Diplomarbeit

The Prevalence of Metabolic Syndrome in Children and Adolescents:
An Update of the Current Literature

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Graz, am 17.09.2019

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 17.09.2019 *Carolin Reisinger eh*

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Abstract

Introduction: The Metabolic Syndrome (MetS) describes the clustering of cardio-metabolic risk factors including abdominal obesity, insulin resistance, elevated blood pressure, high levels of triglycerides and low levels of high-density lipoproteins. With the rising prevalence of childhood obesity, MetS is considered to become more frequent among this age group too. This development raises great concerns, since MetS is associated with increased risk for cardiovascular diseases and diabetes mellitus type 2. However, until today there is still no generally accepted definition of this syndrome for pediatric patients.

Objectives: The aim of this work is to summarize current prevalence data of childhood MetS as well as to discuss the ongoing disagreement between different pediatric definitions and the clinical importance of such diagnosis.

Methodology: A systematic literature research on the prevalence of pediatric MetS was conducted. Only articles that where published during the past five years and that used at least one of four predetermined classifications (International Diabetes Federation IDF, Cook et al., Ford et al. or de Ferranti et al.) were included.

Results: The literature research resulted in 1167 articles, of which 31 publications met all inclusion criteria.

Discussion: MetS was present in children from developed as well as from developing countries. The results indicate that the number of MetS diagnoses partly depends on the definition used: the IDF definition provided the lowest prevalence (0.3% in Colombia), whereas the classification of de Ferranti et al. yielded the highest (26.4% in Iran). Therefore, it is important to consider the underlying classification when comparing the prevalence data of different studies in pediatric populations. The ongoing disagreement concerning a pediatric MetS definition is due to the poor knowledge about the pathogenic mechanisms, especially in terms of growth and pubertal development. Long-term studies reveal that the prognostic accuracy regarding future health consequences is moderate. In order to develop a more valid definition, further research on long-term consequences of childhood risk factors is needed. A uniform classification would enable comparison between different study results and promote the development of screening, prevention and treatment measures for childhood MetS.

Zusammenfassung (German Abstract)

Einleitung: Das Metabolische Syndrom (MetS) beschreibt einen Symptomenkomplex bestehend aus abdominaler Adipositas, Insulinresistenz, Bluthochdruck, erhöhten Triglyzeridspiegeln und niedrigen HDL-Cholesterinwerten. Im Zusammenhang mit der steigenden Adipositasrate bei Kindern und Jugendlichen wird vermutet, dass auch die Häufigkeit des MetS in dieser Altersgruppe zunimmt. Diese Entwicklung bietet Grund zur Sorge, da das MetS mit einem erhöhten Risiko für kardiovaskuläre und metabolische Folgeerkrankungen vergesellschaftet ist. Bisher ist es jedoch noch nicht gelungen, allgemein gültige Diagnosekriterien des MetS für diese Altersgruppe zu etablieren.

Die Ziele dieser Arbeit waren, einen Überblick über die aktuelle Prävalenz des MetS bei Kindern und Jugendlichen zu geben und die Gründe für das Fehlen einer einheitlichen Definition zu diskutieren sowie die klinische Bedeutung einer solchen Diagnose zu erörtern.

Methoden: Die Literaturrecherche erfasst Publikationen der vergangenen fünf Jahre, welche Prävalenzdaten zum MetS bei Kindern und Jugendlichen enthalten. Es wurden jene Arbeiten berücksichtigt, die zur Prävalenzerhebung mindestens eine von vier vorausgewählten Definitionen (International Diabetes Federation IDF, Cook et al., Ford et al. oder de Ferranti et al.) verwendeten.

Ergebnisse: Von 1167 gesichteten Titeln wurden 31 Publikationen zur Prävalenzanalyse herangezogen.

Diskussion: Die Ergebnisse weisen darauf hin, dass das MetS sowohl bei Kindern und Jugendlichen aus Industrie- als auch aus Entwicklungsländern auftritt. Die Prävalenz des MetS hing unter anderem von der zugrundeliegenden Klassifikation ab: Die IDF-Definition resultierte in den niedrigsten Prävalenzzahlen (0.3% in Kolumbien), wogegen die Definition von de Ferranti et al. die höchsten Werte erzielte (26.4% im Iran). Beim Vergleichen unterschiedlicher Studienergebnisse müssen somit die verwendeten Diagnosekriterien berücksichtigt werden. Ein Grund für das Fehlen einer einheitlichen Definition ist, dass die Pathogenese des MetS während der kindlichen Wachstums- und Entwicklungsphasen noch nicht ausreichend erforscht wurde. Aus Langzeitstudien ging zudem hervor, dass die Diagnose „Metabolisches Syndrom“ während der Kindheit nur mäßig akkurate Prognosen über den Gesundheitszustand im Erwachsenenalter zulässt. Ein Ziel zukünftiger Forschungsarbeiten sollte deshalb sein, die Risikoentwicklung von der Kindheit bis ins Erwachsenenalter zu untersuchen um die wissenschaftliche Grundlage für

eine neue, einheitliche Definition zu schaffen. Dadurch soll es möglich werden, Studienergebnisse untereinander zu vergleichen und die Entwicklung von Screening-, Präventions- und Therapiemaßnahmen des MetS bei Kindern und Jugendlichen voranzutreiben.

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Abbreviations

AGE	advanced glycosylated end products
BAT	brown adipose tissue
BMI	body mass index
BP	blood pressure
CCK	cholezystokinin
CVD	cardiovascular diseases
DAG	Deutsche Adipositas Gesellschaft
ECM	extracellular matrix
FBG	fasting blood glucose
FFA	free fatty acids
GLUT-4	glucose transporter type 4
HDL	high-density lipoprotein
IDF	International Diabetes Federation
IDL	intermediate-density lipoprotein
IGF-I	insulin-like growth factor I
IL-6	interleukin 6
IR	insulin resistance
LDL	low-density lipoprotein
LPL	lipoproteinlipase
MetS	metabolic syndrome
NAFLD	non-alcoholic fatty liver disease
NCEP-ATPIII	National Cholesterol Education Program Adult Treatment Panel III
NHANES	National Health and Nutrition Examination Survey
NO	nitric oxide
OECD	Organization for Economic Co-operation and Development
oxLDL	oxidized low-density lipoprotein
RAAS	renin-angiotensin-aldosterone-system
RF	risk factor
SAT	subcutaneous adipose tissue
SDS	standard deviation score
SSB	sugar-sweetened beverages
T2DM	diabetes mellitus type 2

TG	triglycerides
TNF-α	tumor necrosis factor alpha
TPR	total peripheral resistance
VAT	visceral adipose tissue
VLDL	very low-density lipoprotein
WAT	white adipose tissue
WC	waist circumference
WHO	World Health Organization

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1. Introduction

1.1. Definition and History of Metabolic Syndrome

The Metabolic Syndrome (MetS) comprises five risk factors that are known to predispose an individual to cardiovascular diseases (CVD) and diabetes mellitus type 2 (T2DM). As illustrated in Figure 1, these components include central obesity (characterized by high waist circumference), dysglycemia/insulin resistance (IR), hypertension, high levels of triglycerides (TG) and low levels of high-density lipoproteins (HDL) (1). These metabolic abnormalities occur together more often than expected by pure chance (2). If an individual shows at least three out of the five given risk factors, he or she is diagnosed with metabolic syndrome (1) and, accordingly, is considered to be at high risk for future cardiovascular events and metabolic disorders (1,3).

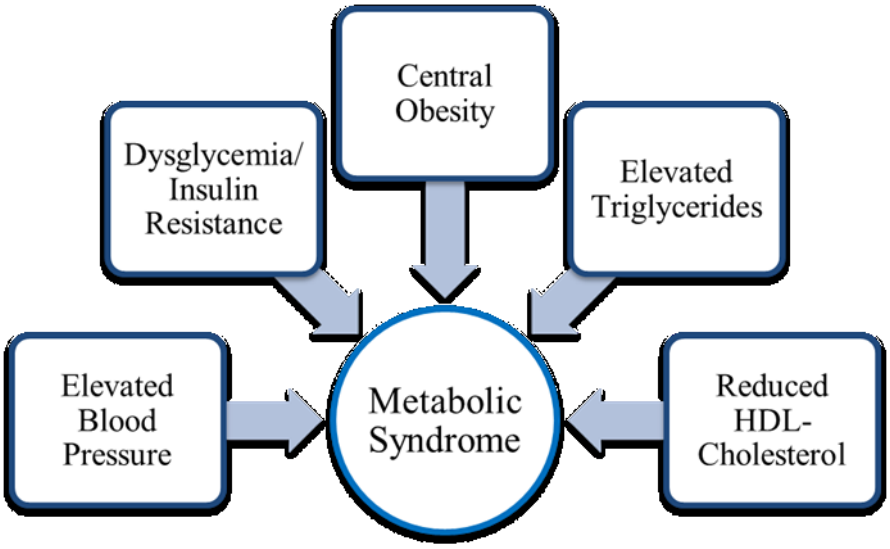

Figure 1 Components of the Metabolic Syndrome. Adapted from Alberti et al. (*Circulation* 2009) (1)

The origins of MetS trace back over decades (1). In 1988, *Reaven* described the connection between insulin resistance and clustering of multiple cardio-metabolic risk factors within an individual (4–6). He implied that insulin resistance initiates the pathogenesis of hyperglycemia, hyperinsulinemia, high levels of very low-density lipoproteins (VLDL), low levels of HDL and high blood pressure (BP) (6). Over time, the original concept was amended several times. In contrast to the original version, newer approaches also included obesity in the syndrome complex. To date, central obesity has received increasing attention and is now considered a driving force behind the initiation and development of MetS (7,8).

Since the late 1990s, various expert groups have tried to find adequate criteria for diagnosing MetS (1). This has resulted in a confusingly high number of definitions, which vary in terms of the measuring methods and threshold values (1,2,9). In 2009, certain major scientific societies finally agreed on a "*harmonized*" set of diagnostic criteria for defining MetS in adults (Table 1) (1).

Table 1 The Consensus Definition of the Metabolic Syndrome. Obtained from Alberti et al. (*Circulation* 2009) (1)

Measure	**Categorical Cut Points**
Elevated waist circumference	population- and country- specific cut-off values
Elevated triglycerides Or drug treatment for elevated triglycerides	≥150 mg/dL
Reduced HDL Or drug treatment for reduced HDL	<40 mg/dL in males <50 mg/dL in females
Elevated blood pressure Or antihypertensive drug treatment	Systolic BP ≥130 mmHg and/or Diastolic BP ≥85 mmHg
Elevated fasting glucose Or drug treatment of elevated glucose	≥100 mg/dL

1.2. Pathogenesis of Metabolic Syndrome

The pathogenesis of MetS is complex and up until now, many aspects are still not fully understood (1–3). It is believed that central obesity and/or insulin resistance initiate many different pathogenic pathways that increase metabolic risk (1) and end up in the full expression of the syndrome (10). However, since not every person with obesity or IR necessarily develops MetS and normal weight people can still be affected, obesity and IR per se seem insufficient to explain the whole pathogenesis of the disease (11–13). As presented in Figure 2, numerous biochemical factors but also the genetic and ethnic background, family predisposition and lifestyle habits have to be considered (11). Since MetS does not account for these contributing factors, it should not be taken as an exact risk assessment tool (1), but rather as a helpful guide to identify those individuals that are likely to develop CVD and T2DM and thus are in need of medical monitoring and/or treatment (3,8).

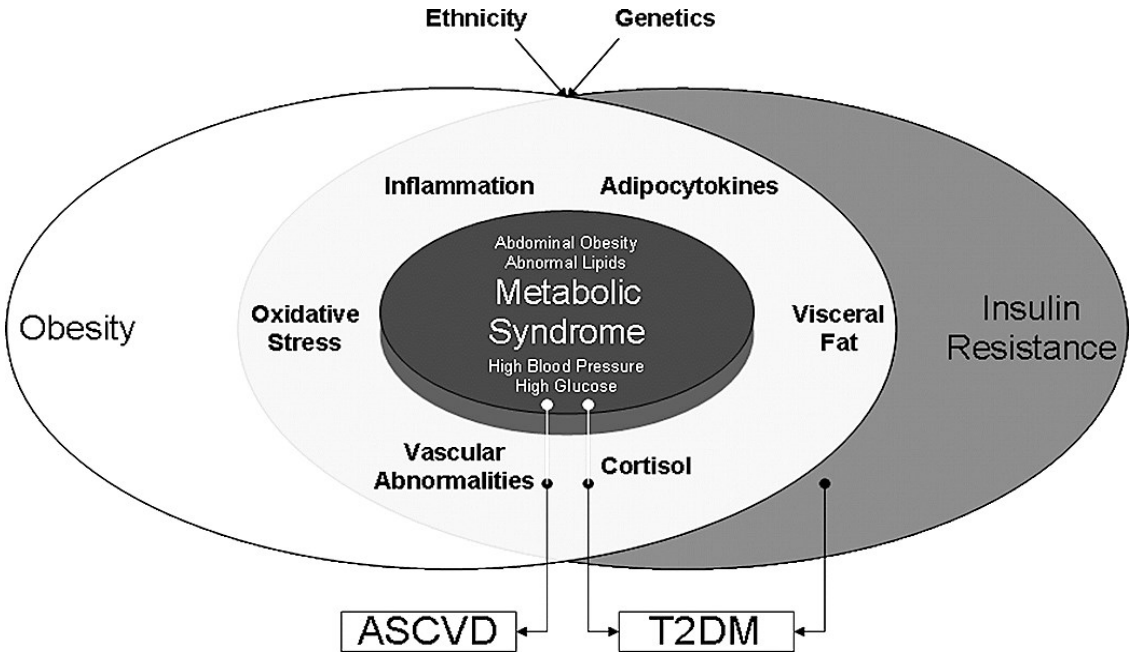

Figure 2 Pathogenic Factors Involved in the Development of Metabolic Syndrome. Obtained from Steinberger et al. (*Circulation* 2009) (11)

1.2.1.1. Obesity and Insulin Resistance

Abdominal obesity is associated with high levels of free fatty acids (FFA) that tend to accumulate within the musculature and interact with hepatic metabolism (12). In the muscle cells, FFA strain reduces the sensitivity towards insulin signaling. As a consequence, the insulin mediated glucose uptake decreases (12). This means that less glucose is removed from the circulation (12,14) and blood sugar concentrations remain elevated. The liver responds to the excess supply of glucose and FFA by enhancing lipogenesis and lipoprotein synthesis (12,15). Consequently, TG and VLDL levels rise, whereas HDL concentrations decrease. The result is dyslipidemia (12). Moreover, the FFA strain causes the liver tissue to become resistant to insulin signaling. This leads to an increase of the hepatic glucose production, so that blood glucose levels rise (12,16). The pancreas can compensate for the hyperglycemic state by enhancing insulin secretion, which results in relative hyperinsulinemia (Figure 3) (12). Since not every target tissue of insulin is affected by insulin resistance (12), hyperinsulinemia causes enhanced effects in the sensitive pathways (17,18). Consequently, insulin resistance and hyperinsulinemia lead to hypertension via stimulation of the sympathetic nervous system, renal sodium and water reabsorption and by modifying endothelial function (11,12,17,18).

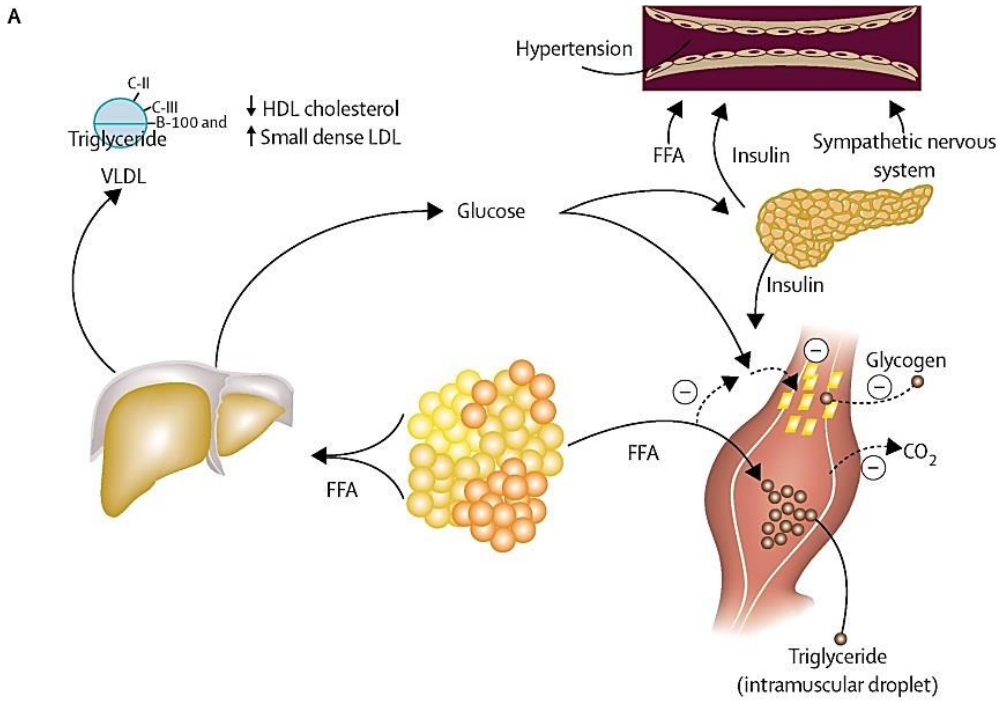

Figure 3 Pathogenesis of Insulin Resistance and Metabolic Syndrome.
Obtained from: Eckel et al. (*Lancet* 2005) (2)
Note: FFA= Free Fatty Acids; VLDL= Very Low Density Lipoproteins, LDL= Low Density Lipoproteins, HDL= High density Lipoproteins

In the following sections, the pathogenic pathways underlying insulin resistance and the associated mechanisms that lead to dyslipidemia and hypertension will be described in detail. Each component of the MetS (abdominal obesity, insulin resistance, hypertension and dyslipidemia) will be examined individually in terms of its definition, physiological and pathophysiological background. Finally, the consequences of MetS, including CVD and T2DM will be summarized.

1.3. Overweight and Obesity

1.3.1. Definition

According to the World Health Organization (WHO), overweight and obesity are defined as conditions of excessive adipose tissue that pose a significant risk to human health. In clinical practice, the nutritional status is commonly assessed by calculating the body mass index (BMI). As Figure 4 shows, the BMI formula only requires two anthropometric measurements - body weight and height (19).

$$\frac{body\ weight\ (kg)}{height\ (m)^2} = BMI\ (kg/m^2)$$

Figure 4 BMI Calculation. Adapted from: WHO 2018 (19)
Via: https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight (Date of access: 30.04.2019)

The WHO categorizes BMI into underweight, normal weight, overweight and obese (20). The categories with the corresponding BMI ranges are shown in Table 2.

Table 2 WHO Classification of Adult Nutritional Status According to BMI Range. Reproduced from: WHO 2019 (20)
Via: http://www.euro.who.int/en/health-topics/disease-prevention/nutrition/a-healthy-lifestyle/body-mass-index-bmi (Date of access: 17.09.2019)

Classification	**BMI (kg/m^2)**
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

1.3.1.1. Pediatric Definition of Overweight and Obesity

As BMI calculations do not reflect the impact of age or sex (19), childhood BMI interpretation is based on age- and sex- specific reference values, which are presented as percentiles (21). Those percentiles illustrate the general distribution of BMI values among a comparable reference population. Guidelines of the "Deutsche Adipositas Gesellschaft" (DAG) define BMI values above the 90th percentile as overweight and define obesity as BMI values above the 97th percentile (21). The WHO suggests the application of age-adjusted BMI-Z-scores to pediatric patients (19). Similar to percentiles, the interpretation of BMI-Z-scores is also based on the comparison with a reference population. The calculation of BMI-Z-scores - also referred to as standard deviation scores (SDS) - is based on the BMI distribution pattern among the reference population using the standard deviation and the median value (21). In the age group of 5 to 19 year-olds, the WHO defines overweight as "*BMI-for-age greater than one standard deviation above the reference median*" (19). "*BMI-for-age greater than two standard deviations above the median*" indicates obesity (19).

