How Are Physical Activity, Fitness, and Sedentary Behavior Associated With Insulin Sensitivity in Children?

MÉLANIE HENDERSON, MD, MSC[1]
KATHERINE GRAY-DONALD, PHD[1,2]
MARIE-EVE MATHIEU, PHD[3,4]
TRACIE A. BARNETT, PHD[3,5]

JAMES A. HANLEY, PHD[1]
JENNIFER O'LOUGHLIN, PHD[5]
ANGELO TREMBLAY, PHD[6]
MARIE LAMBERT, MD[7†]

OBJECTIVE—To describe the associations among moderate-to-vigorous physical activity (MVPA), fitness, sedentary behavior (SB), and insulin sensitivity (IS).

RESEARCH DESIGN AND METHODS—Data were drawn from the baseline assessment of the QUALITY cohort, which included 630 white youth (aged 8–10 years at recruitment), with at least one obese biological parent. IS was measured by two fasting indices (insulin, homeostasis model assessment of insulin resistance) and an oral glucose tolerance test (OGTT)–based index (Matsuda IS index [Matsuda-ISI]). Fitness was measured by VO_{2peak}; percent fat mass (PFM) was measured by dual-energy X-ray absorptiometry; 7-day MVPA was measured with accelerometry. SB indicators included average hours daily of self-report screen time (SBst), and average minutes daily at <100 counts/min from accelerometry (SBacc). Multivariable linear regression models were adjusted for age, sex, season, and puberty.

RESULTS—MVPA and SBacc were independently associated with IS, but this was no longer statistically significant after accounting for PFM. SBst was negatively associated with IS in girls only, even after controlling for physical activity (PA), fitness, and adiposity; for each additional hour of SBst daily, IS decreased by 4.6–5.6% across all IS indices. Fitness was positively associated with IS (measured by Matsuda-ISI) after accounting for PA, SB, and PFM; for every 1 unit increase in VO_{2peak}, Matsuda-ISI increased by approximately 1.0% ($P < 0.05$).

CONCLUSIONS—In children with an obese parent, PA and SBacc are associated with IS, but this association is mediated by adiposity. SBst is negatively associated with IS in girls, beyond its known impact on adiposity. Finally, fitness is independently associated with better IS measured by OGTT.

In adults, insulin resistance is an independent predictor of type 2 diabetes mellitus, hypertension, coronary heart disease, stroke, and cancer. In several large population–based studies in youth (1,2), clustering of cardiovascular disease (CVD) risk factors is highest among children and adolescents with the lowest levels of insulin sensitivity (IS), suggesting that youth with low IS may be at the highest risk for developing CVD, type 2 diabetes mellitus, and premature mortality.

Physical activity (PA) promotes IS through numerous pathways, including increased numbers of GLUT4 transporter proteins (which are responsible for intracellular transport of glucose) and their redistribution, an increase in muscle mass (and specifically an increase in insulin-sensitive muscle fibers),

as well as capillary recruitment and proliferation and enhanced cellular insulin signaling (3,4). It is unknown whether higher levels of PA translate into clinically meaningful increases in IS in children, however, with some but not all studies reporting a beneficial effect of PA on IS. Thomas et al. (5) measured intravenous glucose tolerance (which primarily reflects glucose uptake and utilization by skeletal muscle, and encompasses IS) and resting energy expenditure in 32 adolescents aged 12–18 years. They reported that PA measured by accelerometry was positively correlated with both better glucose tolerance and higher resting energy expenditure. Likewise, in a randomized crossover trial of exercise training over 4 months in 79 healthy obese children aged 7–11 years, exercise training was associated with improved fasting insulin; moreover, these benefits dissipated when the children became less active (6). In contrast, there is evidence that the association of PA and cardiometabolic outcomes is largely explained by increased fitness (7).

Conflicting results have also been reported in cross-sectional studies examining the relationship between cardiorespiratory fitness and IS. Allen et al. (8), Kasa-Vubu et al. (9), and Ruiz et al. (10) all found that fitness was independently associated with IS, even after controlling for adiposity, suggesting that the negative impact of adiposity on IS may be counteracted by greater cardiorespiratory fitness (10). In contrast, Ball et al. (11) and Lee et al. (12) found that fitness measured by VO_{2max} was not associated with IS when adiposity (measured by dual-energy X-ray absorptiometry [DXA]) was taken into account, suggesting that the effect of fitness on IS is indirect and likely a function of body composition. Although inconsistencies across studies may be methodological in origin, the underlying mechanisms of associations between both PA and fitness with IS in youth remain uncertain.

