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Metabolic Syndrome Severity and Lifestyle Factors Among Adolescents

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Abstract

The continued rise of pediatric obesity globally has raised concerns for related sequelae. One marker of risk is the metabolic syndrome, a cluster of cardiovascular risk factors that is associated with future cardiovascular disease and type 2 diabetes. MetS has at its core visceral adipocytes exhibiting dysfunction as a result of excess fat content. MetS in children and adolescents is linked to unhealthy lifestyle practices such as sedentary lifestyles and excess consumption calories. As such, the optimal means of addressing MetS targets a decrease in adiposity through lifestyle modification, a decreases in MetS following increases in physical activity and improvements in the quality and content of food intake. Efforts remain needed in increasing motivation to these changes and maintaining adherence to avoid long-term sequelae.

Introduction & Epidemiology

Global rates of pediatric obesity have risen dramatically in the last three decades. In 2010, there was an estimated number of 43 million children worldwide that are overweight or obese [1]. This represents almost a 60% increase in prevalence of overweight and obese children as rates increased from 4.2% to 6.5% between 1990 and 2010 [1]. This epidemic, which was previously a phenomenon that was present in mainly developed countries, has spread to developing countries, perhaps due to globalization and cultural exchange. Of the 43 million overweight or obese children worldwide, 35 million children are from developing countries. Still, in the U.S., prevalence is much higher, with 16.8% of children and adolescents overweight or obese, a number that has not abated in recent years [2]. With increasing rates of pediatric obesity, there is increasing scrutiny towards pediatric metabolic syndrome (MetS), and important sequela of obesity [3]. Though obesity does not guarantee the presence of MetS, the two are correlated and closely intertwined. This epidemic is of significant concern for pediatricians worldwide, demanding urgent attention and intervention.

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Diagnosis criteria of metabolic syndrome

MetS is defined as a clustering of metabolic abnormalities (central obesity, hypertension, elevated glucose, dyslipidemia) that result in a synergistic effect to increase risk for cardiovascular disease (CVD) and type 2 diabetes (T2DM), with mechanistic underpinnings of oxidative stress and insulin resistance [3, 4]. Whereas obesity in some cases appears to have less long-term risk than in other cases (sometimes referred to as “healthy obesity” [5]), MetS appears to be a much more specific marker of risk. For example, odds ratios (OR’s) for future T2DM and CVD among adolescents with MetS (vs. no MetS) were 11.5 [6] and 14.6 [7], compared to OR’s among adolescents with obesity (vs. normal weight) of 1.7 [8] and 1.33 [9]—underscoring a key reason for assessing risk factors for MetS in this age range.

First characterized in adults, MetS has been classically defined by criteria such as those of the National Cholesterol Education Program (NCEP) Adult Treatment Program-III (ATP-III) the presence of three or more of the following abnormalities: elevated waist circumference indicating central obesity, high blood pressure, low HDL, and high fasting glucose [4]. The International Diabetes Federation (IDF) similarly characterizes MetS in adults as the presence of central obesity according to ethnicity specific values, and the presence of two of the following: high triglycerides or treatment of such abnormality, low HDL or treatment of such abnormality, elevated blood pressure or treatment of previously diagnosed hypertension, and elevated fasting glucose or previously diagnosed T2DM [10].

In the field of pediatrics, there is currently no consensus for a set of standard diagnostic criteria for MetS, with multiple studies proposing various differing sets of criteria [11–14]. Most commonly, adult criteria have been adapted by keeping the same cut-off for glucose but using either a BMI z-score or 90th percentile cut-offs of waist circumference [15] and age appropriate pediatric cut offs for blood pressure [16], HDL, and triglycerides. The most commonly-used criteria are adaptations of the adult NCEP ATP-III criteria (Table 1) [17]. In 2007, IDF proposed a set of criteria for diagnosing childhood MetS, applicable in children ages 10 and older [10]. IDF diagnostic parameters required the presence of central obesity in addition to two other risk factors: obesity, blood pressure, triglycerides, or HDL. The age cutoff was created with the assertion that MetS cannot be diagnosed in children ages 6-10 years, but that central obesity with waist circumference 90th percentile and family history of metabolic abnormalities warrant increased surveillance. This set of pediatric IDF MetS criteria can be used alongside the adult IDF MetS criteria [18].

There are, however, limitations to the traditional criteria of determining the presence of MetS. As a binary estimate, it can only indicate the presence or absence of MetS in a qualitative manner and cannot provide quantitative data [19]. Longitudinal studies have demonstrated that individual adolescents (potentially those near the limit of individual cut-offs) may go back and forth regarding their MetS classification, suggesting a lack of durability [20, 21]. Additionally, traditional MetS measures are not nuanced enough and fail to address variations in sex and ethnicity [22]. Our group demonstrated that MetS, as defined according the traditional criteria, is underdiagnosed among the black population in the

United States [18, 23–26], which is at odds with the high prevalence of CVD and T2DM within this particular population.