1.3.2. Physiology of Nutritional Status and Body Weight

1.3.2.1. Energy Balance and Nutritional Status

In order to ensure vital processes like body temperature, biochemical balance and organ functions, the body is in constant need of energy. The minimal required energy to maintain those vital functions at rest is defined as the "basal/resting metabolic rate". As Figure 5 shows, numerous influencing factors additionally increase the overall metabolic rate and determine the body´s energy expenditure (22).

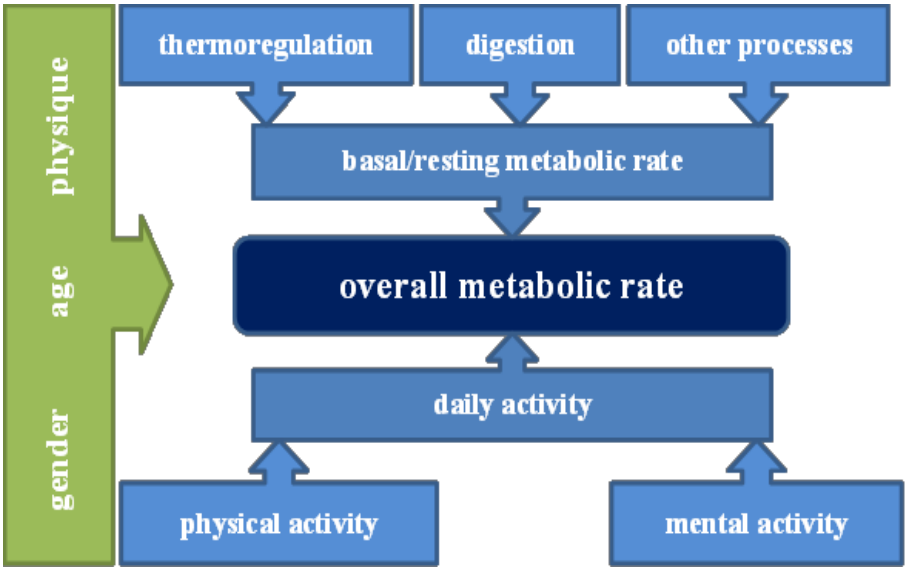

Figure 5 Factors Determining the Overall Metabolic Rate
Modified from: Die Landwirtschaftliche Sozialversicherung 2019 Available via: http://www.svlfg.de/30-praevention/prv051_fachinfos_a_z/e/03_essen_trinken_forstarbeiten/prv003302/index.html (Date of access: 30.04.2019)

The organism takes up the required energy via food consumption and metabolization of contained nutrients such as carbohydrates, proteins and fat (22). Energy balance, as shown in Figures 6 and 7, describes the relation between energy intake and energy expenditure, which in turn determines the nutritional status (23). The former depends on the quantity and quality of food intake (22), the latter depends on the metabolic rate and physical activity (22,23). If energy intake and expenditure are even, body weight remains in a stable condition. If energy intake surpasses energy expenditure, positive energy balance is reached. In this case, the body stores the energy surplus in the form of glycogen (within muscle- and liver cells) and triglycerides (within fat cells) (23). Consequently, long-term over-nutrition combined with low physical activity sustains a positive energy balance, which manifests in an increase of adipose tissue and weight gain (14,22,23). Two opposing processes - lipogenesis (fat mass is built up) and lipolysis (fat mass is mobilized) are

responsible for the dynamic adipose tissue remodeling (24). In times of energy surplus, lipids - especially triglycerides - are deposited within the adipose tissue (23). If the organism is in need of energy, lipolytic processes generate free fatty acids (FFA) by breaking down the fat storage. The degradation products are released into the blood stream and serve as energy source for several metabolic processes (24). In other words, quantitative changes in fat mass depend on the energy balance (23), whereby either lipogenesis and energy deposition or lipolysis and release of energy equivalents is induced (24).

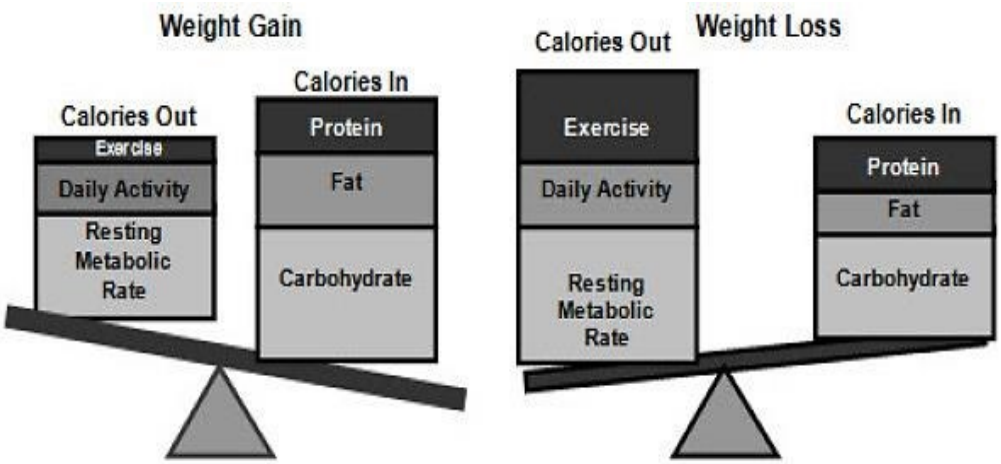

Figure 6 Illustration of Energy Balance 1
Obtained from: http://www.wellbuiltstyle.com/energy-balance-and-your-body-weight/ (Date of access: 30.04.2019)

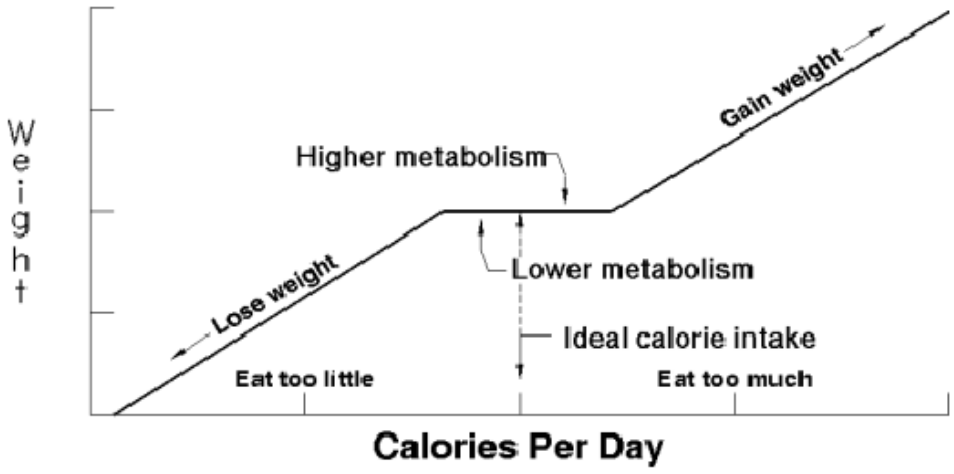

Figure 7 Illustration of Energy Balance 2
Modified from: https://www.fourmilab.ch/hackdiet/e4/feedback.html (Date of access: 08.09.2019)

1.3.2.2. Regulation of Food Intake

Depending on the current energy requirement, the body regulates energy intake via endocrine and neuronal pathways (23). Some of these pathways act during food intake, while others have long-term effects on maintaining body weight. In both cases, the central nervous system takes over the mediatory role between the current nutritional status (input) and maintaining a balanced energy state (output) (23,25). Peripheral tissues send endocrine signals to the hypothalamus and thereby provide information whether food is currently consumed or food intake is required. As a response, the hypothalamus coordinates energy intake and expenditure by stimulating the vegetative nervous system and endocrine glands (23). For instance, gastrointestinal hormones including ghrelin, cholecystokinin (CCK) and insulin are secreted during the digestive process and suppress appetite right away (25). Besides this, stomach filling and gastric wall expansion also induce an immediate feedback signal with appetite-suppressing effects (23,25). In order to regulate energy balance on the long term, the adipose tissue secretes a hormone called “leptin”. The plasma concentrations of leptin proportionally increase with the amount of adipose tissue. In this way, the central nervous system is constantly informed about the current proportions of body fat. If leptin levels are high, hypothalamic signals stimulate energy-consuming processes and suppress energy intake. Conversely, decreasing fat tissue goes along with low levels of leptin, which stimulate energy intake and diminish energy expenditure. In other words, the leptin-feedback loop is a self-regulating mechanism of the adipose tissue, intended to stabilize body fat content on the long term (23,25).

1.3.2.3. Types of Adipose Tissue

Lipid storing cells, the so-called adipocytes, make up the majority of the adipose tissue. There are two types of fatty tissue that differ in terms of the morphology and metabolic properties. The white adipose tissue (WAT) and the brown adipose tissue (BAT). WAT accounts for most of the body´s adipose tissue and is deeply involved in weight gain and weight loss processes. Its adipocytes typically contain a single lipid vacuole (unilocular) that represents the actual energy reservoir. The main functions of WAT are energy storage, organ protection and thermal isolation. In order to meet those requirements, WAT spreads over several anatomic regions: Subcutaneous fat prevents heat loss, while visceral fat protects the abdominal and thoracic organs against mechanical stress. Both, subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT) are the body´s main means of

storing excess energy (24). Brown fat cells differ from the white type in that they are smaller and contain multiple vacuoles (multilocular) as well as a higher number of mitochondria. The main purpose of BAT is to generate body heat via metabolizing lipids. In infants, this mechanism is essential for thermal regulation. With increasing age, alternative processes take over temperature control and the quantity of BAT decreases (24). With this in mind, the following sections will only concentrate on WAT as it determines overweight and obesity.

1.3.3. Pathological Aspects of Body Fat Distribution

Individual factors like age, gender, genetics, ethnicity, hormones, nutrition and physical activity determine the topography of body fat. Precisely, these factors affect the tendency and capacity of both, SAT and VAT, to store lipids (26). There are two widely recognized types of body fat distribution - the “android” and the “gynoid” type (compare with Figure 8). Abdominally accentuated fat deposition - called “android” or “apple-shaped” - is predominately found among males. In terms of weight gain, individuals of the android distribution type will preferably build up fat deposits around visceral organs (VAT) and in the abdominal subcutis. In contrast, the “gynoid” or “pear-shaped” distribution pattern shows higher amounts of subcutaneous fat, especially in the hip and gluteo-femoral region.

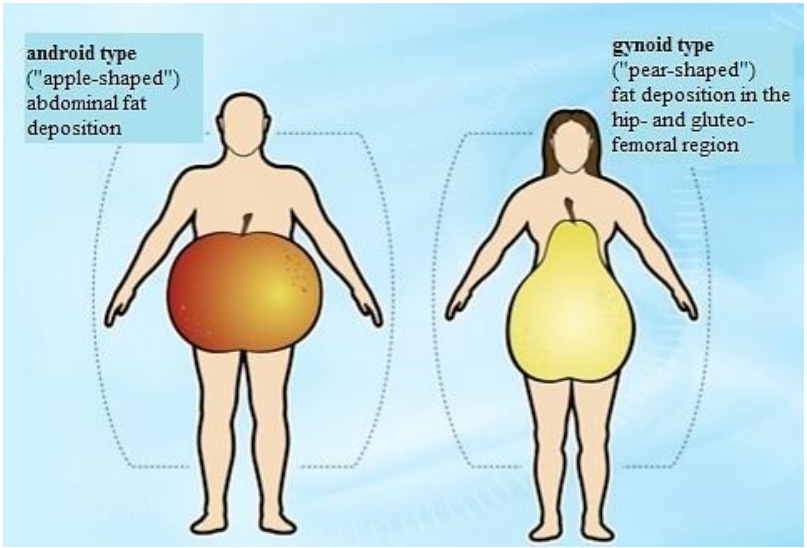

Figure 8 Android and Gynoid Type of Body Fat Distribution
Modified from: http://www.myhealthywaist.org/the-concept-of-cmr/intra-abdominal-adipose-tissue-the-culprit/causes-and-correlates-of-intra-abdominal-obesity/gender-differences/print.html?printebook=true&cHash=5205fa63b2
(Date of access: 08.09.2019)

This distribution pattern reflects the typical female body shape (27). With regard to the cardio-metabolic risk, the android type of bod fat distribution is considered less favorable than the gynoid type (28). Excessive VAT is associated with increased risk for developing cardiovascular disorders and metabolic diseases, independent of the total amount of body fat. These include, amongst others, insulin resistance, atherogenic dyslipidemia, hypertension, CVD, sleep apnea and different types of cancer (26). On the other hand, SAT and gynoid fat distribution have lower impact on the health status (28). For this reason, body fat distribution became an essential parameter in evaluating overweight-related health risk (27,28).

1.3.3.1. Assessment of Body Fat Distribution

Body composition is a central part of nutrition and obesity research. It is assumed that the assessment of body fat distribution allows a more precise estimation of obesity-related health risk than bodyweight or BMI (26). Until today, a wide range of diagnostic tools has been developed to investigate the quantities of both fat mass and fat-free mass. These include medical imaging (magnetic resonance imaging, and computed tomography), physical methods (bio-impedance measurement and plethysmography) as well as simple anthropometric measurements. Since most of them are either too expensive, time consuming or impractical for clinical purposes, anthropometric measurements are still the most commonly used (26,29). Among these, waist circumference (WC) measurement is generally recommended for approximately estimating VAT volume (12,25).

1.3.3.2. Waist Circumference Measurement

During the measurement procedure, the patient should be lightly clothed and in a standing position. The measuring tape is placed in the middle between the lowest rib and the iliac crest. Waist circumference is measured at the end of exhalation (30). Values between 75 and 80 cm for females and between 90 and 95 cm for males are considered within the normal/physiological range (25). Measurements above this range are associated with an elevated risk for future cardiovascular and metabolic diseases (27,30,31). Increased WC may again be divided into two risk-categories: WC values equal or greater than 80 cm for women and 94 cm for men are associated with an increased cardio-metabolic risk, while measurements exceeding 88 cm for women and 102 cm for men, respectively, are associated with substantially high risk for cardio-metabolic abnormalities (30,31). The

latter category is referred to as "abdominal obesity" (31). Furthermore, ethnic-specific cut-off values (as shown in Table 3) have been introduced to account for the genetic differences of body fat distribution patterns (32).

Table 3 Ethnic-specific Thresholds of Waist Circumference. Modified from Alberti et al. (*Circulation* 2009)(1)

Ethnic group	**Waist circumference (central obesity)**	
	Women	Men
Europids, increased risk	≥80 cm	≥94 cm
Europids, substantially increased risk	≥88 cm	≥102 cm
United States	≥88 cm	≥102 cm
Asian	≥80 cm	≥90 cm
Ethnic Central and South American	≥80 cm	≥90 cm
Sub-Saharan African	≥80 cm	≥94 cm
Middle East, Mediterranean	≥80 cm	≥94 cm

Similar to BMI, pediatric WC evaluation demands age- and sex- specific criteria as well. For this reason, WC data obtained from specific reference populations is used to define age- and sex- specific risk-thresholds (33). Besides this, the International Diabetes Federation (IDF) suggests incorporating ethnicity factors in the pediatric assessment as well, meaning that WC should be interpreted by using age-, sex- and ethnicity- specific percentiles (33,34).

1.3.4. Contributing Factors and Global Expansion of Obesity

Regarding the etiological aspect, obesity is divided into two main categories. Primary obesity, which accounts for 95% of cases, includes genetic disposition and syndromes, lifestyle factors and psychological burden. Secondary obesity covers endocrine disorders such as hypercortisolemia and hypothyreoidism as well as neurological dysfunctions. It makes up for the remaining 5% of cases (27). Obesity gains high attention from public health policy as it affects a growing number of people (3). During the past decades, the world population has undergone significant changes in health- and eating behavior and lifestyle, which is attributed to the industrial development and growing urbanization (35–37). These changes are seen in the increasing consumption of high-calorie food and sugary beverages as well as more sedentary behavior and severe lack of physical exercise (36,38,39). One major cause of obesity that has become more prominent in the

recent past is the time people spend in front of TV screens, computers, tablets and smartphones (40). As a consequence, the global prevalence of overweight and obesity has continuously been growing and has now reached epidemic proportions (19,41–44). Epidemiological data of the past forty years (1975-2016) confirm a worldwide trend towards increasing BMI values, also among the young population (45). Statistical data provided by the Organization for Economic Co-operation and Development (OECD) indicate that the worldwide prevalence of overweight and obesity amounts to 54% and 19%, respectively (46). As for the young population, overweight and obesity have been increasing as well (see Figure 9). The combined prevalence reached from 15% in Norway to a maximum of 45% in Chile (compare with Figure 10) (46). In general, a quarter of the pediatric population is considered to be overweight or obese (46).

