

Metabolic Syndrome in Children and Adolescents

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Keywords

Juvenile obesity · Therapy · Multicomponent approach · Prevention · Metabolic syndrome

Summary

Background: Juvenile obesity is associated with multiple cardiometabolic comorbidities, which may culminate in the metabolic syndrome (MetS). **Methods:** Based on a narrative review, the current knowledge of prevalence and the underlying metabolic principles regarding juvenile obesity and MetS are summarized to compile up-to-date information. In addition, the role of lifestyle as well as positive and negative influencing factors are focused on. **Results:** The prevalence of MetS occurs between 1 and up to 23% in the total pediatric population and in up to 60% amongst the obese and overweight. It can be considered as the consequence of multiple processes in terms of lifestyle, perinatal programming, and (epi-)genetic pathways; however, the complex underlying mechanisms and their interplay are not completely understood. **Conclusion:** Besides preventive approaches, the growing number of obese children and youth as well as its consequences call for effective and lasting therapeutic measures.

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Introduction

Overweight and obesity in childhood and adolescence are one of the greatest challenges of healthcare systems worldwide. The global rate of overweight and obese children has increased from 4.2% in 1990 to 6.7% in 2010. According to estimates, the rate will further increase to 9.1% in 2020, which accounts for approximately 60 million children. In the USA alone, the prevalence of obesity has

increased from about 5% in the 1960s and 1970s to 17% in 2003/04, whereas no further increase has been shown until 2009/10 [1, 2]. Similarly, the prevalence rates in Europe and Canada have neither increased nor declined between 2002 and 2010 but are in a state of high-level stagnation [3, 4]. Accordingly, data from the ‘Kinder- und Jugendgesundheitssurvey’ (KiGGS) reveals that roughly 9% of children are overweight and 6% obese [5]. Compared to the data from the meta-analysis by Kromeyer-Hauschild et al. [6], this poses an increase in childhood overweight of 22% and in obesity of 100%. The current development is being determined by the ongoing KiGGS survey. Albeit emerging results may signify stagnation, it is indicative that even normal-weight children exhibit a higher body fat percentage [7]. This is relevant since possible comorbidity does not only increase in accordance with the calculative body mass index (BMI) but also with increased (visceral) body fat content. Even at that young age negative impacts due to cardiovascular disease risk factors such as hypertension, glucose intolerance, dyslipidemia, endothelial dysfunction, musculoskeletal disorder, and particularly psychological burdens such as depression, decreased quality of life, and so forth are prevalent [8, 9].

From the KiGGS data collective, Flechtner-Mors et al. [10] compared 63,025 overweight or obese children and adolescents to 14,298 participants that were of normal weight. The key findings are shown in table 1.

This narrative review aims to compile data on prevalence, positive and negative influencing factors, and preventive strategies, paying special attention to movement therapy.

Definition and Prevalence of the Metabolic Syndrome in Childhood and Adolescence

Friend et al. [11] analyzed 85 papers on the prevalence of the metabolic syndrome (MetS), which can be understood as a culmination and combination of the abovementioned risk factors, by means of a systematic review. The article concludes that MetS occurs in 3.3% of the general population but 11.9% in overweight

Table 1. Occurrence of selected cardiovascular disease risk factors in a data set of normal-weight versus overweight/obese children and adolescents (modified after Flechtner-Mors et al. [10])

	Normal-weight children (n = 14,298), %	Overweight and obese children (n = 63,025), %
Elevated blood pressure	6.1	35.3
Elevated total cholesterol	8.6	13.8
Elevated LDL cholesterol	7.0	14.5
Elevated triglycerides	3.0	13.6
Reduced HDL cholesterol	3.0	10.1

LDL = Low-density lipoprotein; HDL = high-density lipoprotein.

children and 29.2% in those obese. It occurs most often in boys and those that are older (5.1% in boys vs. 3.0% in girls and 5.6% in the elderly vs. 2.9% in the youth). Taylor et al. [12] analyzed 36 studies and observed an occurrence between 1.2 and 22.6% in the total population and up to 60% amongst the obese and overweight. This large range can mainly be attributed to the inconsistent definition of the term metabolic [13]. According to Agudelo et al. [14], the current cutoff points are highlighted in table 2. Depending on classification, the occurrence varies between 0.9, 3.8, 4.1, 10.5, and 11.4% corresponding to International Diabetes Federation [19], Cook et al. [15], Ford et al. [17], Agudelo et al. [18], and de Ferranti et al. [16], respectively.

