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Physical Activity in Adolescents and Children and Relationship to Metabolic Health

Rachel Whooten, MD[1,2,*], **Liya Kerem, MD**[1], and **Takara Stanley, MD**[1]

[1]Department of Pediatrics, Division of Pediatric Endocrinology, Massachusetts General Hospital for Children

[2]Department of Pediatrics, Division of General Academic Pediatrics, Massachusetts General Hospital for Children

Abstract

Purpose of review: To summarize the recent developments relating to the role of physical activity in improving insulin resistance and metabolic syndrome in children and adolescents.

Recent findings: The current literature (1) strengthens previous findings on the relationship between PA and metabolic health in children, (2) suggests a protective role for PA in the setting of obesity, (3) examines population-specific findings, (4) addresses specific effects of different modalities of PA in improving health (5) reveals potential mediators in the relationship between PA and metabolic health, and (6) suggests new markers of metabolic health that could potentially be used as outcomes in future PA studies.

Summary: Recent research generally confirms the role of PA in decreasing insulin resistance and metabolic syndrome in children and adolescents. However, the current literature is limited by unstandardized research methods and definitions as well as aggregation of different age groups, genders and weight status. Future research should address these issues in order to offer targeted PA interventions.

Keywords

Physical activity; cardiorespiratory fitness; muscular fitness; insulin resistance; metabolic syndrome

Introduction

Although physical activity (PA) is considered a promising tool for child obesity prevention and treatment of obesity-related metabolic dysregulation, PA interventions reported in the literature often have a limited impact on body mass index (BMI) (1, 2). This is likely due to limitations of BMI as the primary outcome measure, which may not be sensitive to changes in the short-term and may be confounded by improvements in lean mass that are not

*Corresponding author: rwhooten@mgh.harvard.edu; Massachusetts General Hospital for Children, 55 Fruit Street, Boston, MA, 02114.

Conflicts of interest
None

reflected in BMI. As a result, it is important to evaluate additional markers of metabolic health that may be affected by physical activity interventions.

Within adult populations, a large body of evidence supports a positive role for exercise interventions in improving metabolic parameters, including lipid profile, markers of insulin resistance, and other related hormones(3). Pediatric research confirms a role for exercise training in decreasing insulin resistance(4, 5) and improving cardiometabolic health(6, 7).

This review evaluates recent research relating to the impact of child and adolescent PA on metabolic health. Of note, a challenge within this area of research is variation in the outcome measures that capture insulin resistance (IR) and metabolic syndrome (MetS). There is also variation between studies in how physical activity and fitness are assessed (Table).

Physical Activity, Insulin Resistance, and Metabolic Syndrome

Recent research has strengthened evidence of a correlation between PA levels and risk for IR and MetS. This has been shown in both cross-sectional analyses as well as longitudinal observational studies, with follow-up ranging from 6 months to 4 years.

In a cross-sectional study of 1,426 Hispanic and Latino youth, Strizich et al. found that lower levels of PA were associated with unfavorable glucose/lipid metabolism and increased inflammatory markers(23). Additionally, a three year longitudinal study by Agostinis-Sobrinho et al. demonstrated that lower cardiorespiratory fitness was associated with higher systolic blood pressure at both baseline and follow-up(19).

Increased levels of PA, in turn, have been associated with favorable metabolic outcomes. In a longitudinal study of healthy children at ages 8 and 12, higher PA levels were associated with lower C-peptide levels in the setting of preserved glycemia at baseline and follow-up, suggesting decreased insulin resistance(24). Similarly, Skrede et al. conducted a prospective study of 700 healthy children with 7-day accelerometer data at baseline and 6-12 month follow-up(25). Moderate PA at baseline predicted lower triglyceride concentration and lower HOMA-IR at follow-up, regardless of sex, socioeconomic status, Tanner stage and waist circumference.

These studies strengthen the evidence of an association between low levels of physical activity and early precursors of metabolic syndrome and extend support for PA as a strategy to improve metabolic health early in life. PA is associated with improvements in insulin sensitivity in childhood, which may have lifelong implications for beta cell health and future diabetes risk.