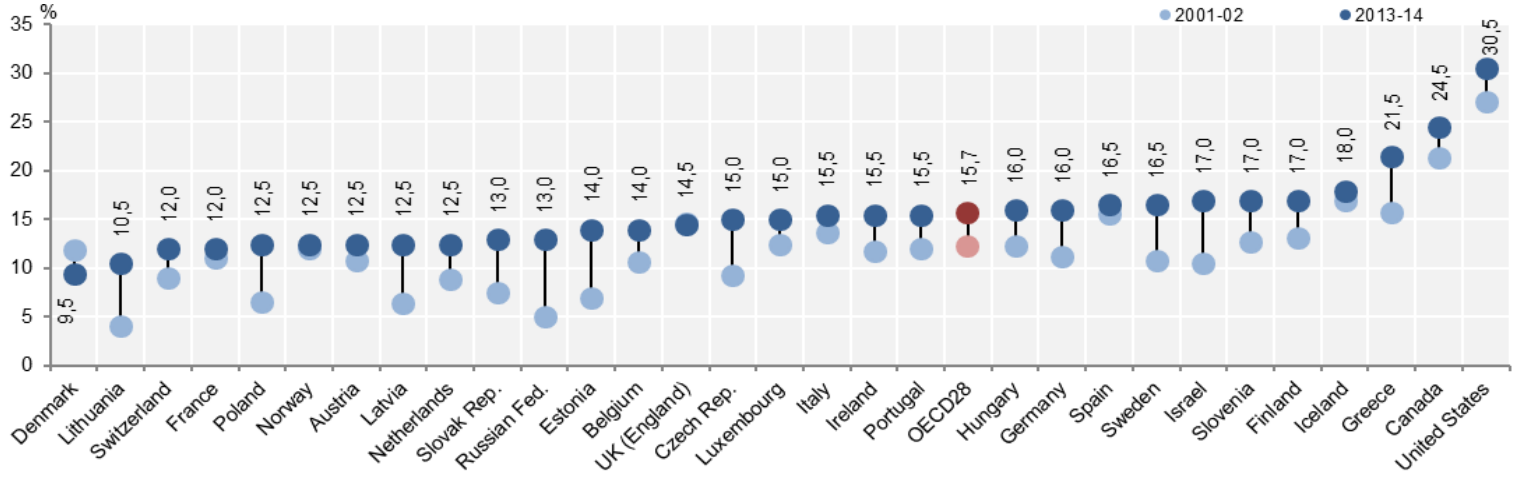

Figure 9 Changes in the Prevalence of Overweight and Obesity between 2001-02 and 2013-14 among 15-year-olds.
Obtained from: OECD (*Health at a glance* 2017) (46)

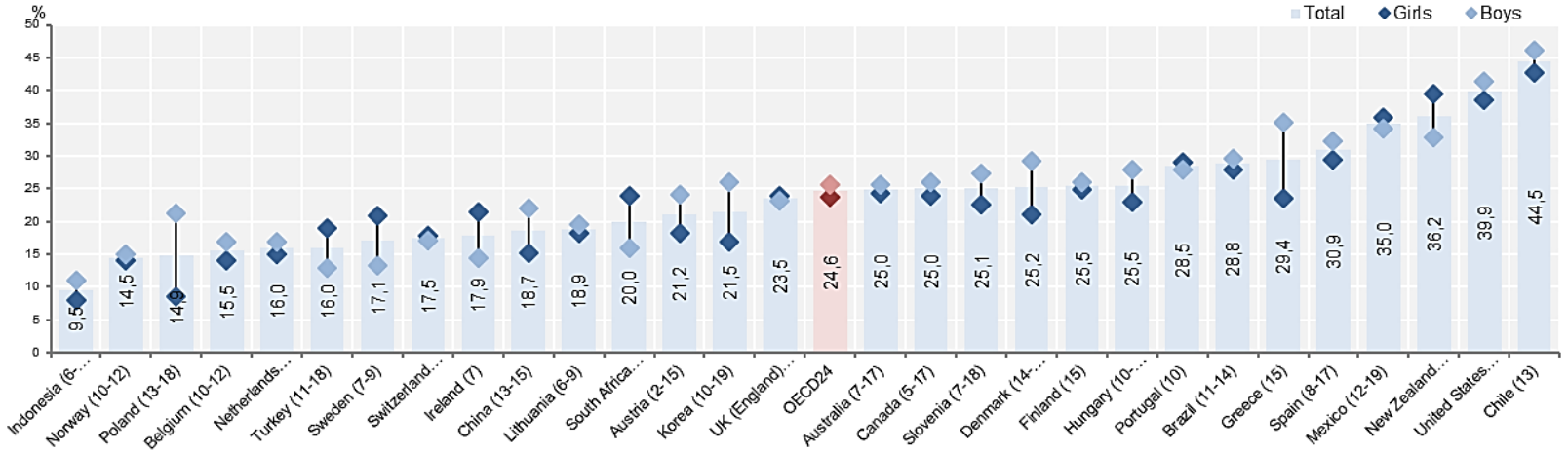

Figure 10 Combined Prevalence of Overweight and Obesity among Children and Adolescents. Obtained from: OECD (*Health at a glance* 2017) (46)
Note: The age ranges of the study cohorts are shown in parentheses.

1.4. Insulin Resistance

1.4.1. Definition

Insulin resistance describes a metabolic state in which higher-than-normal levels of insulin are needed to maintain physiological glucose concentrations. The pancreatic insulin synthesis and secretion rates rise, which in turn appears as hyperinsulinemia (17).

1.4.2. Physiological Background of Glucose Homeostasis

The pancreatic hormone insulin plays an essential role in the management of blood glucose homeostasis (23). Elevation of blood sugar (postprandial) is the main stimulus for pancreatic β-cells to secrete insulin into the blood (22). Insulin is responsible for removing excess sugar from the circulation and counterbalancing a hyperglycemic state via two mechanisms: Firstly, by stimulating the cellular glucose uptake and secondly, by promoting glucose-consuming metabolic processes, whereas glucose-generating processes are inhibited (14,22,23). Insulin-regulated glucose uptake mainly takes place in cells of the skeletal muscle (myocytes) and, for a smaller part, in adipocytes. There, insulin binds to specific receptors. The formation of the insulin-receptor-complex sets off an intracellular cascade, which in turn stimulates the translocation and integration of GLUT-4 (glucose transporter type 4) into the cell membrane. GLUT-4 molecules are transporting proteins that facilitate glucose diffusion into the cells (14). Thus, glucose molecules can easily move along the concentration gradient into the cytoplasm an enter the metabolic pathways (14). Insulin mediated glucose uptake is considered the most effective mechanism of lowering postprandial blood-sugar levels (47).

1.4.3. Effects of Insulin on Cellular Metabolism

Insulin can be defined as the most important anabolic hormone of the human organism (14). Anabolism is characterized by the predomination of synthesis processes, whereas degradation processes - which characterize catabolism - are suppressed (22). As Figure 11 shows, insulin-mediated anabolic processes aim to build up carbohydrates, lipids and proteins, which either serve as substrate/energy reservoir or are needed for cell development, differentiation and growth (22). During anabolic states, insulin causes the muscle cells to transform glucose molecules into glycogen, which is the intracellular

storage form of carbohydrates (23). Besides this, insulin signaling enhances the myocellular influx of amino acids and promotes protein synthesis (23).

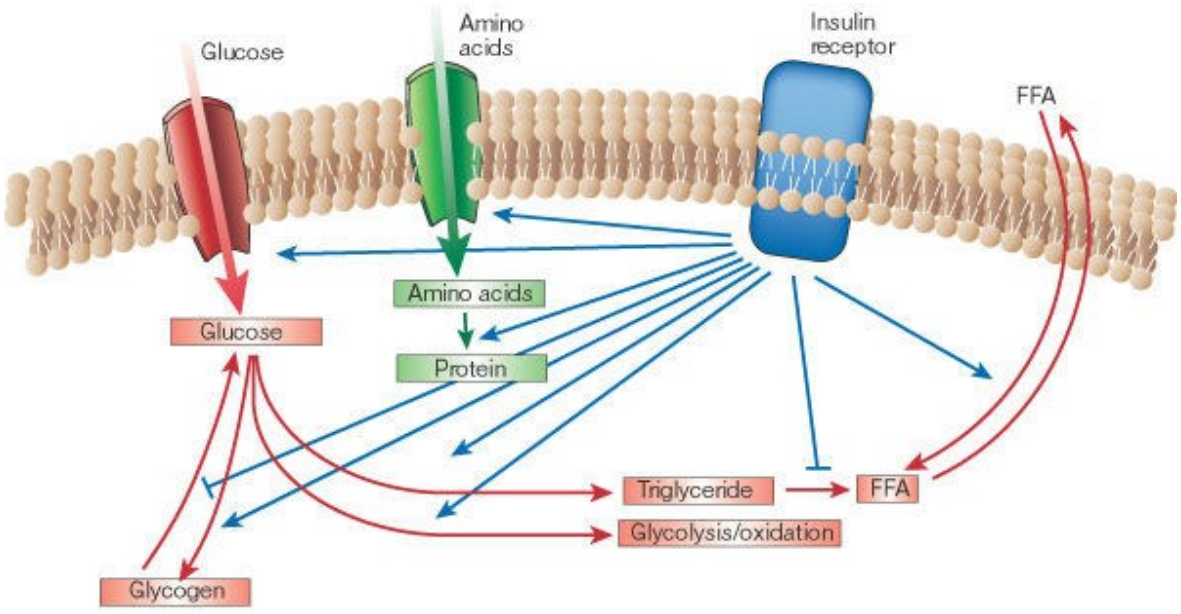

Figure 11 Anabolic Effects of Insulin on the Cellular Metabolism.
Obtained from Saltiel et al. (*Nature* 2001) (47)

In adipose tissue, insulin stimulates triglyceride/lipid synthesis (lipogenesis) via three different mechanisms. Firstly, it promotes the expression and activation of certain lipogenic enzymes. Secondly, it provides FFAs and glucose molecules, both serving as basic material for lipid synthesis. Finally, insulin suppresses lipolytic processes in fat cells mainly by inhibiting the lipolytic enzyme "hormone sensitive lipase" (47).

Insulin has significant impact on the hepatocellular metabolism: As is the case with muscle cells, anabolic glycogen synthesis is enhanced, whereas catabolic, glucose-generating processes like glycogenolysis and gluconeogenesis are suppressed (14). Shutting down hepatic glucose production is an essential anti-hyperglycemic measure (14), which typically becomes dysfunctional in the course of IR and T2DM (12). As is the case with adipose tissue, insulin also promotes lipogenesis in liver cells by stimulating the FFA-synthesis and diminishing FFA-degradation (14). Table 4 and Figure 12 provide an overview of the tissue specific responses towards insulin signaling.

Table 4 Physiological Effects of Insulin in the Skeletal Muscle, Adipose Tissue and Liver Tissue
Adapted from Heinrich et al. (*Biochemie und Pathobiochemie* 2014) (14)
Note: "+" symbolizes stimulating effect; "-"symbolizes inhibiting effect.

Metabolism	Skeletal muscle	Adipose tissue	Liver
Glucose uptake	+	+	
Glycolysis	(+)	+	+
Glycogen synthesis	+		+
Glycogenolysis			-
Gluconeogenesis			-
Lipogenesis		+	+
Lipolysis		-	
Uptake of amino acids	+		
Protein synthesis	+		

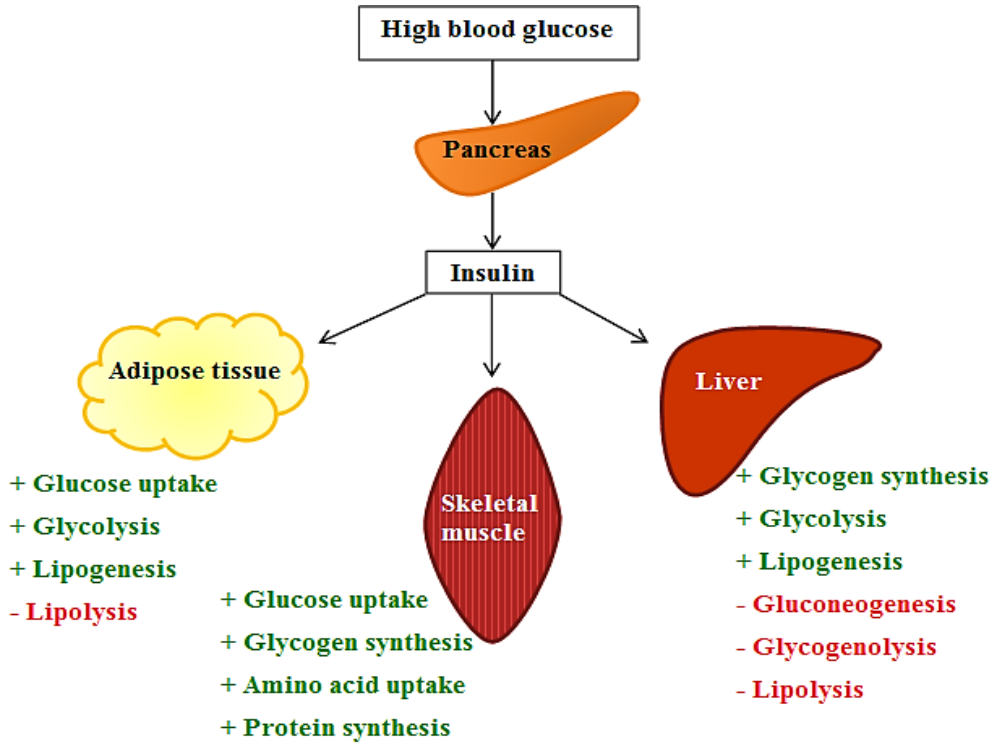

Figure 12 Anabolic Effects of Insulin in the Main Target Tissues.
Adapted from Heinrich et al. (*Biochemie und Pathobiochemie* 2014) (14)
Note: stimulating effects are marked green; inhibiting effects are marked red.

1.4.4. Pathogenesis of Insulin Resistance

The term “Insulin Resistance” (IR) describes a metabolic state, in which normal levels of insulin no longer achieve physiological effects. Instead, insulin concentrations need to rise (17). The underlying mechanisms behind IR are still not completely understood. However, epidemiological studies could demonstrate, that overweight and obesity show a strong causal relationship with the appearance of IR (48). In this context, three obesity-related pathomechanisms are often mentioned (14,26,48): High levels of circulating FFAs, ectopic fat accumulation as well as the endocrine and inflammatory activity of the adipose tissue (14). It is supposed that these mechanisms disturb the intracellular signaling cascade and diminish the effects of insulin, which means that the underlying defect of IR is located on the post-receptor level (14,27).

1.4.4.1. High Levels of Circulating Free Fatty Acids

As mentioned before, android type of body fat distribution - also referred to as “abdominal obesity” - is considered a cardio-metabolic risk factor (26,27,49). In particular, excess amounts of visceral adipose tissue are closely related to the development of IR, T2DM and CVD (12). One underlying cause of this relation might be the fact that abdominal adipose tissue releases high amounts of FFAs into the circulation (49). Indeed, VAT is more sensitive towards lipolytic effects of catecholamines than SAT and thus shows higher lipolytic activity (14). In addition, the sensitivity towards insulin-mediated inhibition of lipolysis was found to be lower in VAT and abdominal SAT, especially in terms of insulin resistance. Such loss of inhibition results in higher lipolytic activity, which further increases the FFA flux (12,28). FFAs distribute within the systemic and splanchnic circulation and reach the liver and muscle cells (12,28). There, the lipid overload interacts with the glucose metabolism and decreases the sensitivity towards insulin signaling (12,14,15).

1.4.4.2. Ectopic Lipid Accumulation

Ectopic lipid accumulation results from two obesity related conditions: First, over-nutrition putting strain on the cellular metabolism (28) and second, adipose tissue becoming unable to store further lipids (also referred to as adipose failure) (shown in Figure 13) (48). Energy surplus (energy intake > energy expenditure) is normally deposited in the form of

triglycerides within the adipose tissue. However, if the storage capacity becomes saturated and/or dysfunctional, further energy surplus alternatively accumulates within non-adipose tissues. This kind of lipid deposition - also referred to as “ectopic fat” - is predominately located in the skeletal muscle, liver, heart, pancreas and kidneys (28,48). These intracellular lipids adversely modify cellular functions (lipotoxicity) (14), thereby causing a decrease in insulin sensitivity, secretory malfunctions and cell death (48). In other words, the capacities of the adipose tissue to store caloric surplus in the form of TG protects the non-adipose tissue against ectopic lipid accumulation. Saturation or malfunction of these storage sites is believed to determine the manifestation of IR and MetS (28).

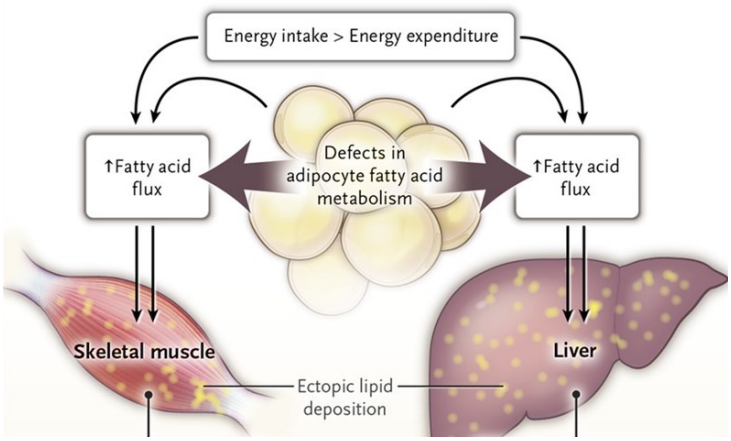

Figure 13 Mechanisms Leading to Ectopic Lipid Accumulation in Muscle and Liver. Obtained from: Shulman et al. (*New England Journal of Medicine* 2014) (15)

1.4.4.3. Endocrine and Inflammatory Activity of the Adipose Tissue

The adipose tissue secretes inflammatory factors and hormones that are summarized under the term “adipocytokines”. These include, amongst others, adiponectin, leptin, tumor necrosis factor alpha (TNF-α) and certain types of interleukins. Disorders in the secretory activity were found to be involved in the pathogenesis of IR and MetS (compare with Figure 14) (14). In the course of weight gain and expanding fat mass, macrophages immigrate into the adipose tissue. There, they promote the secretion of pro-inflammatory cytokines like TNF-α and interleukins 1, 6 and 18 (IL-1, IL-6, IL-18). These cytokines induce inflammation, contribute to insulin resistance and stimulate lipolysis, which in turn increases the amounts of circulating FFAs and thus further exacerbates IR (12).

The hormone adiponectin is exclusively produced by the adipose tissue and has numerous protective effects on cardio-metabolic health (9). These include anti-inflammatory and antiatherogenic effects, regulation of the glucose- and lipid metabolism as well as an improvement of insulin sensitivity in skeletal muscle cells and in the liver tissue (9,12,14). In individuals with MetS, adiponectin levels are often found to be decreased (12), which means its beneficial effects on insulin sensitivity and on the overall cardiovascular health fade out.

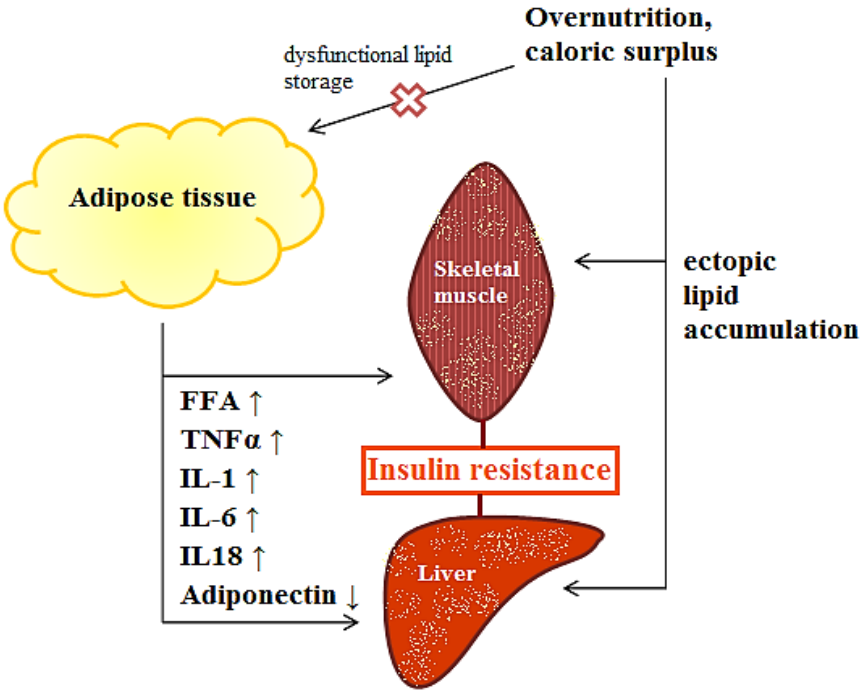

Figure 14 Pathophysiologic Mechanisms that Cause Development of Insulin Resistance in the Skeletal Muscle and Liver. Expanding (visceral) fat mass releases high amounts of FFAs into the circulation. The secretion of inflammatory markers like TNF-α and different types of interleukins is increased, whereas the adiponectin secretion is diminished. If adipose tissue becomes dysfunctional in storing lipids adequately, triglycerides accumulate within ectopic sites like skeletal muscle and liver. Ectopic lipid accumulation further disturbs the cellular metabolism (lipotoxicity). Consequently, the musculature and liver tissue become resistant to insulin.

1.4.5. Progression of Insulin Resistance

Insulin resistance primarily manifests in target tissues like skeletal muscle, liver and adipose tissue. In myocytes and adipocytes, cellular glucose uptake becomes insufficient (17) and the metabolic utilization of glucose decreases (12). In insulin resistant hepatocytes, inhibition of hepatic gluconeogenesis is dysfunctional. Consequently, hepatic glucose production further drives the development of hyperglycemia (12). Taken together, insulin resistance of both musculature and liver tissue, cause blood sugar levels to rise (12).