Lifestyle Factors

The central risk factor concerning the MetS in adolescence is juvenile obesity [14]. Apart from genetic disposition, this factor is particularly influenced by lifestyle choices. In terms of nutrition it is currently assumed that the crucial element is an excess of daily calories, i.e. 70–140 [20] or 200 kcal [21] per day, e.g. because of the high consumption of sugar-sweetened beverages [22]. Furthermore, there is strong evidence of a relationship between the amount of sedentary time and obesity. Moreover, evidence of moderate influence has been observed in connection with blood pressure and total cholesterol, self-esteem, social behavior problems, physical fitness, and academic achievement [23]. In the current literature sedentary behavior is defined in two different ways. One is mainly concerned with energy consumption below a certain threshold, e.g. resulting from sitting or lying. This threshold is generally defined as 1.5 METs (metabolic equivalent of task). METs describe the energy cost of physical activities as well as the factor by which the resting oxygen intake of 3.5 ml/kg (body weight) increases during a certain activity (summarized in Graf et al. [24]). The other, more ‘exercise-oriented’ approach defines every activity as sedentary whose intensity remains below the moderate to vigorous physical activity threshold. Thus, an hour of activity per day including everyday chores would satisfy the former definition but not the latter. This lack of a uniform definition is confounding and makes it difficult to agree upon set minimums of activity or their

intensity. The Sedentary Behaviour Research Network [25] hence suggests that sedentary behavior describe every sitting or lying activity whose energy cost remains below 1.5 METs. Inactivity should be defined as activities whose intensity does not exceed moderate to vigorous. It is important for studies, publications, and recommendations to adhere to such an accuracy and selectivity in their definitions. However, in practice a rather plain concept may be sufficient: the avoidance or reduction of sitting (and lying) occupations. In their current review, Carson et al. [26] compiled the associations between sedentary behavior and health indicators from 235 studies (194 unique samples) including 1,657,064 unique participants from 71 different countries. Most of those studies are quantitative cross-section analyses. 162 of the studies show that higher durations or frequencies of screen time and TV viewing were significantly associated with adverse measures of body composition across all study designs; and 32 of the studies show that a higher duration or frequency of TV viewing was significantly associated with higher clustered cardiometabolic risk scores across all study designs. However, the quality of those studies is ranked between very low and low. Physical activity or fitness seems to have protective qualities since a current review shows a negative correlation between physical activity or fitness and overweight or obesity [27]. These findings are based on 12 cross-section analyses and 2 longitudinal studies. Andersen et al. [28] analyzed the connection between the occurrence of cardiovascular disease risk factors (blood pressure, lipid profile as well as a composite risk factor score) and physical activity or fitness and described an inverse relationship. Both muscle strength and, even more significantly, endurance exercise had an effect on blood lipids and insulin sensitivity. In children, aerobic training programs have the potential to effectively improve cardiovascular disease risk factors [29]. The relationship between the occurrence of MetS and insulin resistance has been summarized in a review by Guinhouya et al. [30]. Therein, 37 studies were included; two thirds (26 studies) were cross-sectional observation studies, and 2 studies (8%) were prospective cohort studies. The remaining 8 studies (22%) were interventions. Generally, higher physical activity levels were consistently associated with an improved metabolic profile and a reduced risk for MetS and/or insulin resistance in these populations. However, almost all participating authors criticize the poor quality of the reviewed studies, particularly the absence of longitudinal studies to determine causation. Furthermore, methodologically sound intervention studies which result in specific recommendations are lacking. Based on this, only one assumption can be drawn: with increasing reduction of physical activity or fitness comes an increase of cardiovascular disease risk factors. It is reported as early as in kindergarten that the WHO recommendation of at least 60 min of physical activity per day is not being reached [31]. Consequently, this has an adverse effect on overall fitness. Tomkinson [32] hypothesizes a decrease of roughly 1% every 2 years. Whether or not the internationally updated physical activity recommendation of 60 min per day may lead to an increase in fitness remains to be determined, especially since these minimal values are derived from empiricism and not from what is actually relevant for a healthy development.