Protective Role for Physical Activity

There is growing evidence that physical activity specifically attenuates the cardiometabolic risk associated with obesity. This has been suggested by observational studies showing that both cardiorespiratory (CRF) and muscular fitness are protective against the metabolic risk associated with obesity.

Among a sample of 1247 children ages 8-11 years old, Nystrom et al. found that CRF attenuated the relationship between BMI and increased cardiometabolic risk scores, particularly in the highest BMI categories(12). Further, while increased inflammation is often associated with insulin resistance, Agostinis-Sobrinho et al. demonstrated that muscular fitness minimized this association in a cohort of 529 adolescents(22).

Cadenas-Sanchez et al. evaluated physical activity, cardiorespiratory and muscular fitness in a sample of 237 overweight/obese adolescents(21). Levels of MVPA were higher in metabolically healthy participants ("MHO", having ≤1 cardiometabolic risk factor) than in non-MHO (having > 1 risk factor), while sedentary time was higher in non-MHO adolescents than in their MHO peers. Interestingly, there was no difference in CRF different between MHO and non-MHO adolescents.

The findings of Cadenas-Sanchez et al. conflict with those of Nystrom et al. While both studies support a protective role for physical activity against cardiometabolic risk, Cadenas-Sanchez suggests that activity itself is protective against metabolic dysregulation, irrespective of improvements in fitness. On the other hand, Nystrom et al. suggest that improvements in CRF are necessary to achieve metabolic benefit. It should be mentioned that CRF was measured differently in these two studies, which emphasizes the challenge of integrating findings into a single conclusion when different methods are used.

Interventional studies also support PA as an effective treatment for obesity-related metabolic sequelae. Mendelson et al. found that a 12-week exercise program improved cardiovascular risk profile in 20 obese adolescents with decreased insulin resistance, as well as improved adiposity and reduced inflammatory markers(17). These findings persisted even in the absence of weight loss, although those who lost visceral fat mass had greater improvements in triglycerides, insulin resistance, and maximal fat oxidation. While BMI is often a primary outcome in similar trials, this study demonstrates the importance of including additional outcomes.

In a study of forty Korean adolescent girls with obesity (BMI ≥30 kg/m2), prehypertension, hyperinsulinemia, and abdominal obesity, Son et al. randomly assigned participants to either a 12-week resistance and aerobic exercise training group or a control group that was asked to maintain their regular activity level(18). Following the intervention, participants in the exercise group had significant improvements in HOMA-IR as well as body composition and other hemodynamic parameters versus the control group, suggesting that combined resistance and aerobic exercise can be a useful treatment for obesity comorbidities without any intentional dietary intervention.

Physical Activity within Different Populations

The effect of PA may vary by gender and age, but studies to date have conflicting findings. In the Huus et al. study previously discussed, PA had a more pronounced impact on C-peptide levels in 8-12 year old boys than in girls of the same age(24). In contrast, Martinez-Vizcaino found that girls who participated in a cluster-randomized trial of standardized PA had reduced adiposity and lower LDL compared with controls, but no effect was seen in boys(26).

These conflicting findings may be explained, at least in part, by gender specific behavior or variance in timing of puberty initiation, which occurs earlier, on average, in girls. Huus et al. noted that boys overall had higher activity levels compared with girls, which may have explained their improved C-peptide levels. Martinez-Vizcaino questioned whether boys who participated in their intervention may have decreased their outside physical activity, contributing to the null result. Further work is necessary to explore what gender differences may exist in the relationship between PA, IR, and MetS.

The fact that IR peaks in early adolescence independent of pubertal status (27) raises the question of whether the effect of PA on IR may also vary by age. Metcalf et al. explored this, following a cohort of 300 children from ages 9 to 16 years with annual measurements of PA and metabolic markers(28). At 12-13 years of age - when insulin resistance was at its peak - adolescents who were more active had 17% lower peak HOMA-IR ($p<0.001$) independent of body fat percentage and pubertal status compared with those that were less active. This difference diminished progressively over the next 3 years and disappeared by age 16, when IR returned to pre-pubertal levels. Although insulin resistance in adolescence is temporary, increased beta cell load at this time may have implications for later function in adulthood. As a result, IR of early adolescence may represent a unique opportunity for intervention.