In order to prevent hyperglycemia and maintain normal blood sugar levels, higher insulin concentrations are required. In the initial phase of insulin resistance, the pancreas compensates the dysfunctional glucose metabolism by increasing the insulin secretion, which in turn results in hyperinsulinemia (see Figure 15) (12).

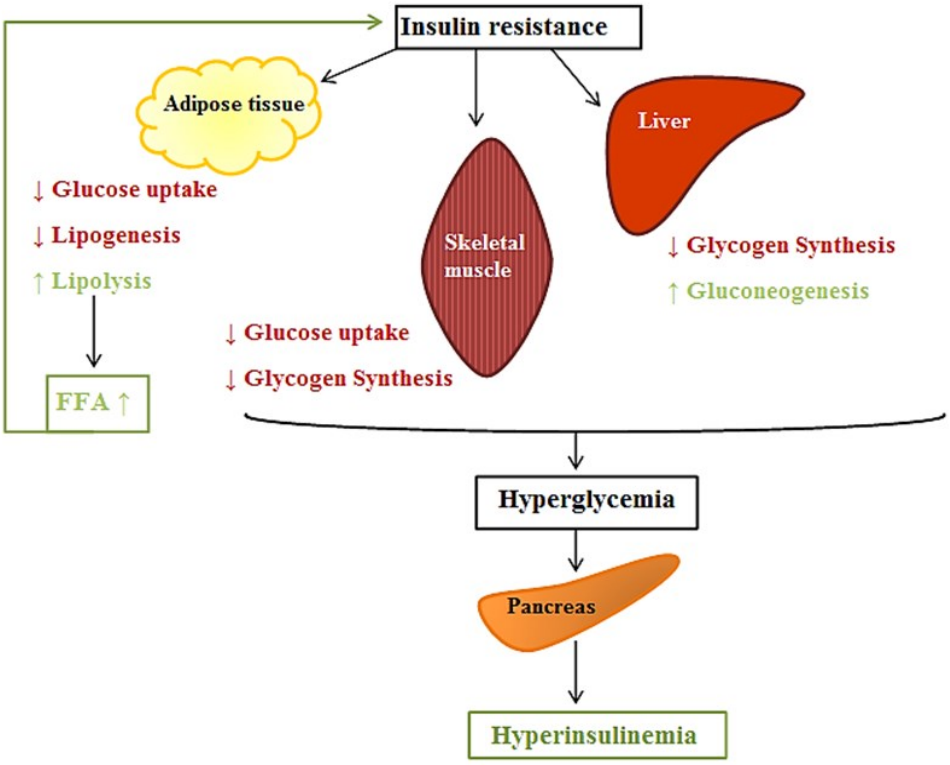

Figure 15 Progression of Insulin Resistance and Tissue-specific Alterations in the Cellular Metabolism.
The impairment of insulin-mediated glucose uptake and the non-inhibition of hepatic glucose production induce hyperglycemia. This in turn stimulates pancreatic insulin release and results in hyperinsulinemia.
Adapted from Heinrich et al. (*Biochemie und Pathobiochemie* 2014) (14)

1.5. Hypertension

1.5.1. Definition

Hypertension is diagnosed when the systolic blood pressure is higher than 140 mmHg and/or the diastolic value exceeds 90 mmHg. At this point, blood pressure lowering measures are indicated (27). In children and adolescents, blood pressure is evaluated by using age, gender and height specific percentiles. Hypertension is defined as systolic and/or diastolic blood pressure values above the 95th percentile. Values between the 90th and 95th percentile are referred to as “prehypertension” (12).

In clinical practice, hypertension is divided into a primary type and a secondary type. Primary hypertension – or idiopathic hypertension – accounts for 90% of cases. For this category, it is not possible to identify one definite cause behind the elevated blood pressure. Among others, genetic predisposition and environmental conditions are thought to initiate the pathogenesis. Contributory factors are nutritional and metabolic status (overweight and obesity, insulin resistance, high consumption of alcohol and table salt), stress, smoking, high age, lack of physical exercise, low socio-economic status and low intake of calcium and potassium (27). Secondary hypertension makes up the remaining 10% of cases. It covers different diseases, in which hypertension occurs as a complication or consequence. The pathophysiological mechanism behind secondary hypertension can clearly be determined (12,27).

1.5.2. Physiology of Arterial Blood Pressure

Blood pressure can be understood as the essential prerequisite of blood flow (22). The highest pressure is reached during the systole of the cardiac cycle and is called "systolic blood pressure". It should normally be about 120 mmHg. At the end of the diastole, the blood pressure falls to its minimum of 80 mmHg - also referred to as "diastolic blood pressure" (22). The arterial blood pressure is determined by two main factors that are demonstrated in Figure 16: The cardiac output, which describes the blood volume (stroke volume) being pumped by the heart per minute, and the total peripheral resistance (TPR), which depends on the diameter of the vascular lumen (vasoconstriction vs. vasodilatation) and the constitution of the vessel wall (12). Both, an increase in the stroke volume and/or

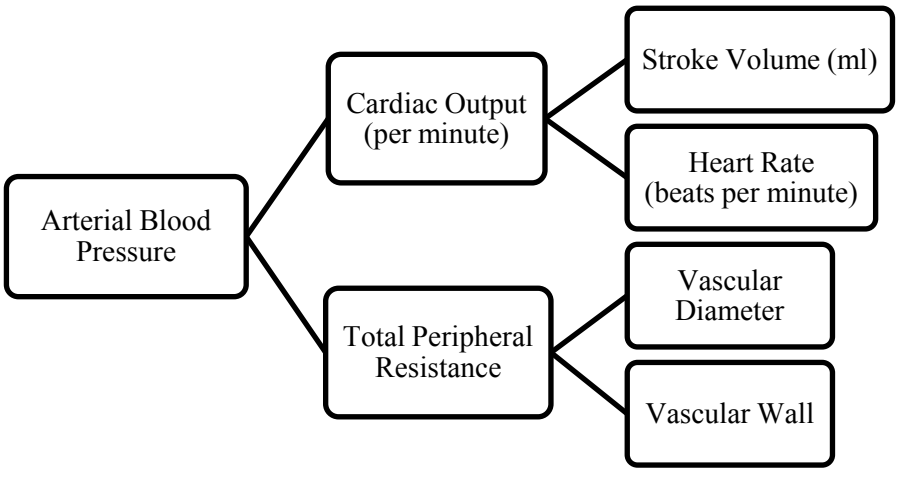

Figure 16 Determinants of Arterial Blood Pressure.
Adapted from: Suttorp et al (*Harrisons Innere Medizin*, 2016) (12)

an increase in the TPR (for example due to a decrease of the vessel diameter) raise the blood pressure (23,27).

1.5.3. Pathophysiology of Hypertension

The body has several options for modifying blood pressure and ensuring adequate blood flow. These options involve, amongst others, the intravascular blood volume, the autonomic nervous system, the renin-angiotensin-aldosterone-system (RAAS) and the vasculature itself (12). An increase in the extracellular volume - for example due to elevated sodium ingestion - causes an increase in the cardiac output. Accordingly, the intravascular volume and the systemic blood pressure increase as well (12). The sympathetic nervous system, on the other hand, immediately reacts to hemodynamic changes (e.g. changes in blood pressure, volume and biochemistry) by adapting the vascular diameter. Such reflexes are mediated via catecholamine signaling and are necessary to maintain continuous blood flow (12). Norepinephrine primarily mediates vasoconstriction, whereas epinephrine also mediates vasodilation (22). Long-term elevation of the sympathetic tone results in a constant elevation of blood pressure. This phenomenon is commonly observed in hypertensive patients and especially among those with obesity-related hypertension (12). The RAAS, on the other hand, is responsible for regulating blood pressure in the long-term. Its two main target points are the total blood volume and the vessel diameter. RAAS functions via a complex system of hormones, in particular renin and aldosterone, and enzymes such as angiotensin II. Angiotensin II stimulates aldosterone synthesis and acts as growth factor in cardiomyocytes and vascular smooth muscle cells. It is also a potent vasoconstrictor. Excessive levels of angiotensin II contribute to atherogenesis and hypertrophic cardiomyopathy. The mineralocorticoid aldosterone stimulates the renal reabsorption of sodium and water. Thereby, renal elimination rate is diminished and the total blood volume rises. As with angiotensin II, aldosterone is also under suspicion of causing structural and functional modifications in the vascular system (12).

Besides the vascular diameter and total peripheral resistance (TPR), blood pressure also depends on the “compliance” of the vessel wall, which can be described as elasticity. The elasticity enables the vasculature to compensate for any increase of the intravascular volume and stabilize the blood pressure on adequate levels. If the compliance decreases, additional intravascular blood volume inevitably results in an increase of the blood

pressure. This is a typical finding in patients with atherosclerosis. Due to atherosclerotic remodeling processes, the compliance decreases, meaning that the vessel wall becomes more rigid. Such arterial stiffness primarily manifests in elevated systolic values, while the diastolic values remain normal. Furthermore, atherosclerosis comes along with vessel wall thickening and narrowing of the luminal diameter, which further increase the TPR (12).

1.5.4. Insulin Resistance and Hypertension in Metabolic Syndrome

IR and accompanying hyperinsulinemia are assumed to promote the development of hypertension by increasing the intravascular volume, decreasing the diameter of the vascular lumen and modifying the elasticity of the vessel wall (12). The rationale behind this theory is the fact that IR does not equally affect each signaling pathway (12). In those target tissues, where the signaling pathways remain sensitive to insulin, hyperinsulinemia causes an exaggerated response (12). Regarding the pathogenesis of hypertension, three insulin-related mechanisms are frequently mentioned: renal sodium and water reabsorption, elevation of sympathetic tone and endothelial regulation of the vascular diameter.

In the kidneys, insulin mediated stimulation of renal sodium reabsorption remains sensitive, so hyperinsulinemia further enhances this effect. Since the reabsorption of sodium is linked with the water reabsorption, the intravascular volume increases (12,17). Regarding the sympathetic nervous system, insulin-signaling pathways remain sensitive as well. Thus, chronic hyperinsulinemia is accompanied by an elevation of the sympathetic tone, which in turn causes vasoconstriction and an increase of TPR (12,18). In the vascular endothelium, insulin normally regulates nitric oxide (NO) and endothelin-I secretion (11). In terms of insulin resistance, the vasodilatative effect of insulin - mediated via NO release - becomes dysfunctional (11,12). Consequently, vasoconstrictive signals - mediated via endothelin I - dominate and cause a decrease in vessel diameter (12).

Besides this, insulin normally stimulates growth and differentiation processes in the vasculature. Since insulin resistance does not affect these mechanisms, it is assumed that hyperinsulinemia promotes vascular wall remodeling, contributes to atherogenic changes and increases the blood pressure (12).

However, to what extent IR and hyperinsulinemia actually contribute to hypertension in patients with MetS remains debated (12).

1.5.5. Consequences of Hypertension

Systolic blood pressure exceeding 120 mmHg and/or diastolic blood pressure exceeding 80 mmHg is associated with an increase in cardiovascular risk (12). The consequences of long-term hypertension primarily address the vasculature, the heart and the kidneys. It is considered an independent risk factor for cardiac insufficiency, coronary heart disease, stroke, renal diseases and peripheral artery disease (12).

1.6. Dyslipidemia

1.6.1. Definition

Disorders in the metabolism of lipoproteins, which are characterized by abnormal levels of plasma cholesterol and/or triglycerides, are generally referred to as "dyslipidemia" (12). Since such conditions are known to evoke atherosclerotic changes and CVD, evaluation of blood lipid levels became a routine part of clinical practice (12).

1.6.2. Physiology of Lipoprotein Metabolism

Due to their hydrophobic properties, lipid molecules are poorly soluble in aqueous media like blood. Accordingly, they need to bind to specific transport proteins – the so-called "lipoproteins" (14). These molecule complexes circulate within the blood stream in order to supply peripheral tissues with lipids (23). Lipoproteins consist of a hydrophobic core containing triglycerides and cholesterol-ester and a hydrophilic shell containing cholesterol and phospholipids (12). Depending on their composition and density, lipoproteins are divided into five different types: Chylomicrons, very-low-density lipoproteins (VLDL), intermediate-density lipoproteins (IDL), low-density lipoproteins (LDL) and high-density lipoproteins (HDL). Each of them takes over a particular task of the lipid transporting system (compare with Table 5) (23).

1.6.2.1. Triglyceride-rich Lipoproteins

Chylomicrons and VLDL are responsible for delivering TG to the periphery, in particular to the adipose tissue and the musculature. Chylomicrons receive exogenous/ingested TG from the intestine, while VLDL takes up endogenous TG from the liver (14). In the

periphery, the capillary enzyme lipoproteinlipase (LPL) hydrolyzes TG into fatty acids and glycerides. This way, the myocytes and adipocytes can absorb the fatty acids and either use them as immediate energy substrate (e.g. for muscular activity) or deposit them in the adipose tissue (23).

1.6.2.2. Cholesterol-rich Lipoproteins

Cholesterol fulfils multiple functions: It is an important component of the cellular membrane and acts as an essential precursor for the synthesis of bile acid and steroid hormones. Besides its vital role, cholesterol gained increasing importance in medical practice, as it is known to contribute to atherosclerotic changes (23). LDL and HDL are responsible for carrying and distributing the cholesterol molecules throughout the organism. LDL submits its cholesterol load to the peripheral tissue via binding to specific cell surface receptors. This way, the lipoprotein complex is internalized into the cytoplasm and cholesterol can be used in further intracellular processes. HDL conducts the reverse cholesterol transport by removing excessive cholesterol from peripheral tissues and carrying it to the liver. In the hepatocytes, cholesterol is converted into bile acid, which in turn is excreted into the intestinal tract (14). Interestingly, this process is the only notable way how cholesterol is eliminated (14) and thus plays a crucial role in maintaining adequate concentrations (27). Table 5 provides an overview of the properties and functions of lipoproteins.

Table 5 Characteristics and Functions of Different Types of Lipoproteins, Sorted by Increasing Density. Modified from Herold et al. *(Innere Medizin* 2018) (27) and Pape et al. (*Physiologie* 2014) (23)

Lipoproteins	**Composition (%)**		**Functions**
	Cholesterol	**Triglycerides**	
Chylomicrons	1-3	84-89	Absorption and transport of ingested TG into the periphery
VLDL	5-10	50-65	Transport of endogenous TG Precursor of and LDL
LDL	7-10	7-10	Transport of cholesterol and cholesterol-ester into the periphery Regulation of cholesterol homeostasis
HDL	3-4	3-5	Transport of cholesterol-ester to the liver Regulation of cholesterol homeostasis Lipolysis

1.6.3. Pathophysiology of Dyslipoproteinemia

Dyslipidemia (syn.: Dyslipoproteinemia) is characterized by abnormal levels of serum lipids including triglycerides (hypertriglyceridemia) and cholesterol (hypercholesterolemia). According to etiological aspects, dyslipidemia can be divided into three types: primary, secondary and reactive-physiological dyslipidemia (27). The primary/ hereditary type is based on genetic alterations and occurs cumulatively within families. In the this type, hypercholesterinemia and/or hypertriglyceridemia might already become manifest in youth and is associated with increased risk for coronary heart diseases and early-onset cardiovascular damage (27). The secondary type of dyslipidemia develops in the course of metabolic derangements such as diabetes mellitus, metabolic syndrome, obesity, alcoholism, pregnancy, fatty liver disease, kidney diseases and hypothyroidism. Besides, pharmaceutical therapies with glucocorticoids, hormones or diuretics can interfere with the lipid metabolism as well. Reactive/ physiological alterations in blood lipids are due to certain lifestyle habits and represent a common type of dyslipidemia. More precisely, high consumption of animal fats contributes to hypercholesterinemia, whereas high consumption of alcohol and/or calories and/or sugar is said to cause hypertriglyceridemia (27). The three types of dyslipidemia are likely to interact or develop simultaneously. This means that unhealthy eating habits and a sedentary lifestyle, combined with a certain genetic predisposition can determine and aggravate the clinical presentation (27).

The pathogenicity and atherosclerotic risk of dyslipidemia depends on which types of lipoproteins are elevated or decreased. High levels of IDL and LDL were found to be the main driving factors behind atherosclerotic changes and CVD (27). LDL is often referred to as “bad cholesterol”, whereby small dense LDL particles have been identified to pose an even higher health threat (12). In contrast, HDL is considered as “good” due to its importance in eliminating cholesterol. Its anti-inflammatory, anti-oxidative and lipolytic properties protect the endothelium against atherosclerotic changes as well. By implication, low levels of HDL, which are considered as typical feature of unfavorable lifestyle habits, are associated with rising atherosclerotic risk (27).

1.6.4. Atherogenic Dyslipidemia in Metabolic Syndrome

Patients with MetS and/or T2DM typically present with the following lipid profile: high levels of TG and VLDL, presence of small, dense LDL particles and reduced HDL-

cholesterol levels (2,12,50). Such lipid profile is closely associated with atherosclerotic risk and CVD and thus is referred to as “atherogenic dyslipidemia” (49). The key factor behind atherogenic dyslipidemia is thought to be the excessive amounts of circulating FFAs that reach the liver tissue and enter hepatic metabolism (12,28). There, FFAs are transformed into triglycerides and integrated into VLDL particles. The high release of newly synthetized VLDL particles into the circulation comes along with an elevation of TG levels as well (12). Furthermore, obesity and IR diminish the activity of LPL. Because of this, the peripheral processing of triglyceride-rich lipoproteins like VLDL becomes insufficient, which again contributes to hypertriglyceridemia (12). It is assumed that hypertriglyceridemia causes changes in the composition of HDL-particles. They become smaller and denser and for this reason are eliminated more easily (12). Consequently, the levels of HDL-cholesterol decrease (12), which is a typical finding in patients with obesity, MetS or T2DM (27).

1.7. Diabetes Mellitus Type 2

Diabetes mellitus generally describes a chronic condition of hyperglycemia due to impaired insulin secretion and/or impaired insulin signaling (27). Concerning diabetes mellitus type 2, the combination of insulin resistance with impaired insulin secretion and increased hepatic glucose production is assumed to evoke postprandial and fasting hyperglycemia (12). Diabetes mellitus is diagnosed when fasting blood glucose concentrations are higher than or equal to 126 mg/dl (27).

1.7.1. Pathogenesis of Diabetes Mellitus Type 2

In the course of insulin resistance, chronic hyperglycemia and excess FFAs (due to the loss of insulin-mediated inhibition of lipolysis) overstrain the pancreatic tissue and induce apoptosis of β-cells (14,15,51). The pancreatic compensatory mechanisms finally become exhausted and insulin concentrations become too low to regulate the blood glucose levels sufficiently. Consequently, postprandial hyperglycemic states occur. This condition is also referred to as “impaired glucose tolerance” (IGT) (12). If the pancreatic function continues to decline and hepatic gluconeogenesis increases, T2DM becomes manifest. At this point, not only postprandial, but also basal (fasting) glucose levels are elevated (12). In other

words, hyperglycemia reflects the dysfunctional β-cell activity, which develops in the course of insulin resistance and characterizes the onset of T2DM (12,49).