Table 2. Criteria and cutoff points for the diagnosis of metabolic syndrome in adolescents

Criterion	Cook et al., 2003 [15]	de Ferranti et al., 2004 [16]	Ford et al., 2007 [17]	Agudelo and Arias, 2008 [18]	IDF consensus definition, 2007 [19]
Triglycerides / HDL-C	≥110 mg/dl; ≤40 mg/dl	≥100 mg/dl; <50 mg/dl <45 mg/dl in 15- to 19-year-old males	≥110 mg/dl; ≤40 mg/dl	≥110 mg/dl; ≤40 mg/dl	≥150 mg/dl; <40 mg/dl
Fasting glucose	≥110 mg/dl	≥110 mg/dl	≥100 mg/dl	≥100 mg/dl	≥100 mg/dl
Blood pressure, mm Hg	≥90th percentile; by age, gender, and height	≥90th percentile; by age, gender, and height	≥90th percentile; by age, gender, and height	≥90th percentile; by age, gender, and height	SBP ≥ 130 mm Hg; DBP ≥ 85 mm Hg
Waist circumference	≥90th percentile; by age and gender	>75th percentile; by age and gender	≥90th percentile; by age and gender	≥95th percentile	≥90th percentile; by age and gender
BMI	none	none	none	none	none
Metabolic syndrome diagnosis	presence of three or more criteria	presence of three or more criteria	presence of three or more criteria	presence of three or more criteria	high waist circumference + two other criteria ^a

^aAdolescents > 16 years; waist circumference in men > 102 cm and in women > 88 cm; triglycerides > 150 mg/dl; HDL-C in men < 40 mg/dl and in women < 50 mg/dl; blood pressure ≥ 130 / 85 mm Hg or treatment for previously diagnosed hypertension; glucose ≥ 100 mg/dl or diagnosed for type 2 diabetes mellitus (T2DM).

IDF = International Diabetes Federation; BMI = body mass index; HDL-C = high-density lipoprotein cholesterol; SBP = systolic blood pressure; DBP = diastolic blood pressure.

Taking this into account, a German expert consensus recommends at least 90 min of physical activity per day [33].

Selected Factors of Molecular Biology and Genetics

Modern knowledge of visceral fat and adipose tissue provides an insight into the secretion of certain substances, such as inflammatory molecules (e.g. tumor necrosis factor- α , interleukin-6, and C-reactive protein (CRP)), cytokines (e.g. leptin, adiponectin, vaspin, and others), and fatty acids [34]. These compounds exert biological actions beyond the adipose tissue, and many directly influence peripheral metabolic, vascular, and endocrine processes. In addition, low-grade systemic inflammation may underlie the clustering of metabolic risk factors, although their role in children has yet to be clarified. An additional and novel approach is made possible by the research focusing on genetic and epigenetic mechanisms and prenatal imprinting. Amongst others, twin and adoption studies show that genetic determination plays a role in juvenile obesity [35]. This has been ascribed mostly to polygenetic arrangement [36]. The gene having the highest correlation with obesity (but also with MetS) is the fat mass and obesity-associated (FTO) gene, 87 variants of which have been detected with an associated increased risk for obesity [37]. It is now known that the FTO gene is active in the hypothalamus and influences food intake and nutritional behavior. Additionally, it seems to be involved in the regulation of various processes dealing with fat burning patterns.