While these findings suggest that gender and age may modify the effect of PA on IR and MetS, they do not paint a unifying picture of the underlying physiology . Additionally, these results may be explained by behavioral differences or may be incidental findings limited to one study. Regardless, this is an area for further research as it may be important to tailor PA interventions by age and gender to achieve maximal impact on IR and MetS risk.

Different Types of Physical Activity

Current research has examined the specific characteristics of PA that determine effectiveness in ameliorating metabolic risk. This research has focused on overall duration of PA as well as specific patterns, types, and intensity of PA.

Duration and Pattern of PA

A recent study by Stabelini Neto et al. found an inverse relationship between time spent in MVPA and cMetS, with at least 88 minutes of daily MVPA needed for a favorable metabolic risk score(13). While this is in excess of the current guidelines from Centers for Disease Control for at least 60 minutes daily, the study found relative improvements in risk with each incremental increase in PA even below this threshold, highlighting that small increases in PA can have a positive impact on metabolic risk.

Interestingly, incremental changes in PA can also have a positive impact when they occur in the context of interrupting sedentary behavior. To examine the acute effect of exercise on insulin secretion, Belcher et al. performed an experimental trial among 28 healthy 7-11 year olds who were exposed to two conditions: continuous sitting for 3 hours or 3 hours of sitting interrupted by 3 minute walks every 30 minutes, each followed by an OGTT(29). In this study, sitting interrupted by brief, low intensity PA was associated with lower OGTT-induced insulin, c-peptide and glucose AUC compared with controls, suggesting lower insulin resistance. These results suggest a simple strategy of interrupting sedentary behavior can be a tool to decrease metabolic risk, and is especially relevant in this era of increasing concern about screen time.

Exercise Type and Intensity

Recent studies have shown benefit of both resistance training and aerobic exercise. Dias et al. demonstrated that a 12-week resistance training program reduced body fat, waist circumference, and waist-to-hip ratio, as well as HOMA-IR and levels of endothelin and fibrinogen, even in the absence of BMI change(30).

In a series of experimental studies, Cockcroft et al. studied the acute effect of short-term high-intensity interval exercise (HIIE) vs moderate intensity exercise (MIE). In each study, a small sample of subjects completed a HIIE trial, a MIE trial, and a rest condition, each of which was followed by an OGTT. Insulin and glucose levels obtained during the OGTT were used to calculate insulin sensitivity, insulin resistance, and beta cell function using the homeostatic model assessment (HOMA) 2 program (31). They first demonstrated that both HIIE and MIE improved insulin sensitivity compared with resting, with a larger effect size for HIIE(32). A subsequent study included measurement of fasting plasma glucose and insulin levels(33). While HIIE and MIE had no effect on fasting levels, both improved insulin sensitivity for up to 24 hours following exercise, again with a greater effect of HIIE compared with MIE. These findings also highlight the advantages of dynamic measurement of glycemia following exercise in addition to assessment of fasting indices to observe the effects of PA on glucose homeostasis.

Hay et al. further studied the impact of HIIE and MIE in reducing T2D risk factors through a randomized controlled trial of 106 overweight and obese adolescents(34). Participants were randomly assigned to high intensity PA, moderate intensity PA, or control for 6 months. There was no difference between the HIIE or MIE conditions and controls with respect to insulin sensitivity or hepatic triglyceride content. The authors highlight overall poor compliance within their study population, with only 55-61% compliance in the HIIE and MIE study arms, which limits any ability to draw conclusions.

This raises the question of HIIE feasibility among children and adolescents, particularly those with obesity. Within their small experimental study of young lean boys, Cockcroft et al. found that participants reported HIIE and MIE as equally enjoyable(31). Weston et al. specifically addressed adherence in an exploratory trial that evaluated both outcomes and feasibility of a school-based high-intensity interval training intervention(35). Compared with controls, the HIIE group had improvement in both triglycerides and waist circumference, as well as acceptable session attendance (77+/− 13% attendance). While HIIE may be a feasible intervention strategy with positive health implications, more data on feasibility - especially within obese and overweight populations - is needed.