1.7.2. Etiological and Epidemiological Background of Diabetes Mellitus Type 2

T2DM is associated with dyslipidemia and obesity, in particular with the abdominal type of excess body fat (12). Indeed, 80% of the patients are estimated to be overweight or obese (12,27), whereby the MetS is considered the main underlying condition behind most T2DM cases (27). Risk factors like sedentary behavior, lack of physical activity and hyperalimentation are mainly responsible for the development and manifestation of T2DM (27), but also age, ethnical background and genetic predisposition show a strong correlation (12). The risk of being affected rises with increasing age and amounts to 22% among individuals aged 70 years and older (12). The prevalence of T2DM also presents with global variability. The highest prevalence of T2DM was found among the population of certain Pacific Islands and the Middle East. This situation is attributed to the environmental conditions, health behavior and genetic disposition found in these regions (12). Considering the inter-ethnic differences, the prevalence of T2DM is estimated to be 13% in Hispanics and non-Hispanic blacks, which is higher than in non-Hispanic whites (8%) and Asian-Americans (9%) (12). In fact, it is well established that the vulnerability towards T2DM and the disease progression vary between different ethnic groups. Among Asians, T2DM typically starts at younger ages with lower levels of BMI, higher degree of central obesity and lower secretion of insulin compared to Europeans or US-Americans (12). Regarding the genetic background, it is well known that clustering of T2DM occurs within families. For children who have one parent with T2DM, the chance of being affected too amounts to 50% (27).

1.7.3. Clinical Appearance and Consequences of Diabetes Mellitus Type 2

T2DM progresses slowly with late onset of unspecific symptoms like tiredness and reduction of physical capacity. Polyuria, thirst, polydipsia and weight loss are due to renal elimination of hyperglycemic urine and the accompanying osmotic diuresis. Dermal symptoms, disorders of the electrolyte balance and disturbances of the sex hormone levels have been described as well (27). Chronic hyperglycemia comes along with various

adverse effects on the vasculature that are classified as unspecific macroangiopathies and diabetes-specific microangiopathies. Diabetic macroangiopathy is characterized by early onset arteriosclerosis with cardiovascular complications such as coronary heart diseases, stroke or peripheral arterial occlusive disease (27). T2DM-associated conditions such as hyperglycemia, dyslipidemia, endothelial dysfunction and alterations of the coagulation system jointly promote the development of macroangiopathy. In the course of diabetic hyperglycemia, irreversibly glycosylated proteins - also referred to as "advanced glycosylated end products" (AGE) - arise. These modified proteins tend to accumulate within vascular walls and exacerbate atherosclerotic changes (51). In capillary walls, AGEs can cause microangiopathic diseases like glomerulosclerosis (diabetic nephropathy), retinopathy, neuropathy and small vessel disease of coronary arteries (27). Other secondary diseases of T2DM include cardiomyopathy, lowered resistance to infectious diseases, dyslipidemia (with high levels of TG and low levels of HDL cholesterol) and hepatic steatosis (27).

1.8. Cardiovascular Diseases

Pathological disorders that primarily affect the heart and the blood vessels are summarized under the term "cardiovascular diseases". These include, amongst others, hypertension, coronary heart disease, heart attack, cerebrovascular disease and stroke. Several risk factors and environmental conditions have been identified to promote CVD (compare with Figure 17) (52).

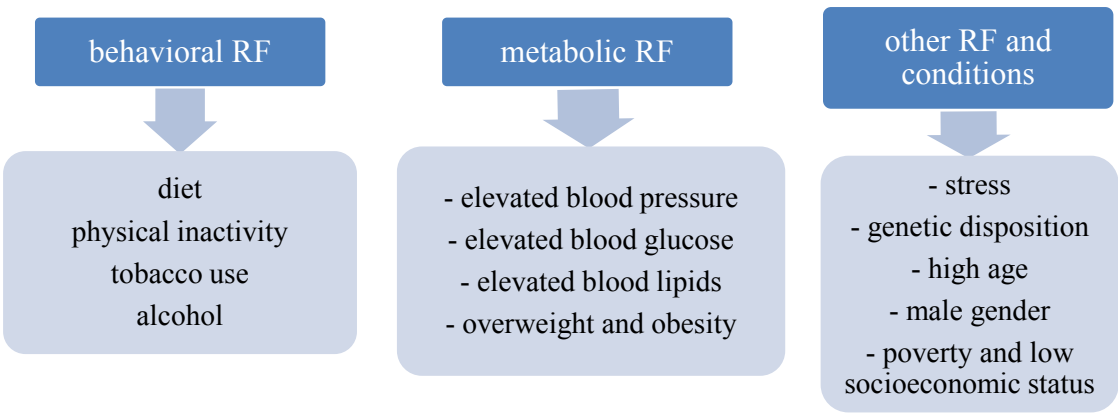

Figure 17 Risk Factors for Atherosclerosis and Cardiovascular Diseases.
Modified from: World Health Organization *(Global Atlas on Cardiovascular disease prevention and control* 2011) (52)
Note: RF= risk factor

1.8.1. Pathophysiology of Atherosclerotic Cardiovascular Diseases

The underlying pathomechanisms of coronary heart diseases and cerebrovascular diseases are mostly based on atherosclerotic changes (52). Atherosclerosis is a gradually progressive vascular disorder, which manifests as alterations of the arterial wall. Its pathological findings are characterized by intravascular plaque formation, thickening of the vessel wall with decrease in vascular compliance and decrease in lumen diameter (51). These conditions diminish the local blood flow and finally lead to an interruption of the circulation. Depending on the affected blood vessel, atherosclerosis might become clinically apparent as angina pectoris, heart attack or stroke and is therefore considered the underlying cause of most CVD-related deaths (52).

1.8.2. Atherosclerosis

The pathogenic processes of atherosclerosis initially address the endothelium - the inner layer of the vessel wall. Factors such as hypertension, nicotine, hyperlipidemia and immunological mechanisms have been identified to induce both endothelial dysfunction and endothelial injuries (51). Endothelial dysfunction describes a condition in which the endothelial cells react to changing conditions via modifying their properties and functions. In terms of atherosclerosis, endothelial dysfunction is characterized by an increase in the permeability and changes in gene expression (for example expression of the enzyme nitric-oxide-synthase) (51). Insulin resistance is considered to contribute to endothelial dysfunction in the sense that the insulin-mediated stimulation of NO synthesis is disturbed, so its protective effects (vasodilatation) fade (11,12). A commonly used concept in explaining the initiation of atherosclerotic processes is the “Response to Injury-Theory”. It states that both blood flow and blood pressure go along with a certain mechanical strain, which causes small injuries to the endothelium (25). In combination with endothelial dysfunction and the increased permeability, circulating LDL-particles become able to pass the endothelium and accumulate within the intima layer of the vascular wall (25,51). There, LDL is oxidized (oxLDL). The oxidized form of LDL-cholesterol causes an inflammatory response and inhibits the NO synthesis, which in turn aggravates the endothelial dysfunction. Endothelial cells react to the local inflammation by enhancing the expression of adhesion molecules. In this way, leukocytes and thrombocytes can migrate into the vascular tissue and interact with the accumulated lipids. By internalizing oxLDL via scavenger receptors, macrophages (and muscle cells) turn into lipid-laden foam cells.

At this initial stage, “fatty streaks” become visible on the surface of the inner vascular wall (see Figure 18). Such fatty streaks can already occur in children and adolescents, indicating that atherosclerotic changes affect people at any age (51).

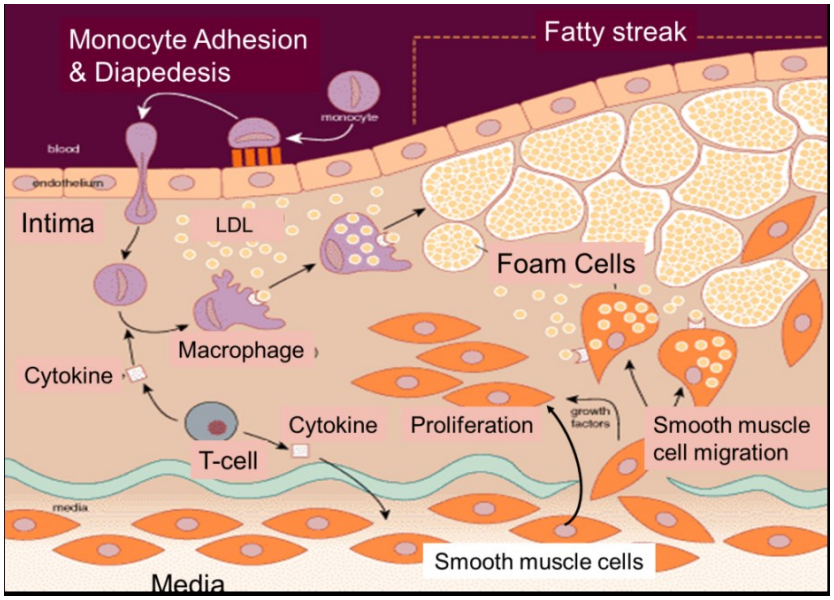

Figure 18 Illustration of the Development of Fatty Streaks and Atherosclerosis.
Obtained from: Boston University School of Public Health. Atherosclerosis. 2016. (Date of access: 30.04.2019)
Available via: http://sphweb.bumc.bu.edu/otlt/MPH-Modules/PH/PH709_Heart/PH709_Heart_print.html

Further inflammation of the lipid plaque induces migration and proliferation of smooth muscle cells. Via secretion of extracellular matrix (ECM), the myocytes turn the lesion into a “fibrous plaque”. The final stage of atherosclerosis - the “complicated atherosclerotic lesion” - can show different qualities: Calcification, focal rupture and/or ulceration, hemorrhage, thrombosis and aneurysm (51).

1.8.3. Plaque Rupture and Thrombosis

Different enzymes and inflammatory factors decrease the synthesis of ECM - the fibrous coat becomes thinner and unstable. This condition is called “vulnerable plaque”. When the plaque surface ruptures, the exposition of the atheromatous lipid core either leads to fat embolism or induces thrombus formation. This results in partial or complete obstruction of the vascular lumen, which in turn can cause cardiovascular events such as angina pectoris, myocardial infarction or stroke (51,52).

2. Aims and Objectives

- *Problem statements*

#1: In parallel with the obesity epidemic (9), the prevalence of MetS (3,7,13,35,37,53), CVD and T2DM has been increasing (3,46,52). According to the IDF, the mean prevalence of MetS among the world population is estimated to be 20-25% (7).

#2: With the growing number of childhood obesity, cardio-metabolic abnormalities and MetS are expected to become more prevalent in youth as well (11,13,36,54). The early onset of risk factor clustering is quite alarming, considering that MetS components track into adulthood and significantly increase the risk for future T2DM and CVD (55). For this reason, children and adolescents represent an important target group for prevention and early treatment of obesity and MetS development (11). However, identifying those who are affected is rather difficult because **concrete recommendations about how to diagnose MetS in the pediatric age group are still lacking** (55). In fact, there is a confusingly **high number of different pediatric MetS classifications**, each of which promotes its own limit values and measurement techniques. Consequently, comparison across prevalence data obtained from different epidemiological studies in children is difficult (56). Furthermore, **the diagnostic accuracy and predictive value of childhood MetS for future health consequences have not yet been validated** (3) and need further investigation (11).

The aim of this literature research is **to provide an overview of the current prevalence numbers of pediatric MetS worldwide** as well as to discuss the **discrepancies between the different definitions** and the **rationales for this continuing disagreement**. Furthermore, the **clinical importance of the pediatric MetS will also be discussed** in order to identify **recommendations for its practical application**. The following sections analyze the results of several epidemiological studies from the past five years that are based on four widely used definitions.

3. Methods

In order to gain a general overview about the Metabolic Syndrome in children and adolescents, the first step was to search for articles and websites that deal with the topic in a general way. Therefore, the search terms "metabolic syndrome", combined with "children" and "adolescents", respectively, were placed in the "Google" search engine. As the number of results reached 22 200 000, the search was then refined to websites provided by national and international research societies (e.g. World Health Organization, International Diabetes Federation). The next step was to find appropriate textbooks and secondary literature in the Library of the Medical University of Graz as well as the "Landesbibliothek Oberösterreich".

For the introduction section of the diploma thesis, textbooks on physiology, pathophysiology, pathology, internal medicine and biochemistry were used. Primary literature, comprising published journal articles and research papers as well as guidelines, were obtained via the PubMed search engine. The Web of Science database was used as an additional source of extra information such as how often the articles were cited or the impact factor of the publishing journals. The chosen articles were downloaded into the literature management program "Mendeley". Afterwards, they were sorted according to topic and relevance. In order to find additional literature, reference lists as well as related articles, which were suggested by Mendeley and PubMed, were checked.

The systematic research of the current literature took place in July 2018. The MeSH term "Metabolic Syndrome", declared as "Major Topic", was combined with MeSH subheadings like:

- Definition
- Epidemiology
- Prevalence

In order to expand the range of results, an additional search query was created by replacing the term "Metabolic Syndrome" with the synonym "Insulin Resistance".

As the number of results was overwhelmingly high, the search was specified via defining the exclusion criteria and adding appropriate filters:

- Date of publication within the last five years

- Only articles that were written in English
- Articles that covered human research
- Articles of which the full text was available
- Articles that deal with children, defined as birth - 18 years

For the introduction section as well as for the opening part of the discussion, publications that dealt with the definition and diagnosis of MetS in children and adolescents were investigated. Since many different pediatric definitions are used in scientific literature, a goal of this work was to identify the most frequently used ones. Finally, four MetS classifications (IDF, Cook et al., Ford et al., de Ferranti et al.) were selected and discussed.

For the systematic literature research section that covered the prevalence of pediatric MetS, articles that contained prevalence data of MetS in children and adolescents were searched for. The MeSH terms “Metabolic Syndrome” and “Insulin Resistance” were combined with the MeSH terms “epidemiology” and “prevalence” via using the Boolean operator “AND”. In this way “Metabolic Syndrome” AND “epidemiology” offered 397 results, while “Insulin Resistance” AND “epidemiology” resulted in 416 articles (see Table 6). The most relevant articles were selected according to the titles and abstracts. Those articles that obtained prevalence data exclusively from adults or from specifically pre-defined cohorts (e.g. prevalence of MetS in clinical populations or participants with an underlying illness) were excluded. Likewise, articles dealing with MetS only marginally or on a secondary level were not taken into account. After eliminating the duplicates, 117 papers were downloaded. As the publications differed significantly in terms of their study cohorts and MetS criteria, focus was primarily laid on randomized, preferably population representative trials, which were based on the four chosen definitions (IDF, Cook et al., Ford et al. and de Ferranti et al., respectively). However, in the course of a second evaluation two cross-sectional studies, in which the recruitment was not randomized, were subsequently included as they obtained relevant information for the discussion section. Finally, the research resulted in 31 publications, which reflect the prevalence data of the MetS among children and adolescents in different countries worldwide and which were published during the past five years (see Figure 19). Among these, 24 studies used the definition of the IDF, 15 that of Cook et al., eight that of de Ferranti et al. and six studies used the Ford et al. classification. Twelve publications applied more than one definition to the very same cohort in order to compare the differences between the prevalence rates.

These results are discussed separately in the subsection "Comparative Studies". Furthermore, two longitudinal studies that examined the stability of the MetS status over a follow-up period were analyzed separately in the discussion section.

Table 6 Number of Articles Obtained via PubMed search

MeSH major topic	MeSH term	Number of results	Number of downloaded articles
Metabolic Syndrome	epidemiology	397	95
	prevalence	296	19
Insulin Resistance	epidemiology	416	0
	prevalence	58	3

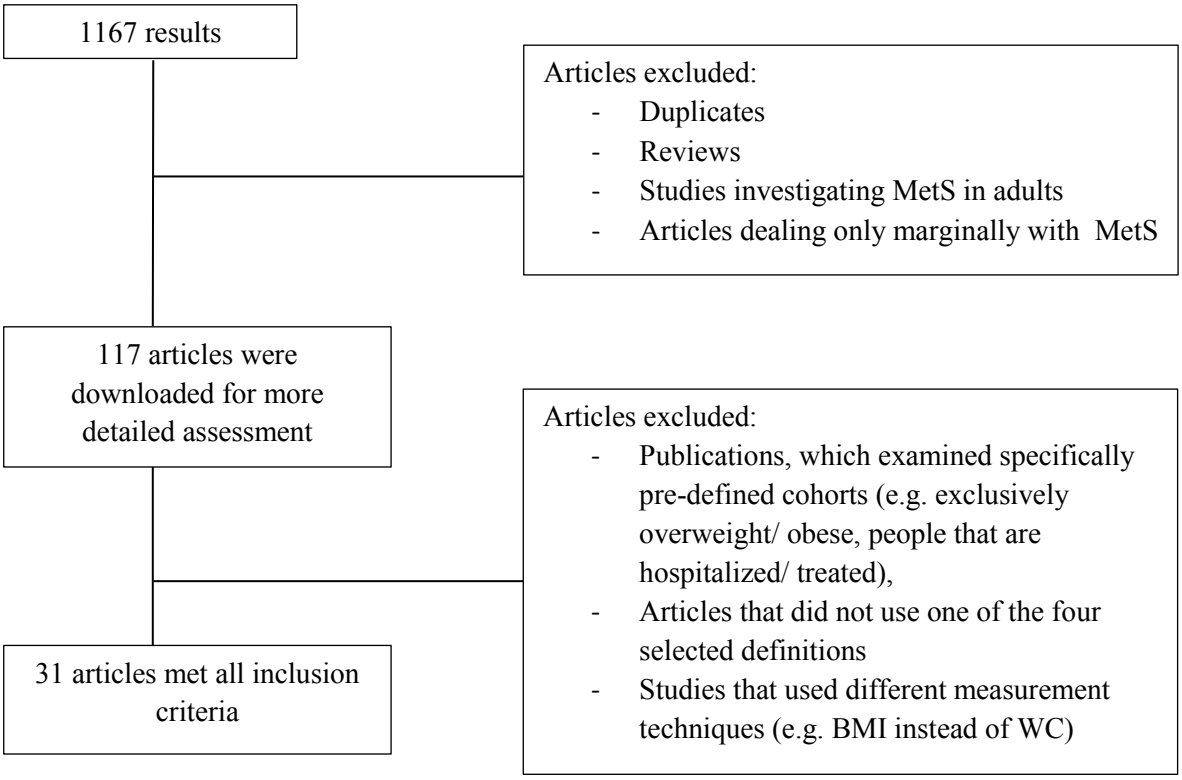

Figure 19 Flowchart Illustrating the Selection Process of the PubMed Research.

4. Update of the Current Literature

4.1. Varying Definitions of Metabolic Syndrome in Pediatrics

Along with the increasing prevalence of childhood obesity the question came up whether cardio-metabolic consequences already develop in childhood (5). Cross-sectional studies therefore investigated the occurrence of MetS among children and adolescents (41). Indeed, it could be demonstrated that some obese young individuals already fulfill the adult diagnostic criteria for MetS, indicating that cardio-metabolic alterations start at an early age (56). Consequently, the demand for appropriate diagnostic criteria for MetS in children and adolescents has become stronger. In response, research groups simply adapted the preexisting adult definitions to the pediatric age group (3). One of the most prominent templates came from the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATPIII). For example, Cook et al., Ford et al. and de Ferranti et al. modified the NCEP criteria by replacing the adult cut-offs with age- and sex- specific percentiles and pediatric thresholds (11,41,57,58). As most of the study groups developed their own unique set of diagnostic criteria, the number of pediatric MetS definitions soon became confusingly large (3). In a literature research published in 2007, Ford et al. identified as many as 46 different definitions being used for assessing the prevalence of MetS in children and adolescents (5). In 2007, the International Diabetes Federation (IDF) proposed a new set of diagnostic criteria with the aim to offer "*a simple easy-to-apply definition*" for clinical practice (34). Table 7 summarizes the IDF criteria and the three NCEP-based definitions provided by Cook et al, Ford et al. and de Ferranti et al.

The IDF definition differs from the other definitions in several aspects: Firstly, it requires the presence of abdominal obesity as a mandatory condition (34). Accordingly, only individuals with large WC plus two or more risk factors are diagnosed with MetS (34). Secondly, in spite of WC, the remaining four risk factors are determined by using cut-off points that normally apply to adults (34). In contrast, the other definitions choose lower limit values or use age, sex and high specific percentiles for determining elevated blood pressure (BP) and dyslipidemia (41,57,58). Thirdly, the IDF suggests that only children above 10 years of age should be examined for MetS, whereas in younger individuals, WC measurement alone should be used for screening (34).