The maternal body weight and the associated lifestyle before and during pregnancy are closely correlated with juvenile obesity. Hypercaloric nutrition, for instance, as well as a lack of physical

activity raises the risk for both increased weight and/or gestational diabetes [38, 39]. The associated maternal hyperglycemia leads to continuing fetal hyperglycemia and overstimulation of the perinatal pancreatic B cells as well as to hyperinsulinemia with an increased risk of the development of type 1 diabetes in the fetus [40]. The elevated insulin concentration in the infantile hypothalamus (especially in the ventromedial nucleus of the hypothalamus) is causing a faulty programming of neuroendocrinological regulation of food intake, body weight, and metabolism [41]. In terms of perinatal imprinting, this is associated with a permanently increased disposition for obesity, type 2 diabetes, MetS, and – in the long term – cardiovascular disease [40, 42–44].

Another aspect has been highlighted by the so-called ‘Barker hypothesis’. It postulates that the cardiometabolic risk or a faulty metabolic regulation does not only occur in children with overweight or obese mothers but also in children with a birthweight that is too low. The thrifty phenotype hypothesis proposes that the epidemiological associations between poor fetal and infant growth and the subsequent development of type 2 diabetes and MetS result from the effects of poor nutrition in early life, which ensues in permanent changes in the glucose-insulin metabolism. These changes also include reduced capacity for insulin secretion and insulin resistance, which, in combination with effects of obesity, ageing, and physical inactivity, are the most important factors in determining type 2 diabetes [45]. The time frame of this imprinting is not restricted to mother and infant. According to epidemiological and experimental findings, an epigenetic maternofetal transmission of such acquired persistent modifications can run over several generations, mediated by gestational hyperglycemia and fetal or neonatal hyperinsulinemia. It remains to be discovered which additional

mechanisms and organ systems can additionally influence this process, e.g. the (maternal) intestine as the largest human immune organ or rather the microbiome, which is highly (epi-)genetically, transcriptionally, and metabolically active [46]. The role of the father is increasingly gaining attention among the scientific community since their epigenetic information can also be transferred, e.g. through the sperms and the associated RNA regulation [47, 48]. The Generation R study shows a higher maternal and paternal pre-pregnancy BMI, which is associated with an adverse cardiometabolic profile (body composition, lipids, insulin, C-reactive protein, and blood pressure) in offspring, with stronger associations present for maternal pre-pregnancy BMI [49].

More research and clarification of the abovementioned aspects and their complex interrelations will undoubtedly pave the way for new opportunities and avenues in prevention and therapy. The benefits of the mothers' physical activity on their unborn offspring is well documented by now with the recommendation of at least 150 min of physical activity per week during pregnancy [50]. This leads to a reduced increase in body weight, reduced risk for gestational diabetes, and reduced pregnancy-associated complications as well as a better metabolic regulation in the offspring. The role and the influence of physical activity in mothers and fathers prior to pregnancy need to be examined. Circumstantial prevention has turned out to be of utmost importance as it relates to one's general working and living environment. A healthy living environment and situation does not only facilitate the implementation of a healthy lifestyle on an epidemiological level but also affects the health of the individual and its offspring through possible epigenetic activation or silencing of relevant parts of our genome.

Prevention and Therapy of Juvenile Obesity

It seems that reduction of juvenile MetS is the most crucial task in the prevention of juvenile obesity. However, even in normal-weight children the percentage of body fat is increasing [7]. Hence, it is even more important to not only implement a balanced diet but also reduce time spent sitting or increase physical activity and thus fitness as a preventive factor. Until today, however, there does not exist a straightforward or infallible approach. Most research is conducted in the (pre-)school setting and documents small improvements with a reduction of BMI by roughly 0.2 kg/m² [51]. Programs on the communal level have shown to be most successful although requiring great effort and the participation by many stakeholders from the respective settings, e.g. schools, clubs, businesses, or political support [52]. 3 years after the end of such a program in Australia, a lasting reduction of overweight and obesity of 8% was recorded [53]. In a wider sense, therapy of juvenile obesity can in turn act as prevention for the resulting MetS. Generally, management interventions showed greater effects regarding weight loss compared to prevention interventions.