There is also emerging interest in the role of active school transport to increase physical activity in children and adolescents. Ramirez-Velez et al. studied the association between cycling to/from school and physical fitness as well as metabolic health among a sample of Colombian children and adolescents(20). Among a sample of 2877 healthy youth, active commuters (defined as cycling to school ≥3 times / week) performed better on measures of cardiorespiratory fitness compared with passive commuters. For girls, active commuters also had a lower likelihood of metabolic syndrome compared with passive commuters; this effect was not seen for boys. These findings are limited by their associational nature, as the findings may be due to other lifestyle habits that are associated with active commuting.

Potential Mediators of PA effects

Many of the previously reviewed studies suggest various mediators of the relationship between physical activity and metabolic health. With all studies in this area, assessments of mediation are complicated by the reality that many of the variables are closely related, and it is challenging to tease apart which factors may contribute to the positive effects of PA. The two most pertinent questions in this area are whether the benefits of PA are mediated by reductions in adiposity or by improvements in physical fitness.

Adiposity

A few recent studies suggest that benefits of PA are mediated by reductions in adiposity. In a longitudinal study of 723 healthy 8-11 year olds, Hjorth et al. demonstrated that the relationship between PA and MetS at follow-up was not significant after adjusting for fat mass and removing waist circumference from the MetS(14). Similarly, Skrede et al. reported that both moderate PA and MVPA initially had similar impacts on metabolic syndrome risk, but controlling for waist circumference attenuated this effect for MVPA(25). Henderson et al. evaluated the impact of lifestyle habits on T2DM risk in childhood through a 2-year prospective, longitudinal cohort study of 630 children with at least one obese parent(16). Higher levels of MVPA were associated with improved insulin sensitivity (as defined by HOMA-IR and OGTT AUC), in part through an effect on adiposity levels. Taken together, these findings suggest that decreased adiposity may be a mediator on the causal pathway between PA and improved cardiometabolic risk profile.

Physical Fitness

Another area of interest is whether PA itself or improved physical fitness following PA interventions results in metabolic improvements. Within a sample of 482 children and adolescents, Segura-Jimenez et al. examined the independent associations of physical activity and physical fitness with metabolic syndrome risk factors as well as the mediating effect of physical fitness on MetS(15). While there was an independent relationship between PA and MetS in adolescents, physical fitness fully mediated the relationship in children but not adolescents. The authors do not provide a potential mechanism for this difference between age groups. Earlier studies assessing this relationship have had conflicting results(36, 37), although there is evidence from previous studies that PA has an effect on metabolic risk independent of changes in fitness(38).

Novel Directions

While proxies of insulin resistance and the components of MetS are clearly identified as biomarkers of poor metabolic health, there is continued effort to identify other meaningful markers of metabolic health. Recent studies have examined the relation between adiponectin, BDNF, cortisol, and autonomic activity with PA.

Adiponectin is a biologically active multimer that is secreted by adipocytes, with lower levels present in obese children and those with metabolic syndrome(39, 40). Nascimento et al. found that obese and overweight adolescents who participated in an 8 month physical activity program had improved fasting adiponectin, total cholesterol, LDL and insulin levels, as well as HOMA-IR, compared with controls. These results suggest a beneficial effect of PA on adiponectin levels; however, it is unclear if other metabolic improvements noted in this trial have a causal relationship with adiponectin.

Brain-derived neurotrophic factor (BDNF) is a protein crucial for neuronal differentiation that is abundant in the hypothalamus and may have a role in cardiometabolic homeostasis. Among adolescents participating in a PA education program, Pedersen et al. found a positive association between BDNF levels and cardiovascular risk score(41). There was less of an effect in females, potentially due to a correlation between BDNF and estrogen levels throughout the menstrual cycle. Also, it should be noted that BDNF levels in peripheral blood have been shown to vary by age, gender, and weight . This relationship is poorly understood, and may influence the results in the previous study (42).