Table 7 Different Definitions of Pediatric Metabolic Syndrome, proposed by the IDF (34), Cook et al. (41), Ford et al. (58) and de Ferranti et al. (57)

	Abdominal obesity	Hypertension	Dyslipidemia	Fasting glucose
IDF (34) Central obesity + 2 of 4 [a]	10-15 years WC ≥90th percentile > 15 years WC ≥94 cm (males)[b] WC ≥80 cm (females)[b]	Systolic BP ≥130 mmHg or Diastolic BP ≥85 mmHg or specific treatment	TG ≥150 mg/dl or specific treatment HDL <40 mg/dl (males) <50 mg/dl (females)	≥100 mg/dl or diagnosed type 2 diabetes mellitus
Cook et al. (41) 3 out of 5 [a]	WC ≥90th percentile [c]	≥90th percentile [d]	TG ≥110 mg/dl [e] HDL ≤40 mg/dl [f]	≥110 mg/dl
Ford et al. (58) 3 out of 5 [a]	WC ≥90th percentile [g]	≥90th percentile [d]	TG ≥110 mg/dl [e] HDL ≤40 mg/dl [f]	≥110 mg/dl (additional analysis with ≥100 mg/dl)
De Ferranti et al. (57) 3out of 5 [a]	WC ≥75th percentile	≥90th percentile	TG ≥100 mg/dl HDL ≤50 mg/dl	≥110 mg/dl

[a] number of criteria that must be fulfilled for diagnosing MetS.
[b] for Europid males/ females; ethnic-specific percentiles are recommended for other population groups (34)
[c] age and sex specific, recommended by NHANES III (National Health and Nutrition Examination Survey)
[d] age, sex and height specific, recommended by NHBPEP (National High Blood Pressure Education Program)
[e] age specific, recommended by NCEP (National Cholesterol Education Program)
[f] all ages/sexes, recommended by NCEP
[g] sex specific, recommended by NHANES

Given the discrepancies between the limit values and the diagnostic requirements, it is not surprising that these definitions do not always identify the very same individuals as being MetS-positive or -negative (56).

4.2. The Prevalence of Metabolic Syndrome among Children and Adolescents - Findings of Current Scientific Research

This section will demonstrate the results of a systematic literature research concerning prevalence data of the MetS in children and adolescents, published during the past five years. As mentioned above, the results of this literature research are limited to those publications that used at least one of four highly accredited definitions (IDF, Cook et al., Ford et al. and/or de Ferranti et al.). Table 8 provides an overview of 31 epidemiological studies that met the inclusion criteria. Arranging the selected papers according to their geographic location revealed the following distribution: eleven studies were obtained from

the Asian continent, eight from South America, four from Europe, four from North America, three from Africa and one study from Australia.

The chosen publications included both large population-based studies as well as smaller surveys, which were conducted in schools or in certain country regions. Sample sizes reached from 371 students in a South African cohort (59) to a maximum of 37504 adolescents participating in a nationwide study in Brazil (60). In the majority of studies, the participants were at least ten years old. There were two studies, one European multi-country survey (61) and one Colombian study (62) that had by far the youngest cohorts with age ranging from two to almost eleven years and five to nine years, respectively. In general, the upper age limit was 18 years, except for two US studies, which chose 19 as maximum age (54,63).

The results of this literature research (as presented in Table 8 as well as in Figures 20 and 21) indicate that MetS can be diagnosed in children and adolescents from all over the world. Among the 31 included papers, the prevalence of pediatric MetS ranged from 0.3% to 26.4% (see Figure 23) (64,65). The lowest prevalence (0.3%) was found in a population-based survey of Colombian schoolchildren by using the definition of the IDF (65). The highest prevalence (26.4%) was found among Iranian children and adolescents by using the definition of de Ferranti et al. (64). The median calculation of the whole dataset of prevalence numbers yielded 3.8%. Regarding each definition separately, the median values were 2.1% for the IDF, 3.8% for Cook et al., 5.7% for Ford et al. and 11.2% for de Ferranti et al. (as exhibited in Figures 22 and 23). The mean value of the whole dataset was higher, namely 5.23%, which is probably due to the high prevalence levels yielded by the de Ferranti definition. Prevalence was high in the Middle East (13% and 6% in Iran (64,66,67) and almost 5% in Saudi Arabia (68) according to the Cook definition), in the United States (5.4% by IDF (63) and 10.1% (54) by the Ford et al. classification) and in South American countries (9.5% in Chile by IDF and 6.2% in Colombia by the Cook definition (65,69)). In general, the majority of the IDF results lay within the range between 0.3% (65) and 5.4% (63). However, there were three studies, in which the IDF based prevalence was considerably higher, namely 7.6% in China (70), 8.4% in Iran (64) and 9.5% in Chile (69) (see Figure 22). The application of the modified NCEP criteria, on the other hand, showed prevalence rates varying from 1.4% (61) to 26.4% (64) (as exhibited in Figure 23) and median values from 3.8% (Cook criteria) to 11.2% (de Ferranti criteria).

Table 8 Epidemiological Studies Investigating the Prevalence of Metabolic Syndrome in Children and Adolescents Based on the Diagnostic Criteria of Cook et al., Ford et al., de Ferranti et al. and the IDF

Author	Year	Country	Study cohort	Study design	IDF criteria	modified NCEP criteria
Europe						
Ostrihoňová et al. (71)	2017	Slovak Republic	1294 children and adolescents aged 10-17,99a	visitors of Health Advice Centers no randomization	♂2.7% ♀2.8%	
Vanlancker et al. (72)	2017	10 European Countries	1004 adolescents aged 12.5-17a	randomized multi-center study not population-representative	2.7%	Cook 3.5%
Galera-martínez et al. (73)	2015	Spain	379 adolescents aged 12-16,9a	population based sample of adolescents living in Almería	3.8%	Ford 5.7%
Ahrens et al. (61)	2014	8 European Countries	12319 children aged 2-10,9a	population based not nationally representative	0.4%	Cook 1.4%
North America						
Reina et al. (74)	2017	USA	1137 children and adolescents aged 10-16a	population-based study of Latino/Hispanic people living in the US; SOL Youth[a]	3.1% in 10-15year olds ♂2.8% ♀6.3% in 16 year olds	
Rodríguez et al. (63)	2016	USA	1623 adolescents aged 12-19a	nationally representative sample of adolescents; NHANES[b] 2005-2012	5.4%	

[a] Study of Latino Youth

Author	Year	Country	Study cohort	Study design	IDF criteria	modified NCEP criteria
MacPherson et al. (75)	2016	Canada	1228 children and adolescents aged 10-18a	population representative survey; CHMS[c] 2007-2009, 2009-2011	2.1%	
Miller et al. (54)	2014	USA	3495 adolescents aged 12-19a	nationally representative sample of adolescents; NHANES 2001-2010		Ford 10.1%
South America						
Burgos et al. (76)	2018	Brazil	1200 adolescents aged 12-17a	population representative sample of adolescents from Southern Brazil	2.1%	Cook 1.9% de Ferranti 5.0%
Ramírez-Vélez et al. (65)	2016	Colombia	1922 children and adolescents aged 9-17,9a	population-based sample of schoolchildren in Bogota; FUPRECOL[d] study 2014-2015	0.3%	Cook 6.2% Ford 7.8% de Ferranti 11.0%
Suarez-Ortegón et al. (62)	2016	Colombia	494 children aged 5-9a	cross-sectional study of the scholar population in the city of Cali; IFRECNTEC[e] study		de Ferranti 8.7%
Kuschnir et al. (60)	2016	Brazil	37.504 adolescents aged 12-17a	representative of adolescents from medium- and large-sized cities; ERICA[f] Study	2.6%	

[b] National Health and Nutrition Examination Survey
[c] Canadian Health Measures Survey
[d] *In Spanish* Associación de la Fuerza Prensil con Manifestaciones de Riesgo Cardiovascular Tempranas en Niños y Adolescentes Colombianos
[e] Identification of Risk Factors for Adult Non-Communicable Chronic Disease in Schooled Population
[f] Estudo de Riscos Cardiovasculares em Adolescentes (Study of Cardiovascular Risk in Adolescents)

Author	Year	Country	Study cohort	Study design	IDF criteria	modified NCEP criteria
Burrows et al. (69)	2015	Chile	667 adolescents aged 16-17a	adolescents of low to middle SE-status residing in the city of Santiago not population representative	9.5%	
Villalobos Reyes et al. (77)	2014	Venezuela	916 children and adolescents aged 9-18a	representative sample in the city of Mérida; CREDEFAR[g] Study 2010-2011	1.5%	Cook 2.2%
Dias Pitangueira et al. (78)	2014	Brazil	540 children and adolescents aged 7-14a	random sample from the municipality of Mutuípe, Brazil		de Ferranti12.8%
Agudelo et al. (79)	2014	Colombia	851 adolescents aged 10-18a	beneficiaries of a health-promotion company in the city of Medellín no randomization	0.9%	Cook 3.8% Ford 4.1% de Ferranti 11.4%
Asia						
Song et al. (80)	2017	China	831 children and adolescents aged 7-18a	"national household-based study in nine Chinese provinces"; CHNS[h] 2009	1.4% in 10-18 year olds	Cook 3.4% in 7-18 year olds 3.6% in 10-18 year olds
Xu et al. (81)	2017	China	11174 children and adolescents aged 10-17a	population survey conducted in six provinces in 2007-2011		Cook 3.8%

[g] Evaluation of Growth, Development, and Cardiometabolic Risk factors in Schoolchildren and Adolescents from Mérida, Venezuela
[h] China Health and Nutrition Survey

Author	Year	Country	Study cohort	Study design	IDF criteria	modified NCEP criteria
Lee et al. (82)	2017	South Korea	623 children and adolescents aged 10-18a	population representative; KNHANES[i]	1.0%	
Asghari et al. (64)	2017	Iran	1424 children and adolescents aged 11-18a	randomly selected, population representative; TLGS[j], baseline 1999	8.4%	Cook 13.1% de Ferranti 26.4%
Bahrani et al. (67)	2016	Iran	538 adolescents aged 14-18a	random sampling procedure. 12 high-schools in Shiraz, Iran		Cook 6.1%
Kim et al. (83)	2016	Korea	2330 children and adolescents aged 10-18a	population representative; KNHANES 2010-2012	2.1%	Ford 5.7%
Wang et al. (84)	2015	China	1770 children and adolescents aged 7-17a	random sample of 10 schools in urban area of Guangzhou, China	1.1% in 10-17 year olds	Cook 2.5% in 7-17 year olds
Al-Hussein et al. (68)	2014	Saudi Arabia	2149 children and adolescents aged 6-17a	random sample of students in Riyadh; S.Ch.O.O.Ls[k] study	2.0%	Cook and Ford 4.9% de Ferranti 17.5%
Fadzlina et al. (85)	2014	Malaysia	1014 adolescents; aged 13a	population based study; students from urban and rural schools	2.6%	
Li et al. (70)	2014	China	910 children and adolescents 11-16a	students from 30 high school classes in North East China	7.6%	
Hosseinpanah et al. (66)	2013	Iran	1424 children and adolescents aged 11-18a	randomized, population representative; TLGS, baseline 1999-2001		Cook 13.3%

[i] Korea National Health and Nutrition Examination Survey
[j] Teheran Lipid and Glucose Study
[k] Saudi Children´s Overweight, Obesity and Lifestyles Study

Author	Year	Country	Study cohort	Study design	IDF criteria	modified NCEP criteria
Australia						
Huang et al. (86)	2013	Australia	964 adolescents aged 17a	representative sample of adolescents from Western Australia	2.7%	
Africa						
Sekokotla et al. (59)	2017	South Africa	371 adolescents aged 13-18a	selected high schools in Mthatha, South Africa		Cook ♂6.0% ♀3.1%
Benmohammed et al. (87)	2015	Algeria	989 adolescents aged 12-18a	Randomized recruitment of school children in the city of Constantine	♂ 1.3% ♀ 0.5%	Cook ♂2.6% ♀0.6% de Ferranti ♂4.0% ♀2.0%
Matsha et al. (88)	2013	South Africa	1272 children and adolescents aged 10-16a	randomly selected from primary schools 2007-2008	1.9%	

4.2.1. Europe

In a European multi-country survey, conducted among 12-17 year old adolescents, 2.7% met the IDF criteria for MetS. Using the definition of Cook et al., the prevalence of MetS was slightly higher, namely 3.5% (72). This small difference between the results corresponds to another multi-country study conducted in European children between two and almost eleven years of age. There, the prevalence of MetS was 0.4% and 1.4% according to the definitions of the IDF and Cook et al., respectively (61). Interestingly, the highest prevalence of 5.7% was found among a cohort of 379 Spanish adolescents by using the definition of Ford et al (73).

4.2.2. North America

In the United States, two studies used data from a national-wide population-based survey called "National Health and Nutrition Examination Survey" (NHANES). Both of these two studies investigated the occurrence of MetS in US adolescents between 12-19 years of age. Applying the IDF definition, Rodríguez et al. showed that the MetS was present in 5.4% of US adolescents (63). Miller et al., on the other hand identified a considerably higher number of MetS-positive individuals, namely 10.1%, by using the definition of Ford et al. (54). Comparing the results based on the IDF definition, the prevalence of MetS observed in the US population was twice as high as the prevalence in European adolescents (5.4% vs. 2.7%) (63,72). In the study cohort of 1228 Canadian adolescents, the IDF criteria identified 2.1% as being affected by the MetS, which is more in line with the European prevalence data (2.7%, according to the IDF criteria) (75).

4.2.3. Asia

The highest prevalence rates, based on the Cook et al. definition, were found among Iranian children and adolescents: Over 13% in a study cohort of 11-18 year olds and over 6% in a study cohort of 14-18 year olds were classified as having MetS (64,66,67). Similar results were obtained by a Saudi Arabian survey, in which the Cook et al. definition classified almost 6% of the study participants as having MetS (68). In contrast, two population-based Chinese studies yielded lower prevalence rates by using the same definition: Among children and adolescents between 10 and 18 years of age, the prevalence of MetS varied between 3.59% (80) and 3.83% (81).

Among the Asian pediatric populations reported in this work, the IDF criteria often showed low prevalence rates. For example, in two Chinese surveys, the IDF criteria classified 1.37% (80) and 1.1% (84), respectively, as being affected by the MetS. These numbers resembled those obtained in two Korean studies when applying the same definition (1.0% (82) and 2.1% (83)). However, there were two exceptions where the IDF classification resulted in rather high prevalence numbers, namely 7.6% among Chinese students (70) and 8.4% among Iranian minors (64). The unusually high prevalence of the Chinese study was attributed to the low economic development and poor healthcare provision, typical for the examined region (70). The Iranian results appear less surprising, considering that other studies in this country population generally reported higher prevalence numbers as compared to other Asian studies (Figures 20 and 21) (66,67).

4.2.4. South America

The prevalence of childhood MetS varied widely among the South American studies. Considering the IDF criteria, the lowest rate was 0.3% in a population-based study of 1922 Colombian children and adolescents aged between 9 and 17 (65). In contrast, by far the highest prevalence rate (identified by the IDF classification) amounted to 9.5% and was found among Chilean adolescents between 16 and 17 years of age (69). However, this strong disparity may partly be due to the age difference between the two study populations. In the largest population-representative survey of 37504 Brazilian adolescents, the IDF definition classified 2.6% as having MetS (60). Using the definition proposed by Cook et al., the prevalence rates were 2.2% among Venezuelan school children (77) and amounted to 6.2% in the above mentioned Colombian study (65). Among the South American studies, the definition of de Ferranti et al. was frequently used for evaluating the prevalence of MetS. Interestingly, this classification yielded higher numbers than the remaining three definitions. For example, in a cohort of 7-14 year-old Brazilian children and adolescents, this definition classified a considerable amount of 12.8% as being affected by MetS (78). In a study cohort of 5-9 year-old Colombian children, the prevalence was 8.7% (62), whereas the smallest number of cases (5%) was found among Brazilian adolescents (76).

4.2.5. Australia

In Australia, the prevalence of the MetS among 17-year-old adolescents was 2.7%, according to the definition of the IDF (86). This result is similar to those found in Brazil (2.6%), Malaysia (2.6%) and Europe (2.7%) (60,72,85).

4.2.6. Africa

Prevalence of MetS among Algerian adolescents varied between different definitions: It ranged between 0.5 - 1.3% with the IDF classification, 0.6 - 2.6% with the Cook definition and 3.0 - 4.0% with the de Ferranti definition (87). In South Africa, the IDF criteria yielded a prevalence value of 1.9% (88), whereas - in a smaller cross-sectional study - the Cook et al. definition classified 6.0% of male and 3.1% of female participants as being MetS-positive (59).