The focus of appropriate multimodal professional training lies on (family) diet as well as physical activity habits and behavior

with collateral psychological support [54]. The goal is the reduction of soft drinks and of fatty and sugary foods of a mostly high-caloric diet as well as an increase of vegetables and fruit [55]. Regarding physical activity, the aspiration is a general increase of everyday life activities and an increase of duration and intensity of exercise as well as the minimization of sedentary behavior, particularly media consumption [55]. This approach is supported by means of pedagogical and psychological supervision during therapy, e.g. the examples set by parents, monitoring, goal setting, stimulus control, etc. [55]. Management interventions should focus on parents as the 'agents of change' for physical activity and nutrition while integrating behavioral therapy techniques and interactive education [56]. Results from all the existing meta-analyses indicate small or moderate short-term improvements of obesity, mainly due to the varying approaches of the integrated studies (monodisciplinary, short duration, diverging sample groups, etc.) and their heterogeneous nature, as summarized in Janicke et al. [55]. Their meta-analysis of 20 multimodal family-based studies describes a small success in general but more specifically the single variables with the biggest impact on therapy success. Those with significantly positive impact are: duration, design (individuals or groups), scope and number of interventions as well as the age of the participating children. Other studies indicate that the initial body weight, the initial weight loss, and a positive self-concept are all aspects with a positive impact on (long-term) weight loss and maintenance. Conversely, eating disorders and noticeable psychopathology in the mother, such as depression, are shown to have a negative effect on study success (summarized from [57–59]). Special educative approaches, e.g. integration of behavioral modifying strategies, seem to improve the success of obesity treatment (reduction of BMI by approximately 0.9 kg/m² and of belly circumference by about 3 cm) [60].

It is worth noting that, in practice, physical exercise interventions do not necessarily reduce BMI because of the beneficial shift in body composition in favor of muscle mass and less body fat [61].

A completely other approach is made possible by bariatric surgery. Originally designed for morbidly obese adult patients with a BMI either above 50 kg/m² or a BMI above 40 kg/m² with comorbidities, this option is also available for affected adolescents nowadays [62, 63]. However, the total number of adolescents under 18 years of age who have undergone this type of surgery is (fortunately) very low and ranges between 0.1 and 1%. The long-term success of this intervention is generally positive: depending on different surgery methods, a follow-up after 6 years shows a BMI reduction between 12 and 20 kg/m² as well as a reduction of possible comorbidities. Complications depend on the respective techniques and can be very serious, ranging from deficiencies in micronutrients (iron, vitamin D, etc.) to pulmonary embolism, but have so far been recorded rather inconsistently and infrequently. The S2 guidelines of the 'Arbeitsgemeinschaft für Adipositas im Kindes- und Jugendalter' from 2014 (and in part from 2012) define for which adolescents, if any, this course of action is viable (www.a-g-a.de). Criteria may include morbid obesity, compliance, exclusion of psychological disorders or sufficient intellect, etc.

Conclusion

The prevalence of obesity and MetS in children and adolescents is increasing. Therefore, the emphasis of all studies and programs related to the MetS should be focused on prevention, early detection of metabolic risk factors, and interventions that will have a significant impact on future adult and offspring health. Consequently, as supported by current findings, the most crucial course of action is early facilitation and promotion of a healthy diet and adequate physical activity. Unfortunately, the existing data cannot provide a definitive and satisfactory answer regarding intensity, duration, frequency, most appropriate sports, the interconnections with motivation, etc. However, it is paramount that the focus of physical

activity is not to decrease the BMI but to improve body composition and other surrogate measures, e.g. blood pressure, lipids, insulin, blood sugar, adipocytokines and so forth, as well as fitness and motor capabilities. Next to the abovementioned microbiome and adipocytokines (as factors of the (visceral) fat mass), especially myokines of the muscle tissue seem to play an equally important role in influencing neurometabolic and inflammatory processes [64].

Disclosure Statement

The authors do not have any conflict of interest.

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