As an alternative to binary criteria, some pediatric studies have used a MetS z-score [19, 27], including scores created by our research group [28, 29]. In using a z-score, one can track the severity of the syndrome over time [30, 31] and compare values among individuals or a population [31]. Our MetS severity z-score in particular, was created using confirmatory factor analysis using cross-sectional data from 12-19 year old participants of the National Health and Nutrition Examination Survey (NHANES) in the United States (<http://mets.health-outcomes-policy.ufl.edu/calculator/>). This score was standardized to this representative sample U.S. adolescents and thus represents a nationally-representative z-score of MetS severity [28]. This MetS z-score has been validated and shown to be correlated with measures of insulin resistance [28, 30, 32]; prediabetes [33], cardiovascular biomarker abnormalities [28, 34, 35], the presence of MetS in adulthood [30, 36], and future disease [32, 36, 37]—all attesting to its durability as a biomarker of cardiometabolic risk.

Mechanism behind the syndrome

The specific mechanism behind MetS has not been established, though as mentioned, central obesity plays a critical role. Currently, it is hypothesized that an excess of stored fat in visceral adipocytes contributes to a proinflammatory state, oxidative stress, and insulin resistance—each of which appear to be involved with the development of MetS [3, 38, 39]. Given the close relationship between obesity and MetS, studies have shown close relationships between hsCRP, uric acid, and fasting insulin levels and MetS components, with relationships established in both adult and pediatric populations [17, 23, 28, 30, 32–35, 40, 41]. While some genetic influences on insulin resistance have been identified, there are likely more genetic underpinnings of MetS that have yet to be discovered [42].

Relevance of Lifestyle Factors

Lifestyle factors have long been established as correlated with MetS and as modifiable risk factors play a vital role in therapy in adult medicine [43] and are the cornerstone of treatment of MetS in children and adolescents as well (Figure 1). Current pediatric recommendations include decreasing physical inactivity, and modifying dietary habits by decreasing total calorie intake and avoiding diabetogenic foods [44]. Pharmacological agents do not play a role in treating pediatric MetS as of yet, although should patients also have concurrent diagnoses of hypertension, T2DM, and/or dyslipidemia, they should be treated with appropriate medications these individual processes. The lack of an overarching medical treatment for MetS places even greater emphasis upon lifestyle modification as the main treatment of MetS. Though the number of pediatric studies examining the relationships of dietary intake and physical activity with MetS pales in comparison to the number of studies that have been conducted in the adult world, the studies focused on in this review addresses various components of diet and exercise from multiple perspectives.

Physical Activity

Physical exercise should be a part of any adolescent's daily activities, regardless of the diagnosis of MetS, as it is vital in maintaining one's physical and psychological wellbeing. The World Health Organization (WHO) and Center for Disease Control and Prevention (CDC) in the United States has released statements about daily recommended amounts of physical activity (PA) in adolescents [45]. The WHO suggests a minimum of 60 minutes of moderate to vigorous aerobic PA daily for children ages 5-17 years. In addition, vigorous bone density building and muscle strengthening exercises, such as jumping and running, should be performed at least three times a week. The statement from the CDC is similar in content but recommends such exercises for children ages 6-17 years [46].

In general, however, children do not achieve this level of physical activity. Nader et al. assessed the amount of moderate- to vigorous physical activity using accelerometers among children in the NIH Study of Early Child Care and Youth Development birth cohort, finding that the amount of time in activity decreased sharply from age 9 to 15 years [47]. By age 15 years, adolescents only engaged in moderate- to vigorous physical activity 49 minutes on weekdays and 35 minutes on weekend days, with 69% and 73% of adolescents failing to have at least 60 minutes of activity time on weekdays and weekend days, respectively [47].

Studies investigating adolescents for relationships between MetS or its components often focus on the amount of time spent exercising, PA intensity, and cardiorespiratory fitness (CRF). Ekelund et al. conducted a cross-sectional study with children and adolescents of the European youth heart study to examine the relationships between PA variables (light, medium, or vigorous intensity—as assessed using accelerometers), CRF, and a MetS z-score as well as individual components [48]. A total of 1709 children from Denmark, Estonia, and Portugal were included in the study, with ages ranging from 9-10 years and 15-16 years. Minutes spent in PA were weakly but significantly negatively correlated with systolic and diastolic blood pressure, fasting glucose, fasting triglycerides, fasting insulin, and a continuous MetS z-score. Moderate and vigorous PA had more significant associations than light PA and had relatively stronger correlations [48]. Overall these data emphasize the need for pediatricians and parents to encourage and enable regular activities of a more rigorous cardiovascular nature for children who are at risk for MetS.