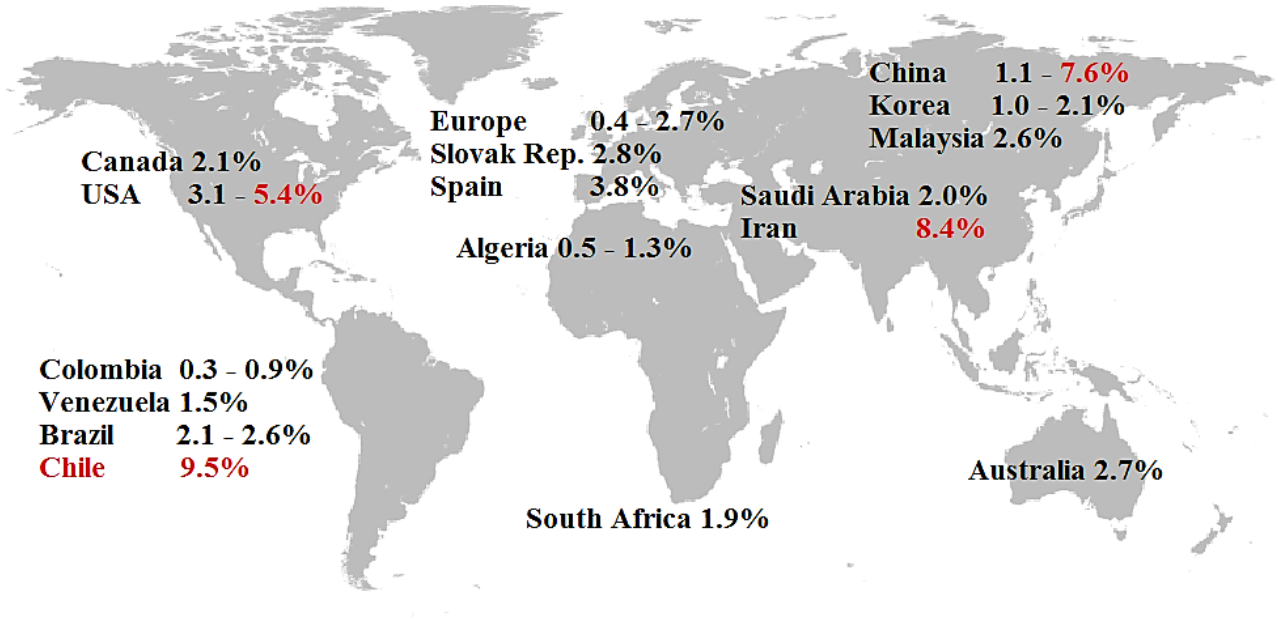

Figure 20 Prevalence of Metabolic Syndrome in Children and Adolescents According to the IDF Classification.
Note: the highest prevalence values are written in red

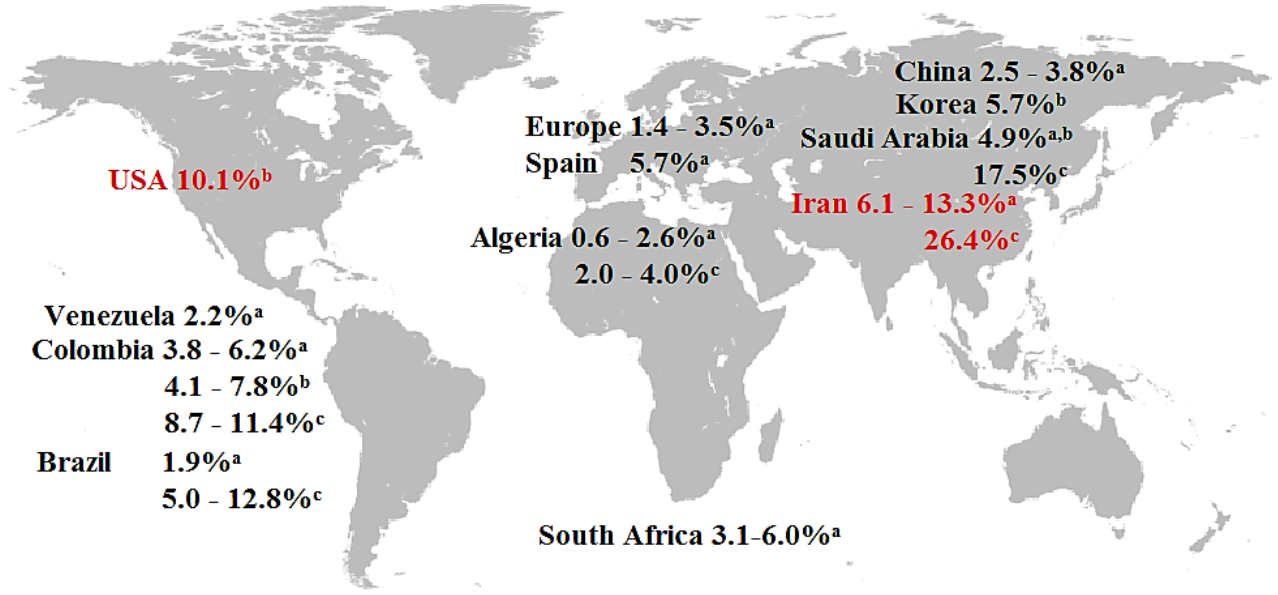

Figure 21 Prevalence of Metabolic Syndrome in Children and Adolescents According to the Definitions Proposed by Cook et al.[a], Ford et al.[b] and de Ferranti et al.[c]
Note: the highest prevalence values are written in red

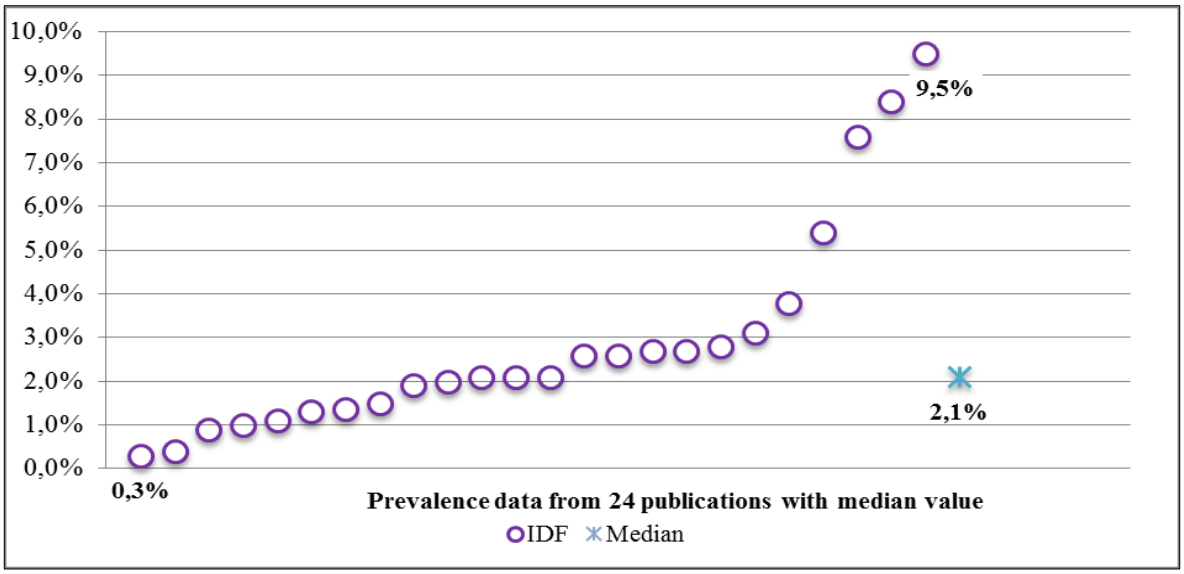

Figure 22 Prevalence of Metabolic Syndrome Based on the IDF Definition
Minimum: 0.3% Ramírez-Vélez et al, Colombia (65), Maximum: 9.5% Burrows et al., Chile (69)

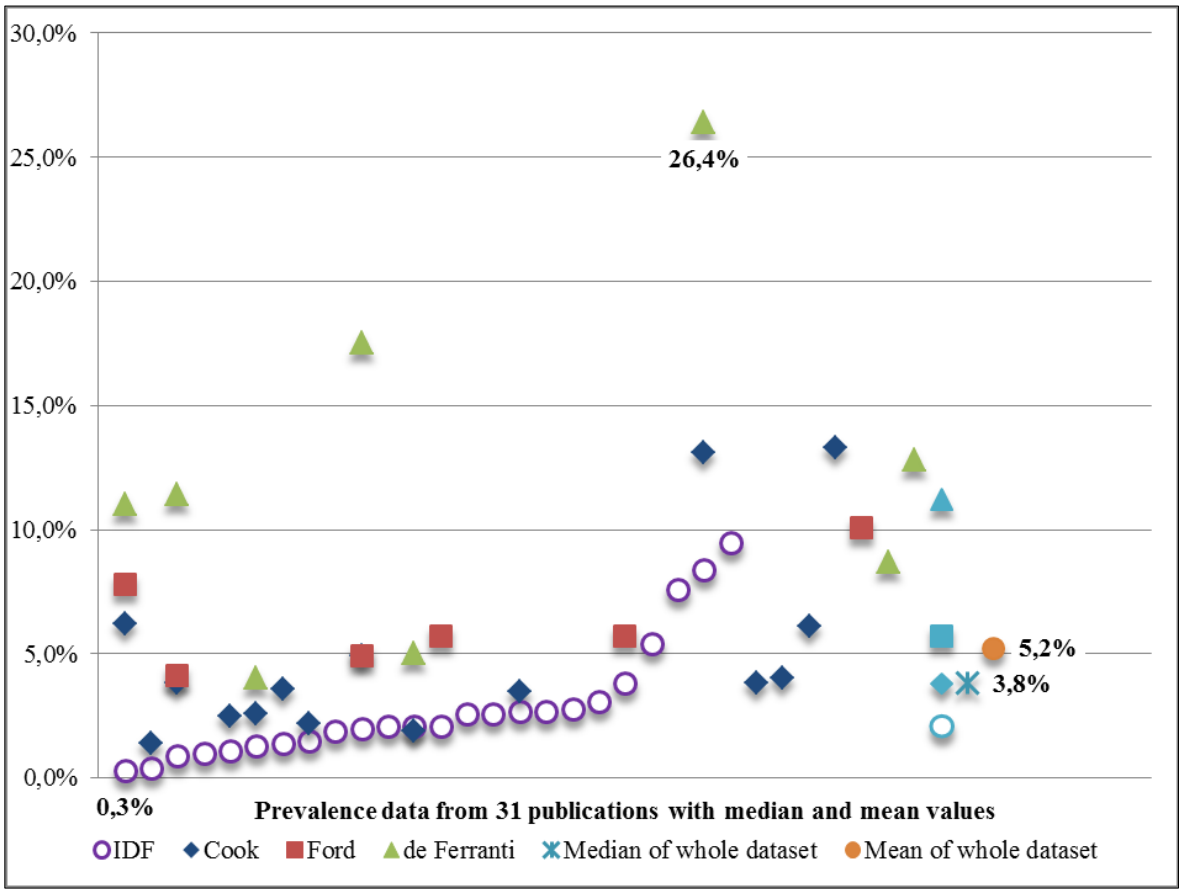

Figure 23 Prevalence of Metabolic Syndrome Based on the Definitions from the IDF, Cook et al., Ford et al. and de Ferranti et al.
Minimum: 0.3% Ramírez-Vélez et al., Colombia (65), Maximum: 26.4% Asghari et al., Iran (64)
Note: Median values are marked in light blue

4.3. Analyzation of Prevalence Numbers

Although most of the IDF-based results seem rather low, it is important to note that these young individuals already present with central obesity plus two or more additional risk factors. In other words, these children already show multiple cardio-metabolic abnormalities exposing them to high risk of developing cardiovascular diseases and T2DM. Considering the young age and the rather strict diagnostic criteria (adult thresholds for blood pressure and blood lipids), these numbers indicate the seriousness of the situation. Besides, the number of children presenting with at least one risk factor is considerably higher. For example, Miller et al. identified two third (73.2%) of the NHANES study population as having one or more metabolic abnormality (54), whereas Dias Pitangueira et al. even identified 85.7%. This observation is important and noteworthy, considering that the prevalence of childhood obesity and cardio-metabolic risk factors in youth has been increasing over the past decades (46,54). The prevalence rates might seem even more alarming when extrapolated to the total population. According to Song et al., prevalence of 3.4% would mean that more than 11 million Chinese children are affected with MetS (80) and prevalence of 10.1%, found by Miller et al., would mean that 3.3 million US adolescents fulfill the diagnostic criteria (54).

Another aspect that needs to be taken into account is the distribution of the five MetS components among the study cohorts. When the prevalence of MetS was examined taking into account the effect of every single risk factor individually, central obesity (assessed via WC measurement) and/or dyslipidemia (low HDL and/or high TG) were the most frequent risk factors seen (54,60,62,64,66,70,73,75,77,84,85,87,88), whereas high fasting glucose was the least frequent (59,60,67,68,77–80,85). On a closer look, the prevalence of abdominal obesity varied between nations and ethnic groups. It was high among European (73), North American (54,75) and South African (59,88) study groups. In contrast, central obesity was less frequently found among Asian study populations. In two studies, conducted in China and Korea, abdominal obesity was even the least prevalent risk factor (81,83).

Not only did the prevalence of each individual risk factor vary between different ethnicities, but also the prevalence of MetS per se. For example, when analyzing the results by ethnic groups, Miller et al. could demonstrate that Hispanic adolescents presented with the highest prevalence of MetS (14.6%) among the US study population. Non-Hispanic whites were following behind (9.8%), while non-Hispanic blacks had the lowest proportion

of MetS-positive cases (5.2%) (54). These findings are in accordance to former studies conducted in the US-American NHANES population (10,41,57,63,89,90). In this context, Reina et al. particularly investigated the prevalence of the MetS among 10-16-year-old US minors of Hispanic origin. Among the 10-15 year olds, the IDF definition classified 3.1%, as being affected, whereas among the 16 year-olds, 2.8% of male participants and 3.6% of female participants fulfilled the criteria (74).

The analyzed papers of this literature research generally agree on the direct correlation between body weight and the prevalence of MetS. It appears that the number of MetS-positive individuals is higher among overweight and obese children compared to normal weight ones (60,63,65–67,70,73,77,78,83,85,87). Specifically, the prevalence of the MetS ranged from 10% (85) up to 57.4% (63) among obese children and adolescents. It has been reported, that the prevalence and severity of MetS increase with the degree of excess bodyweight (65,67,70,85,91,92).

Furthermore, some authors assume an association between aging and the occurrence of MetS. Concerning the adult age group, this relationship is well described and is considered as an important influencing factor (12,71,81). However, as there were some discrepancies between the included studies, age dependency of the MetS in children and adolescents still needs to be further explored. In this literature research, five publications reported that the prevalence of the MetS was significantly higher in older subjects (61,62,67,84,93). Lee et al., for example, observed that the prevalence of MetS was significantly lower in 10-18 year-old minors (1.0%) than in 19-25 year-old young adults (2.4%) (82). On the other hand, four studies could not observe any association between age and MetS prevalence (72,73,77,79) while three papers reported an inverse correlation (64,65,94). Ramíres-Velez et al. explained the inverse correlation by the fact that among the younger age group, the prevalence of overweight was higher. Therefore, overweight and obesity - rather than age - appear to have greater impact on the development of pediatric MetS (65). Asghari et al. proposed that the inverse relationship between age and MetS prevalence could be attributed to pubertal development (64).

With regard to the sex differences, several studies observed that boys tended to be more often diagnosed with MetS than girls (54,59,66,67,77,80,84,85,87,88). As these results were not always significant or even inconsistent across different definitions, the relevance of the sex differences seems questionable and should be further investigated (61,62,65,73,80,82,83). However, several authors agree on the need of age-

and sex- specific percentiles for correct diagnosis of MetS in children and adolescents (61,77,88).

4.4. Observed Correlations between Influencing Factors and Metabolic Syndrome Prevalence

4.4.1. Dietary habits

Rodríguez et al., for example, demonstrated that the prevalence of MetS increases with the consumption of added sugar (sugar contained in processed and artificially sweetened foods) (63). According to this study, a diet rich in added sugars is considered an independent risk factor for MetS (independent of total calorie consumption, physical exercise or nutritional status, evaluated by BMI-z scores) (63). Similar results were found for sugar-sweetened beverages (SSB) in a Taiwanese cross-sectional study of 2727 adolescents. Participants who consumed high amounts of SSB were more likely to present with higher values of BMI, WC, hip circumference and body fat. Moreover, high intake of SSB was significantly associated with MetS among male adolescents (95). As SSB scarcely give a feeling of satiety, such drinks are considered to additionally increase the daily calorie intake (39,95). Besides excess sugar intake, a diet high in fat and energy dense food in general is common among young people, whereas the recommended daily amount of fruits and vegetables are rarely met (91). However, correlations between low-quality diets and the occurrence of MetS in children and adolescents are still vague and need further investigation (62,77).

4.4.2. Physical activity

Low levels of physical exercise and a sedentary lifestyle are well-established risk factors for developing MetS: Burrows et al. and Sobrero et al. could demonstrate that the probability of having MetS was significantly higher among children and adolescents who spend little time on physical exercise but more time on sedentary activities (69,91). Reversely, physical activity is considered to have preventive effects on the development of MetS (59). In this context, an Iranian study found out that high levels of physical activity combined with low screen time was associated with more favorable values for BMI, WC and HDL-cholesterol (96). Moreover, a Chinese study showed that the prevalence of the

MetS was highest among those participants who presented with unhealthy dietary habits and poor cardiorespiratory fitness (97). These results lead to the assumption that both factors synergistically act upon the metabolic risk (55,97) and thus, are responsible for the increasing prevalence of MetS in youth (54).

4.4.3. Environmental and Socioeconomic Conditions

Living conditions, residential area, socioeconomic status and parental education contribute to the distribution of MetS prevalence in a country´s population. Kuschnir et al., for example, observed that children and adolescents living in more urban areas of Brazil showed higher prevalence rates compared to those living in other regions (60). This regional difference could be attributed to unfavorable eating habits and lifestyles that are more typical for urban residents (60). These findings were in agreement with another study conducted among 4641 Iranian children and adolescents, where the prevalence of MetS was twice as high in urban areas than in rural ones (92). In contrast, Fadzlina et al. could not identify any significant difference in MetS prevalence between rural and urban adolescents in Malaysia (85). According to the authors, the similar prevalence rates are due to the unhealthy food habits in urban as well as in rural schools (85). To what extent environmental conditions contribute to the development of the MetS still has to be explored.

Socioeconomic status and education levels are assumed to be implicated in the development of MetS. For example, Bahrani et al. found out that Iranian children of high socioeconomic status (higher family income, higher socioeconomic status of school neighborhood) were more likely to exhibit MetS than those living under poor socioeconomic conditions (67). Similar results were also found in a survey among Brazilian children and adolescents (78). Conversely, MacPherson et al. found an inverse correlation between educational level/ socioeconomic status and prevalence of the MetS among Canadian children and adolescents (75). Another study of Colombian children reported similar results (62). These contradictory findings might be due to a country´s level of development (69). For instance, in industrialized and developed countries, low socioeconomic status and low household education are associated with unhealthy dietary and lifestyle habits (67,75), while in developing countries, high socioeconomic status and education are associated with unfavorable eating habits (owing to the access to processed food) and lower physical exercise due to the adaptation of a westernized

lifestyle (67,69,78). However, other studies did not find any correlation between socioeconomic status or parental education level and prevalence of MetS (73,84).

In summary, all of the above mentioned associations are considered to influence an individual´s probability of becoming overweight and/or obese and developing cardio-metabolic abnormalities, finally leading to the manifestation of MetS. However, due to the cross-sectional character of most of the studies it was not possible to validate a causal relationship between the presumed risk factors and cardio-metabolic consequences (54,75). In order to verify these correlations, longitudinal studies observing the progression of cardio-metabolic risk through childhood and into adulthood would be required (72).

4.5. Comparative Studies and Discrepancies between the Definitions

When evaluating the results from different population-based studies, it is striking that the proportion of children being affected by the MetS varies significantly. This dispersion can be attributed to the properties of the study cohorts such as age-range, sex distribution, ethnicity and prevalence of obesity as well as dietary habits, physical (in-) activity (98), environment and socioeconomic status (67,75).

However, when comparing the results form Miller et al. and Rodríguez et al. it appears that these influencing factors are insufficient in rationalizing such great discordance (10.1% vs. 5.4%; see Table 9), as both research groups used data from the same nationwide health survey of the US population (NHANES) (54,63). The most striking difference was that Miller et al. applied the IDF definition (54), whereas Rodríguez et al. chose the definition of Ford et al. (63). The Ford et al. classification resulted in prevalence nearly twice as high than the IDF classification. Considering these two definitions differ in their cut-off values and diagnostic requirements (e.g. the IDF determine abdominal obesity as a mandatory diagnostic criterion), it is plausible that they also differ in prevalence data.

Table 9 Difference in MetS Prevalence among the NHANES Cohorts, Obtained by the IDF- and Ford-Classifications.

Author Year	Study cohort	Recruitment	Definition	Prevalence
Rodríguez et al. (63) 2016	1623 adolescents aged 12-19a	NHANES 2005-2012	IDF	5,40%
Miller et al. (54) 2014	3495 adolescents aged 12-19a	NHANES 2001-2010	Ford	10,10%

In this context, several research groups compared the different classifications in order to explore their degree of discordance. A summary of the 12 comparative studies is shown in Table 10. In applying more than one definition to the very same study population, these studies could determine to what extent the resulting prevalence numbers are inconsistent with one another. Among the comparative studies, the definition of de Ferranti et al. always reached the highest prevalence, while Cook et al. and Ford et al. obtained rather similar results (6.2% vs. 7.8% (65), 4.9% vs. 4.9% (68), 3.8% vs. 4.1% (79)).