There is some indirect evidence in the literature that PA may buffer the effect of chronic stress on adiposity(43). Guseman et al. examined the relationship between PA, cortisol, and cMetS among a sample of 50 obese adolescents(44). Salivary cortisol levels were measured upon waking, 30 minutes after waking, and then at 3-hour intervals throughout the day. They found no association between cortisol and MVPA or cMetS, although findings may be limited due to low levels of PA within their cohort or small sample size.

Autonomic dysfunction is a cardiovascular risk factor that correlates with obesity and components of metabolic syndrome as well as cardiorespiratory fitness(45, 46). Heart rate recovery (HRR) is a simple and non-invasive tool to investigate autonomic dysfunction. Bjelakovic et al. studied HRR after strenuous activity in 56 obese youths (7-17 years) with and without metabolic syndrome(47). As expected, HRR was significantly lower among the metabolically unhealthy obese children. Because HRR is a simple and noninvasive, it may be a useful in the routine assessment of patients with obesity and metabolic syndrome.

Conclusions and Implications

While previous research has established that PA has positive implications for child and adolescent metabolic health, recent work has increased our understanding of potential mechanisms underlying the association between PA and metabolic health in the pediatric population. These studies suggest that differences may exist by age and gender in this relationship, that different modalities of PA may have different effects on metabolic health, and that various downstream effects of PA may account for its metabolic benefits. One notable finding across studies was that most of the observed positive metabolic changes occurred in the absence of BMI change. This highlights that lifestyle intervention studies that only include BMI as an endpoint may be missing meaningful intervention effects.

There are substantial methodological challenges within this body of literature. Several promising studies included in this review were limited by sample size or compliance· Among studies, a variety of methods are used to capture both PA and fitness as well as components of IR and MetS. These variations limit comparisons between studies. Efforts to standardize endpoints, collaborate for larger multicenter trials, and adopt methods to produce valid estimates from trials with poor adherence to interventions are important next steps for the field.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

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Key points:

- Pediatric research supports a beneficial role for PA in the prevention and amelioration of metabolic syndrome, even in the absence of dietary interventions.
- The effects of PA differ depending on age and gender and, in adolescence, may be mediated by physiologic increase in insulin resistance.
- PA has favorable effects that may not be reflected in BMI reduction. Reduced body fat, improved visceral adiposity and insulin resistance can be achieved with PA in despite a steady BMI.
- Standardized endpoints for cardiorespiratory fitness would greatly facilitate integration and comparison of results from studies of PA in children.
- While high intensity exercise programs increasingly seem to improve metabolic health, their feasibility for children with obesity who are at a higher risk for metabolic syndrome should be further studied.

Table 1

Key variables used in studies of physical activity and endocrine/metabolic effects

OUTCOME VARIABLES	
Insulin Resistance (8-10)	
HOMA-IR (10)	Computer model of insulin secretion and glucose metabolism, using serum fasting glucose and insulin to predict beta cell function.
Glucose Tolerance Test(8)	Measurement of serial serum glucose levels following oral or intravenous glucose load; often includes calculation of area under the curve (AUC) as measure of insulin resistance.
Metabolic Syndrome	
Continuous Metabolic Risk Score (cMetS)(11)	Standardized, continuous score derived from sum of z-scores of metabolic syndrome risk factors, including fasting cholesterol (LDL, HDL, total cholesterol), triglycerides, waist circumference, glucose, and systolic blood pressure. Variations of this score used by several studies. (12-15)
Others	Carotid artery intima-media thickness, body composition quantified using DXA, percent body fat (using bioelectrical impedance analysis), triceps skin-fold test, indirect calorimetry, brachial-ankle pulse wave velocity, BDNF, leptin, adiponectin and markers of inflammation (CRP, cytokines).
PREDICTOR VARIABLES	
Physical Activity	Measured via accelerometer or pedometer, with associated classifications as light, moderate, and vigorous physical activity based on movement counts over defined time interval. Thresholds vary by study.
Physical Fitness	VO2 Max (16, 17) Heart rate recovery (18) 20 meter Shuttle Run (12, 19, 20) 4 × 10 meter Shuttle Run (12, 21) Speed-agility test (20)
Muscular Fitness	Isometric Handgrip (12, 15, 22) Standing Long Jump (12, 15, 22)