Sedentary behavior (SB) is increasingly being investigated as an entity distinct from physical inactivity. A cross-sectional study of 496 Australian 10th grade students suggested that, among boys with >2 h of screen time daily on weekdays, the risk of abnormal levels of insulin and homeostasis

model assessment of insulin resistance (HOMA-IR) is twice that of those with less than 2 h after controlling for pubertal status, adiposity, dietary habits, and endurance (13). In contrast, there were no associations between screen time and metabolic risk factors, including lipids, blood pressure, insulin, glucose, and C-reactive protein in girls (13). These results suggest that there may be an increased risk of insulin resistance in boys who accumulate high amounts of screen time. Data from a Norwegian study (n = 86, aged 7–13 years) found that, after controlling for weight status, screen time was statistically significantly and positively associated with increased insulin resistance measured by HOMA-IR in both boys and girls and that this was independent of PA levels (14).

Only 7% of Canadian children are currently meeting the new PA guidelines of 60 min/day (15). Furthermore, Canadian youth aged 10–16 years accumulate on average 6 h/day of screen time on weekdays and more than 7 h/day on weekends, well beyond the recommended daily maximum of 2 h (15). No study to date has examined the relative contribution of PA, fitness, and SB to IS in youth. Understanding the independent impact of these three modifiable risk factors on IS is essential to the development of effective preventive strategies against both type 2 diabetes mellitus and CVD. Our objectives were to determine the independent associations among fitness, PA, SB, and IS; to assess whether these associations differ by sex; and to determine whether fitness modifies the association between PA and IS.

RESEARCH DESIGN AND METHODS

We used data from the baseline assessment of the Québec Adipose and Lifestyle InvesTigation in Youth (QUALITY) Cohort (16). QUALITY is an ongoing longitudinal study of white youth recruited at ages 8–10 years, who are at risk for obesity and its metabolic consequences because of a history of obesity in one or both biological parents. Parental obesity was defined as a BMI >30 kg/m^2 or an elevated waist circumference (>102 cm in males and >88 cm in females [17]). Children with a history of type 1 or type 2 diabetes were not eligible.

All elementary schools located within a 75-km radius of three major urban centers in the province of Québec (Canada) were approached to participate in the study. Of the 1,040 schools approached, 80% agreed to participate. Information pamphlets explaining the study were distributed to all second-, third-, fourth-, and fifth-grade students in participating schools. Interested families were invited to contact the research team. Data on 630 families were available for the current study. Participants underwent a complete assessment that included blood samples, measurement of height and weight, assessment of sexual maturity stage, questionnaires on lifestyle habits, measurement of PA using accelerometers, fitness testing, a DXA for adiposity measures, and an oral glucose tolerance test (OGTT). Written informed assent and consent were obtained from all participants and their parents, respectively. This study received ethics approval from the Ethics Boards of the Centre Hospitalier Universitaire (CHU) Sainte-Justine, McGill University, and Université Laval.

PA was assessed with an Actigraph LS 7164 activity monitor (Actigraph LLC, Pensacola, FL). The Actigraph LS 7164 accelerometer captures vertical accelerations, with magnitude and frequency set to detect human motion while filtering out high-frequency movements, including vibrations. Acceleration signals are converted into activity counts (18). A minimal wear time of 10 h was required for the recordings of a given day to be considered a valid representation of activity level. Nonwear time was defined as any period of 60 min or more of 0 counts, allowing for one interruption (of 1-min duration) or two consecutive interruptions (2 consecutive min). An interruption was defined as a minute during which count values were >0 and ≤100 (19). The average time spent daily in sedentary, light, moderate, and vigorous PA was computed for each participant using validated pediatric cut-points (20). Light PA was defined by counts >100 but <2,296 per min; moderate PA was defined by counts ≥2,296 but <4,012 per min; and vigorous PA was defined as counts ≥4,012 per min. Activity counts <100 per min were considered to indicate sedentary activity (20). Moderate-to-vigorous physical activity (MVPA) was computed by adding the total minutes spent daily in moderate and in vigorous PA and averaging over the total number of valid days of wear. Peak oxygen consumption ($V_{O_{2peak}}$), the gold standard to measure aerobic fitness in youth, was used to estimate fitness. $V_{O_{2peak}}$ was determined during an adaptation of the standard incremental exercise test (21) on an electromagnetic bicycle to volitional exhaustion, with use of indirect calorimetry measurements throughout the test. Attainment of at least one of the following two criteria was needed to consider the $V_{O_{2peak}}$ as a true maximal value: *1*) a respiratory exchange ratio ($V_{CO_2}/V_{O_{2peak}}$) greater than 1.0 or *2*) a heart rate at or above 185 bpm (22). $V_{O_{2peak}}$ was expressed in milliliters per kilogram of lean body mass per minute. Indicators of SB included average daily hours of reported leisure screen time (SBst), including television, video games, and computer use, as well as average daily minutes at <100 counts based on accelerometer data (SBacc).