Table 10 Results from Comparative Studies
Note: The lowest and highest value are marked red

Author Year	**Country**	**Sample size Age-range**	**Prevalence of MetS**			
			IDF	**Cook**	**Ford et**	**de Ferranti**
Burgos et al. (76) 2018	Brazil	1200 10-17a	2,1%	1,9%		5%
Asghari et al. (64) 2014	Iran	1424 11-18a	8,4%	13,1%		26,4%
Vanlancker et al. (72) 2017	10 European countries	1004 12,5-17a	2,7%	3,5%		
Ramírez-Vélez et al. (65), 2016	Colombia	1247 9-17,9a	0,3%	6,2%	7,8%	11%
Kim et al. (83) 2016	Korea	2330 10-18a	2,1%		5,7%	
Al-Hussein et al. (68) 2015	Saudi Arabia	2149 6-17a	2%	4,90%	4,9%	17,5%
Wang et al. (84) 2015	China	1770 7-17a	1,1%	2,5%		
Benmohammed et al. (87), 2015	Algeria	989 12-18a	♂1,3% ♀0,5%	♂2,6% ♀0,6%		♂4,0% ♀2,0%
Galera-martínez et al. (73), 2015	Spain	379 12-16,9a	3,8%		5,7%	
Villalobos Reyes et al. (77), 2014	Venezuela	916 9-18a	1,5%	2,2%		
Agudelo et al. (79) 2014	Colombia	851 10-18a	0,9%	3,8%	4,1%	11,4%
Ahrens et al. (61) 2014	8 European countries	12319 2-10,9a	0,4%	1,4%		

The IDF criteria usually presented the lowest number of children being diagnosed with MetS, except for one Brazilian study, where the IDF classification yielded slightly higher results than the definition of Cook et al. (2.1% vs. 1.9%) (76). However, the results that

differed most came from an Iranian study, where 1424 children and adolescents were classified by three different definitions. According to the criteria of de Ferranti et al., 26.4% of the study cohort were diagnosed with MetS. The definition of Cook et al. resulted in 13%, whereas the IDF classification identified 8.4% as being affected (64). Similar findings were reported by the Saudi Arabian survey, where de Ferranti´s classification yielded 17.5%, Ford and Cook nearly 5% and the IDF only 2% (68).

All comparative studies suggest that the prevalence of the MetS varies substantially across different populations and definitions. Additionally, some studies also evaluated the degree of concordance between these definitions by calculating the Cohens kappa coefficient. According to Agudelo et al., the poorest agreement - represented as a low kappa coefficient - was found between the definition of the IDF and de Ferranti et al. (κ=0.14) (79). Cook et al. and Ford et al., on the other hand, showed the greatest concordance (κ= 0.92) (79). The agreement between Cook et al. and IDF was only fair (κ= 0.25 (61), κ= 0.28 (77) and κ= 0.39 (79)) to moderate (κ= 0.47 (72) and κ= 0.53 (76)). These values indicate that different pediatric classifications sometimes disagree on the MetS state (positive/affected or negative/healthy) of the investigated person. In the European study, for instance, the utilization of the Cook et al. and IDF criteria resulted in 32 cases in which the classification was discordant (72). Among them, 20 individuals were diagnosed with MetS according to the Cook et al. criteria, whereas the IDF classified them as being MetS-negative. On the other hand, 12 cases were positive according to the IDF but negative according to the definition of Cook et al. (72).

Results from comparative studies demonstrate that one major problem of assessing pediatric MetS is the lack of consistency between the research works as well as between the different definitions. It appears that the underlying classifications are partly responsible for the variation in the prevalence of childhood MetS, not only between different countries but also within the same nation or study cohort (65,77). This means that the lack of a standardized, globally accepted definition impedes comparison of the prevalence rates between different populations and communities (83).

4.5.1. Different Weighting of the Components of the Metabolic Syndrome

Although most definitions agree in using the same five components, they differ in terms of the limit values. Thereby, the individual components of the MetS are weighted differently

by setting either strict or generous thresholds (see Table 11). Strict limit values are more likely to be exceeded and thus push the number of diagnoses. For example, de Ferranti et al. set the most stringent limits on WC (>75th percentile), HDL (≤50 mg/dl) and TG (≥100 mg/dl) (57,79). Therefore, the probability of surpassing these strict thresholds is high. This explains why the definition of de Ferranti et al. results in higher prevalence values than the other classifications. However, strict limit values might also increase the risk of overestimating the actual prevalence of the MetS (79).

On the other hand, generously set cut-offs are less likely to be surpassed. This means that among the MetS-positive group, only few individuals show this component as being abnormal. Furthermore, higher limit values (or lower, as in the case of HDL) result in a smaller number of people meeting the diagnostic criteria. For example, the IDF uses adult cut-off points for defining increased blood pressure (systolic BP ≥130 mmHg, diastolic BP ≥85 mmHg) instead of age-, sex- and height- specific percentiles (34,79). These limit values seem too high for children and adolescents and thus might be responsible for the low prevalence rates yielded by the pediatric IDF criteria (65). For example, findings from Kim et al., Agudelo et al. and Villalobos et al. could confirm that the prevalence of elevated blood pressure was considerably lower according to the IDF criteria than by using the Ford et al. or Cook et al. definition (demonstrated in Table 11) (77,79,83). This means that, compared with the remaining components, blood pressure contributes less to the overall number of MetS diagnoses (61).

Similar considerations apply to the definitions of Cook et al. and de Ferranti et al., who chose higher limits for elevated blood sugar (≥110 mg/dl). This way, fewer individuals fulfil the criterion of high fasting glucose. Consequently, blood glucose contributes less to the diagnosis of pediatric MetS than the other components (61). In fact, elevated blood glucose was often found to be the least prevalent component of MetS when using the Cook et al. definition (59,67,76,77,79,80).

Strictly defined risk factors determine the characteristics of the MetS-positive cohort. For example, among the four classifications, the IDF and Ford et al. use the strictest limit value for fasting blood glucose (FBG) (>100 mg/dl). Thus, individuals that are at risk of developing T2DM are more likely to be identified by these two criteria than by the others (Cook et al. >110 mg/dl). On the other hand, the Cook et al. and Ford et al. classifications use age, sex and high specific percentiles for defining elevated blood pressure (in contrast to the IDF classification, which uses adult thresholds) and thus are assumed to better identify those, who are more likely to be affected by future CVD (79).

As stated above, the IDF definition takes a special status among other classifications, since it requires the presence of abdominal obesity as a mandatory diagnostic component. Thereby, normal WC becomes an exclusion criterion that may diminish the prevalence of MetS (60,83). As shown in a Chinese study, the IDF criteria exhibited lower sensitivity than the Cook et al. definition. The authors argued that the low sensitivity of the IDF definition might be due to the exclusion criteria of "normal WC". The fact that Chinese children show lower prevalence of obesity than children of many Western countries may partly explain why the prevalence of MetS is lower as well (84).

Table 11 Different Weighting of the Components of Metabolic Syndrome.

Author Year	**Definition**	**Diagnostic Criterion: elevated BP**	**Prevalence of elevated BP**
Kim et al. (83) 2016	IDF	systolic BP ≥130 mmHg or diastolic BP ≥85 mmHg	2,4%
	Ford	≥90th percentile; specific for age, sex and high	20,4%
Agudelo et al. (79) 2014	IDF	systolic BP ≥130 mmHg or diastolic BP ≥85 mmHg	2,2%
	Cook	≥90th percentile; specific for age, sex and high	10,3%
Villalobos et al. (77) 2014	IDF	systolic BP ≥130 mmHg or diastolic BP ≥85 mmHg	0,7%
	Cook	≥90th percentile; specific for age, sex and high	8,7%
Author Year	**Definition**	**Diagnostic Criterion: high fasting blood glucose (FBG)**	**Prevalence of high FBG**
Agudelo et al. (79) 2014	Cook de Ferranti	FBG ≥110 mg/dl	0,6%
	IDF, Ford	FBG ≥100 mg/dl	2,8%

Until today, there is still no consensus concerning an optimal MetS classification for children and adolescents. Agudelo et al., for example, suggested to apply the definition of Ford et al. as it uses widely recognized cut off values from international research groups (NCEP and IDF). Even though it is quite similar to the definition of Cook et al., the lower threshold value for fasting blood sugar (100 mg/dl vs. 110 mg/dl) is thought to better

identify those individuals that are in need of prevention and/or therapy (79). Ahrens et al., on the other hand, recommended attributing the highest weight to overweight and obesity. The remaining components should be weighted equally, as their individual impact on the overall cardio-metabolic risk is still not fully understood (61). The IDF definition was considered too restrictive due to the application of adult threshold values. In contrast, age- and sex- specific percentiles seem more appropriate for children and adolescents (77).

4.5.2. Rationales for the Difficulties in Developing a Uniform MetS Definition

The reasons for the continuing disagreement among criteria and definitions are numerous. Since knowledge about the pathogenic mechanisms of MetS in children and adolescents is insufficient, the development of one reliable definition is problematic (11). For instance, due to the paucity of long-term studies, it is hardly possible to quantify the extent to which childhood risk factors actually cause health consequences in adulthood (74,99). Therefore, it is difficult to set reliable pediatric threshold values above which the health risk is verifiably increased (74). Thus, pediatric cut-off points generally seem problematic and questionable since their future health consequences are poorly validated (34,55,56,99). In sum, long-term studies that evaluate the causal links between the cardio-metabolic risk in childhood and the health outcomes in adulthood are required. Tracking at-risk children into adulthood - with morbidity and/or mortality as end-points - would help determining appropriate cut-off points for young age groups (11,72,74,99).

As youth is characterized by huge physiological changes and transition, evaluation of the cardio-metabolic state during this period is extremely difficult and insecure (55). In the course of growth and puberty the organism undergoes several modifications in physiological processes that also affect cardio-metabolic parameters (83,100): First, hormonal appetite regulation (via insulin and leptin) as well as fat distribution (android and gynoid) change during pubertal development and might increase the risk of weight gain in this period (54). Second, puberty is associated with a temporary state of physiological insulin resistance, owing to elevated levels of the insulin-like growth factor I (IGF-I) and other growth hormones (101). In most cases, insulin sensitivity returns back to normal after completion of pubertal development (100). However, in the presence of obesity, pubertal insulin resistance might develop towards impaired glucose tolerance or even T2DM (54,101). Therefore, adolescence is considered a vulnerable period for MetS to

become manifest (74). That is to say, the MetS state (negative/positive) partly depends on the maturation stage: In peri-pubertal children, the prevalence of insulin resistance and obesity are probably higher due to hormonal changes, while in the post-pubertal phase, the metabolic processes could return to normal. In fact, long-term studies could provide evidence for fluctuations in the cardio-metabolic state during puberty (64,102,103). Children that were diagnosed with MetS in (pre-) puberty were found to be MetS-negative in the post-pubertal follow-up evaluation and vice versa (64,102,103). Taken together, alterations of hormonal status during puberty are considered to be responsible for the inconstant prevalence of the MetS in this period (55,104,105). For this reason, cardio-metabolic risk assessment in adolescents requires cut-off points that also reflect pubertal development (104).

Another factor that complicates the development of a uniform definition is the fact that ethnic groups differ in terms of their anthropometric (and metabolic) characteristics (32,54,106). Accordingly, ethnic-specific cut-off points and percentiles are required to define abdominal obesity, dyslipidemia, elevated blood pressure and impaired glucose metabolism (34,77,88). Since such percentiles are not available for every population, some studies use preexisting reference values of other population groups instead. This may overestimate or underestimate the actual prevalence of the MetS (59,77) and impedes comparability between different cross-sectional/epidemiological studies. Taken together, cardio-metabolic risk assessment in children and adolescents requires age- and sex- specific percentiles that also consider pubertal development and ethnicity (3,9,32,55,90,104,107).

Another problem of MetS is the dichotomous manner of analyzing its components (98). This means, that each diagnostic criterion is described as either being normal (beneath the cut-off value for WC, BP, FBG, TG or above the cut-off value for HDL, respectively) or abnormal (exceeding the cut-offs for WC, BP, FBG, TG or beneath the cut-off for HDL, respectively). In this way, the definitions do not take into account to what extent an individual risk factor contributes to the overall risk profile (55). Regarding the whole syndrome, an individual can only be diagnosed as either having MetS or not, whereas the severity of the MetS cannot be evaluated (108). Therefore, researchers claim that dichotomizing each diagnostic component (as normal or abnormal) results in loss of important information. Instead, measurements should be treated as continuous variables (11,56), meaning that each risk factor should be involved in the overall risk estimation, regardless of whether it surpasses the threshold or not (72). For this reason, the

continuous metabolic syndrome score (cMetS) has been developed. It is calculated by summarizing the z-Scores of each MetS component (z-Score = *"individual value − sample mean/standard deviation of the sample"*(98)), whereby a high score equates to a poor metabolic profile with higher risk for CVD and T2DM (98). In this way, the overall cardio-metabolic risk can be evaluated with respect to small/gradual changes of each risk factor and thus better reflect the pathophysiological processes (61). With this in mind, Magnussen et al. compared the predictive power of cMetS scores against that of a dichotomous MetS definition regarding adult outcomes (T2DM and carotid intima-media thickness) in Finn children (109). Elevated cMetS scores (higher than one standard deviation above the mean) have been significantly associated with higher carotid intima-media thickness and higher risk of T2DM in adulthood. However, cMetS scores did not perform any better in predicting adult outcomes than the dichotomous classification, suggesting that the calculation of cMetS scores is not superior to the common diagnostic procedure (109).

4.6. The Relevance of Pediatric Metabolic Syndrome in Clinical Practice

Given the continuing disagreement and lack of knowledge regarding pediatric MetS, it is difficult to provide recommendations about its clinical application (110). Major concerns in regards to pediatric MetS include the high number of different classifications and the continuing disagreement concerning the determination of risk factors. This in turn impedes comparison across current scientific findings, thus making it difficult to draw any conclusion about the epidemiological situation (83). Although the existence of MetS in children and adolescents has been reported, it is still unclear how accurately childhood MetS can predict adult health outcomes (3,56,99). Results from longitudinal studies are also not that conclusive. In two Iranian studies childhood MetS was found to be a poor prognostic factor for adult MetS (64,66), while in the "Cardiovascular Risk of Young Finns Study", the accuracy in predicting adult health outcomes was hardly better than prediction by pure chance (109). These findings agreed with the "Princeton Lipid Research Cohort Study", in which the within-person accordance between childhood- and adult MetS severity (evaluated by calculation of a MetS severity z-score) was found to be moderate (111). This instability in MetS status could be explained by changes in weight status as well as by pubertal development during the follow-up period (64,66,103). Individuals, who were obese in childhood but were of normal weight in adulthood, were shown to have a

similar risk for being MetS-positive as those who were never obese (66). This indicates that weight status per se is a predictor of adult health risk (112). Indeed, longitudinal studies revealed that childhood MetS does not perform any better in predicting adult MetS, T2DM or CVD than BMI per se (66,112). These findings foster the discussion whether its clinical application provides any benefit, especially since body weight assessment requires less effort while providing similar results (112). As testing for pediatric MetS not only seems to be impractical but also achieves results of only moderate predictive accuracy, authors recommend applying pediatric MetS definitions with caution (104,109).

Despite these multiple doubts, researchers recognize childhood obesity with premature accumulation of cardio-metabolic risk factors as being one major challenge of public health (55,79,103,106). In parallel with the growing number of childhood obesity (46) cardio-metabolic abnormalities are thought to become more prevalent as well (11,54,55,57). This development raises great concerns, especially when considering that health effects of childhood obesity could already emerge at young ages, track into adulthood and cause premature onset of CVD and T2DM (54,55,78). Findings from the "Princeton Lipid Research Cohort Study" revealed that changes in the severity of MetS, which were observed during the follow-up period between adolescence and young adulthood, can be predictive of future diseases (111). Indeed, the persistence or worsening of childhood cardio-metabolic risk factors and MetS into adulthood is assumed to substantially increase the risk for future diseases (113,114). This emphasizes the importance of early prevention and treatment measures, so that childhood obesity and weight gain during adolescence can be impeded and the increasing prevalence of cardio-metabolic complications can be counteracted (11,60,67,76). Therefore, screening measures seem indispensable for identifying those children that are at high risk - especially when considering that initial cardio-metabolic changes do not cause any symptoms (11,62,104).

Albeit the utility of MetS in pediatric patients is questionable, its concept of risk factor clustering could serve as a rough guide for risk assessment in the clinical setting (110). However, pediatricians should rather focus on established cardio-metabolic risk factors instead of sticking to certain MetS classifications (3,66,110,112). Since weight status correlates closely with cardio-metabolic abnormalities, WC measurement and BMI calculation are considered helpful screening tools for detecting children with high risk of MetS (70,87). Besides this, the individual medical history, familial predispositions, eating habits and lifestyle behavior should also be part of the cardio-metabolic risk evaluation (11,94,99). Considering that MetS already occurs in youth and often in

combination with obesity, it is important to start countermeasures as early as possible (79). Implementing prevention programs against overweight in a school environment would reach a large number of children and might realize a decrease in childhood obesity (68). Such programs should promote knowledge and awareness of a healthy lifestyle with special focus on adapting a healthy diet and boosting physical activity (69). Treatment strategies should also be targeted at managing obesity as well as treating the individual cluster of cardio-metabolic risk factors (11,110).

4.7. Limitations

Several limitations have to be mentioned when discussing and comparing the results of this literature research. First, not every cohort of the included studies was representative for the overall country population. In some cases, the participant recruitment was conducted in specific country regions (73,77,84) or among special ethnic (74) or socio-economic groups (69). In two studies, the participants were not randomly selected (71,79). Secondly, some studies used data that were collected several years ago (54,64,80) and thus might not exactly reflect the current epidemiological situation. Thirdly, due to the exclusion criteria (e.g. studies with particular selection criteria, studies that used different definitions etc.) prevalence data of several other countries could not be taken into account.

4.8. Conclusion and Perspectives for Future Scientific Research

As the prevalence of childhood obesity is increasing worldwide, clustering of cardio-metabolic risk factors and subsequent diseases are considered to become more prevalent among the young population as well. Current epidemiological studies revealed that the prevalence numbers of childhood MetS are high in the US, in the Middle East and in South American countries, with the highest proportion of MetS diagnoses occurring among overweight and obese individuals. Besides obesity, increasing age, a diet high in sugar, low physical exercise, socioeconomic status as well as the level of education were found to be associated with the probability of developing MetS. However, the actual pathogenic mechanisms behind childhood MetS are still unclear and until today, there is no uniform definition.

The high number of different criteria, all of which are in disagreement with each other with regards to diagnostic parameters, measuring techniques or limit values, create variations in the prevalence data from different epidemiological surveys. Indeed, comparative studies found low agreement between the different MetS definitions, meaning that these classifications do not always diagnose the same individuals as having MetS. This literature research demonstrates that prevalence rates considerably depend on the underlying classification, which in turn impedes comparison between different epidemiological studies. Moreover, the actual reliability of the pediatric MetS diagnosis to predict future health consequences is rather poor. This could partly be explained by puberty-associated changes in hormonal status and body weight. Given the disagreement on the criteria to diagnose MetS in children and youth as well as the low predictive power of such diagnosis, the whole concept of pediatric MetS seems questionable. Until there is better understanding of the pathophysiology of MetS in children and adolescents, cardio-metabolic risk evaluation should rather be based on established risk factors such as nutritional status, hypertension, dyslipidemia, insulin resistance and clinical status of the patient.

Future scientific research should take into consideration several aspects: Firstly, in order to validate the causality between childhood risk factors and adult health consequences, longitudinal studies with definite endpoints are required. This will lead to clarification of the underlying pathogenic mechanisms and facilitate determination of appropriate limit values/ ranges (72,74). Secondly, age-, sex- and ethnicity- specific percentiles for growth, weight and waist circumference should become available for every population group in each country (106). Thirdly, the influence of pubertal development on cardio-metabolic parameters needs further investigation (104). Lastly, there is a need to establish one valid, globally accepted definition of metabolic syndrome for pediatric populations (74). This uniform definition would enable comparison across different studies and help drawing conclusions about the actual health risk (72,74).

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