Another study assessed whether the WHO recommendation of 60-minutes daily was adequate to suppress MetS development. Neto et al. evaluated a sample of 391 Brazilian adolescents age 10-18 years old, using accelerometry to categorize light, moderate and vigorous activity and a MetS z-score based on the sample [49]. They found inverse associations between the amount of activity and the MetS z-score. In looking at how much activity was associated with being above the median MetS z-score, they used a ROC analysis and determined that 88 minutes of moderate to vigorous physical activity was associated with protecting their sample from having above-average MetS scores for their cohort [49]. However, their population had a reasonably high amount of moderate to vigorous physical activity (on average 105 minutes for boys and 79.8 minutes for girls), and this cut-off would likely vary by underlying population. Overall, the 60-minute recommendation is likely to benefit most adolescents who may not currently meet these guidelines for activity.

One way to improve physical activity is through incorporating activity into aspects of daily routine. Ramirez-Velez et al. studied a sample of Colombian children age 9-18 years old and compared those who rode their bicycle to school vs. not for their likelihood of MetS [50]. They found that in particular girls who cycled to school had a lower odds of having MetS compared with passive commuters. Encouraging more active commuting, when feasible, is likely a means of achieving a higher amount of moderate and vigorous physical activity and avoiding MetS.

Dietary Intake

Optimal dietary recommendations have varied over time, but current guidelines from the American Heart Association and endorsed by the American Academy of Pediatrics include aspects of consuming fewer calories (to balance with the amount of energy expended in physical activity), eating vegetables and fruits daily, taking in less sugar (particularly as juice and sugar sweetened beverages), consuming less saturated fat, and using more unsaturated fat including vegetable oils [51]. In U.S. studies, there has been some potential progress on this front—though clearly not enough so to divert the continued high prevalence of obesity and MetS. With respect to MetS severity, our group reported that the slight decrease in MetS severity over the time frame of 1999 – 2012 was temporally associated with trends in decreased percent carbohydrate ingestion and increased consumption unsaturated fat—trends which may have contributed to more favorable lipid levels among adolescents, with lower triglycerides and higher HDL cholesterol (Figure 2) [52].

Other researchers have investigated how other aspects of food content were associated with MetS. Taveres et al. assessed a cohort in Brazil, determining that intake of ultra-processed (and thus energy dense) food was independently associated with a 2.5-fold increased risk of MetS [53]. Chan et al. assessed 2727 Taiwanese adolescents and determined that boys consuming >500 mL of sugar-sweetened beverages daily (compared to none) had a 5-10-fold higher risk of having MetS, with similar risk but wider confidence intervals among girls [54].

One point of ongoing investigation is whether increased number of meals daily (and in particular whether breakfast is consumed regularly) is a healthier approach with respect to weight gain in childhood and adolescence. Jaaskelainen et al. evaluated a cohort of 16 year-old adolescents in Finland for associations between consuming multiple meals daily and risk of obesity and MetS factors [55]. They reported that those who consumed 5 small meals daily and those who consumed 4 meals including breakfast were less likely to have central obesity and 3 of the other 4 MetS components. Similarly, in looking at a long-term cohort in Sweden, Wennberg et al. reported that an irregular number of meal consumed daily at age 16 years was associated with a higher odds of MetS at age 43 [56]. However, that study was observational in nature. Additional randomized trials are needed to assess the relationships between breakfast consumption and changes in MetS status.

While prospective data regarding the relationship between dietary quality and pediatric MetS are overall lacking, Velazquez-Lopez et al. recruited a cohort of children and adolescents in Mexico and performed a randomized controlled trial of a Mediterranean-style diet rich in

vegetables and unsaturated fats compared to a standard diet [57]. After 16 weeks of intervention, they noted improvements in multiple components of MetS and a reduced prevalence of MetS from 16% to 5% in the Mediterranean diet group compared to no change or a worsening in the control group—demonstrating the potential power in dietary alteration in improving current MetS in adolescents. While this study did not follow beyond the 16 weeks of intervention, other studies have suggested difficulty in adherence to on-going dietary regimens [58]. Further research is needed into motivators to improve these gains on a long-term basis.

Combined Physical Activity and Dietary Intake

It is likely that successful lifestyle changes to preventing and reducing obesity and MetS will require combined approaches of physical activity changes and lifestyle changes. This is because increased physical activity without attention to diet may lead to an increase in appetite and food intake [59], while isolated decreases in calories leads to a decrease in basal metabolic rate [60], making more significant weight loss difficult. In theory, the combination of increased physical activity with healthy diet provides a means of maintaining energy expenditure while overall restricting calories.

