for the classification of a MetS could be found in 44.9% (44/98).in contrast. Our study revealed that 8.0% (6/75) of the female participants and 4.3% (1/23) of the male participants can be diagnosed with MetS. Also, there was no significant statistical difference regarding sex. It should be noted, however, that one single male study participant had three risk factors, and statistical dispersion for one person alone is not statistically meaningful. This result, however, shows different results regarding sex distribution compared to other studies for example the study published by *Sekokotla et al*. in 2017 (1), which utilized the same criteria. Finding the prevalence for MetS of 3.1% (8/255) in female study participants and 6.0% (7/116) in male study participants in the age group of 13-18-year-old students (1). This difference could be because the number of study participants (255 females/127 males) was significantly higher than our number of study participants (180 females/54 males).

Some authors, such as *Simmons et al*. (65) question the practicability of the MetS as a diagnostic or managing tool. Especially the use of different definitions for the identification of a MetS (31), which can show a completely different result with the same input is cited as a negative point. In addition, the stronger relationship between MetS and T2DM and the usually humbler association between metabolic syndrome and CVD were mentioned as one of the negative points for the clinical necessity of the diagnosis of MetS. It was also mentioned that MetS should be referred to as a premorbid condition and should not be a clinical diagnosis in itself (65).

4.1 Limitations

This study has several limitations. Being a cross-sectional study, it only provides an overview of the metabolic status of a population at a given time. While longitudinal studies provide a better overview of the development of cardiometabolic risk factors over time, cross-sectional studies such as the one presented here are also important to assess the cardiometabolic state of a population at a certain time.

Laboratory conditions were not present in this field study and thus various environmental conditions such as room temperature, air pressure and daylight could have influenced various measurements such as blood pressure measurements. However, in this study, the effects of confounding variables, which could potentially affect the results, were minimized by ensuring that the samples were stored at the correct temperatures once they were collected.

The unequal number of female and male study participants presented us with an additional challenge, especially in terms of statistical dispersion. Similarly, the smaller number of male study participants represented an obstacle in the evaluation of the results. However, it was difficult to have an equal number of sexes in the study, as many of the male participants did not provide consent or had a higher drop-out rate. This has also been reported in other field-based studies in Mthatha (1, 58).

Another limitation was the usage of international percentiles for the definition of MetS in the studied population. Unfortunately, in this study, only the international criteria for MetS were used for the anthropometric measurements, as there are currently no available percentiles for MetS which could be used on Sub-Saharan African youth. This could potentially have introduced an error in our classification of risk factors for the youth of African descent in Mthatha. In the future, such recommendations for MetS definitions should also be extended to African youth, especially those living in Sub-Saharan Africa.

4.2 Conclusions and further directions

There is a high prevalence of overweight/obesity and increased blood pressure in South African Adolescents. The associated higher risks for these adolescents include the risk of cardiovascular disease in addition to the possible development of T2DM and MetS. Continued research is required and longitudinal studies are needed to investigate the etiology of cardiometabolic risk factors for this population. This is necessary for the development of appropriate preventive measures and to protect the population from future complications of MetS such as cardiovascular diseases.

Finally, this study has also shown us that there is an urgent need for developing percentiles that can be used for MetS classification for Sub-Saharan African youth. Usage of the international criteria for MetS can introduce potential errors in the classification of risk factors for MetS and cardiovascular risk.