The effects of this dual approach on pediatric MetS has been tested on a more limited basis in a couple of studies. Caranti et al. assessed the effect of one year of therapy with aerobic exercise, nutrition, psychology counseling, clinical therapy on adiposity and MetS-related outcomes in a cohort of 83 obese adolescents in Brazil [61]. Their intervention included exercise sessions of 60 minutes three times weekly with nutritional training sessions once weekly. The authors reported significant decreases in BMI, fat percent and visceral fat in both boys and after 6 months of intervention, which increased over an additional 6 months of ongoing intervention. The proportion of adolescents with MetS decreased from 27% at baseline to 14.5% at 6 months and 8.3% at one year. The authors thus reported a “dose-response” effect of multidisciplinary therapy to treating MetS.

Leite et al. assessed the effect of a 12-week intervention of a combined exercise and dietary modification on a cohort of 10-16 year-old obese adolescents with and without MetS. Those in the lifestyle modification group exercised 2-3 times a week and received intensive nutritional guidance and reported food intake. At the end of these sessions, they reported reduced total body mass and MetS risk factors [62]. This type of approach, implemented in an ongoing basis among adults in the Diabetes Prevention Program [43], remains the gold standard for targeting durable reduction in metabolic risk. Given long-term associations of heart disease and T2DM among adolescents with MetS, effective strategies are needed for implementing these types of approaches on a clinical basis.

Conclusion

In summary, it is not surprising that unhealthy lifestyle practices associated with obesity are also associated with an increased risk of MetS among children and adolescents. In particular, greater amounts of physical activity and improved dietary quality are associated with less MetS and changes in these directions on a population level are likely to reduce not only the

prevalence and severity of MetS among adolescents but the odds of long-term sequelae including Type 2 diabetes and cardiovascular disease. It remains highly important to use data such as these to motivate children and adolescents from a young age to improve their own weight status and risk trajectory. In addition, when possible, these data should help influence informed policies toward healthy food provision in schools, availability of physical activity and urban planning to allow for safe spaces for children to participate in moderate- to vigorous activity on a regular basis. Above all, parents and healthcare practitioners should encourage these practices of healthy eating and active time from early childhood through young adulthood to establish these healthy habits as normal behavior throughout their lives.

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Figure 1: Metabolic syndrome as related to etiologic factors and disease risk.

Lifestyle factors of sedentary lifestyle and unhealthy diet feed into risk for metabolic syndrome, representing modifiable risk factors to address toward avoiding long-term sequelae.

Figure 2: Temporal changes in metabolic syndrome severity, individual components and dietary factors.

MetS severity Z-score (A) and individual components triglycerides (B) and HDL (C) over time, along with reported intake of (D) total calories, (E) carbohydrate, and (F) unsaturated fat among 12-18 year-old participants of the National Health and Nutrition Examination Survey (NHANES) '99-'12. (From Lee et al. *Pediatrics*, 137 (3) e20153177, used by permission.)

Table 1:

Pediatric and adolescent cut-off values for MetS diagnosis using adapted ATP-III and the International Diabetes Federation.

MetS Criteria	Central obesity (WC)	High BP (mmHg)	High Triglycerides (mg/dL)	Low HDL (mg/dL)	High fasting glucose
Adaptation of ATP-III criteria for use in adolescents[*]	WC 90 th percentile	Systolic or diastolic DBP 90% for age, sex, height	TG 110 mg/dL (1.24 mmol/L)	HDL 40 mg/dL (<1.03mmol/L)	100 mg/dL (5.6 mmol/L) or known T2DM
International Diabetes Federation[*]	Age: 6-9.9 90 th percentile				
	10-15.9 90 th percentile or adult cut-off if lower	Systolic BP 130 or diastolic BP 85 mm Hg	150 mg/dL (1.7 mmol/L)	<40 mg/dL (<1.03mmol/L)	FPG 100 mg/dL (5.6 mmol/L) ^{**} or known T2DM
	16 Europid males: 94 cm; Europid females: 80cm, ethnic-specific values for other groups ^{**})	Systolic BP 130 or diastolic BP 85 mm Hg or treatment of previously diagnosed hypertension	150 mg/dL (1.7 mmol/L) or specific treatment for high triglycerides	Males: <40 mg/dL (<1.03mmol/L); Females: <50 mg/dL (<1.29mmol/L) or specific treatment for low HDL	FPG 100 mg/dL (5.6 mmol/L) or known T2DM

Abbreviations: BP: blood pressure; HDL, high-density lipoprotein; T2DM, type 2 diabetes mellitus; WC: waist circumference.

^{*} MetS is diagnosed in ATP-III for any individual who has abnormalities in 3 of the categories; MetS is diagnosed in IDF for any individual who has central obesity and 2 of the others.

^{**} For those of South and South-East Asian, Japanese, and ethnic South and Central American origin, the cutoffs should be 90 cm for men, and 80 cm for women. The IDF Consensus group recognise that there are ethnic, gender and age differences but research is still needed on outcomes to establish risk.