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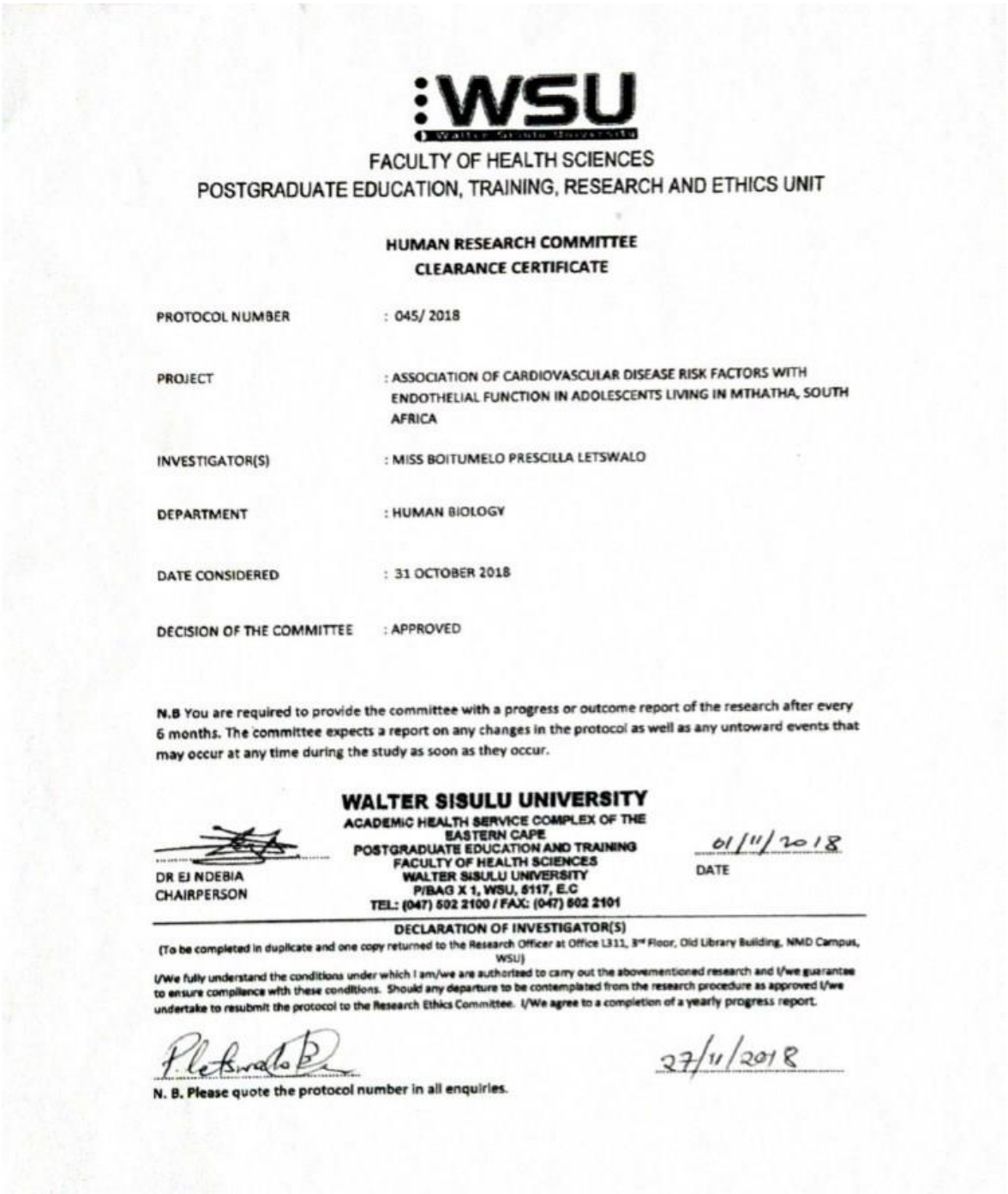
6 Appendices

6.1 Ethical Clearance



WSU

FACULTY OF HEALTH SCIENCES
POSTGRADUATE EDUCATION, TRAINING, RESEARCH AND ETHICS UNIT

HUMAN RESEARCH COMMITTEE
CLEARANCE CERTIFICATE

PROTOCOL NUMBER	: 045/ 2018
PROJECT	: ASSOCIATION OF CARDIOVASCULAR DISEASE RISK FACTORS WITH ENDOTHELIAL FUNCTION IN ADOLESCENTS LIVING IN MTHATHA, SOUTH AFRICA
INVESTIGATOR(S)	: MISS BOITUMELO PRESCILLA LETSWALO
DEPARTMENT	: HUMAN BIOLOGY
DATE CONSIDERED	: 31 OCTOBER 2018
DECISION OF THE COMMITTEE	: APPROVED

N.B You are required to provide the committee with a progress or outcome report of the research after every 6 months. The committee expects a report on any changes in the protocol as well as any untoward events that may occur at any time during the study as soon as they occur.

WALTER SISULU UNIVERSITY
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DR EJ NDEBIA
CHAIRPERSON

01/11/2018
DATE

DECLARATION OF INVESTIGATOR(S)

(To be completed in duplicate and one copy returned to the Research Officer at Office L311, 3rd Floor, Old Library Building, NMD Campus, WSU)

I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Research Ethics Committee. I/We agree to a completion of a yearly progress report.

27/11/2018

N. B. Please quote the protocol number in all enquiries.

6.2 Consent form

Consent form (English)

ASSOCIATION OF CARDIOVASCULAR DISEASE RISK FACTORS WITH ENDOTHELIAL FUNCTION IN ADOLESCENTS LIVING IN MTHATHA, SOUTH AFRICA

Consent form

We are hereby requesting for your permission to include your child in this study.

I have read and understand what the study involves and permit mu child/charge (Name of child) _____ Grade _____ to participate in this study, and to donate 5ml of blood and 20 ml of urine samples.

Parent/guardian: Signature _____ Date _____

6.3 Data sheet

Adolescents study 2017–2018: Cardiovascular disease risk factors

Participants Data sheet

Participant Code: _____

Personal information

Name: _____ Grade: _____

School Name: _____ Sex: Male ☐ Female ☐

Date of birth: _____ Place of birth: _____

Parents' phone number: _____

Anthropometry

Height: _____

Weight: _____ Waist circumference: _____

BMI: _____ Hip circumference: _____

MUAC: _____

Blood pressure

	1	2	3
SBS (mmHg)			
DBD (mmHg)			
Heart Rate			

PWV ☐

Blood Sample & Urine ☐