All subjects underwent a 2-h OGTT after a 12-h overnight fast. Blood samples were collected in tubes containing 1 g/L K2 EDTA 30, 60, 90, and 120 min after an oral glucose dose of 1.75 g/kg body weight (up to a maximum of 75 g). Plasma insulin was measured with the ultrasensitive Access immunoassay system (Beckman Coulter, Inc.), which has no cross-reactivity with proinsulin or C-peptide (23). Plasma glucose concentrations were determined on the Beckman Coulter Synchron LX20 automat using the glucose oxidase method. Analyses were performed in batches at a single site (CHU Sainte-Justine Clinical Biochemistry laboratory) twice a month.

We used both OGTT-derived indices and fasting-based indices to measure IS. The fasting-based measures of IS included the HOMA-IR, calculated as fasting insulin (milliunits per liter) × fasting glucose (millimoles per liter)/22.5 (24). HOMA-IR has been extensively validated against the hyperinsulinemic-euglycemic clamp (HEC), the gold standard method of assessing IS, in adults and children (25,26). We also used fasting insulin (picomoles per liter) as a measure of IS. Fasting insulin has been identified as a valid method to estimate IS in youth (27). We used the Matsuda IS index (Matsuda-ISI) as an OGTT-derived measure of IS. Matsuda-ISI is computed as 10,000/square root [(fasting glucose × fasting insulin) × (mean OGTT glucose × mean OGTT insulin)] (28) and has been validated against the current gold standard method of estimating IS in children (25,29). Body composition was determined with a DXA scan (Prodigy Bone Densitometer System, DF+14664; GE Lunar Corporation) (30). Percent fat mass (PFM) was used as the measure of adiposity. Stage of pubertal development was assessed by a trained nurse and scored according to Tanner stages (31,32).

Analysis

Descriptive statistics were used to describe the baseline characteristics of participants. Whenever possible, measures were analyzed as continuous variables. Age- and sex-adjusted BMI z scores were computed from data from the Centers for Disease Control and Prevention (2000) (33). We used univariable and multivariable linear regressions to examine the associations between PA, fitness, SB, and IS. Season was added to the models that included PA. For parsimony, and given that physical activity tends to decline in the winter months (34), we defined two periods: "winter" from November to March and "nonwinter" from April to October. Potential confounders included sex, age, pubertal stage, and adiposity as measured by PFM. Outcome variables had nonsymmetric distributions and were transformed using 100*ln of the variable; consequently, β-coefficients represent the percentage of change in the outcome associated with a 1-unit increase in the exposure variable (35). Analyses were not stratified by sex to optimize power. Nevertheless, interaction terms were introduced one at a time into the models to examine whether the association between PA and IS, between fitness and IS, or between SB and IS varied as a function of sex. We subsequently tested whether fitness modified the association between PA and IS with the addition of an interaction term (fitness by PA). We ascertained whether models met the underlying assumptions of linear regression by plotting residuals against all continuous independent predictors of final models to ensure that there was no systematic pattern to the residuals. Adjusted R^2 values were also generated to assess model performance.

RESULTS—Of the 630 participants, 206 were excluded because they did not have adequate accelerometer or fitness testing data. Ninety five of these 206 were excluded because they did not meet our predefined criteria of minimal accelerometer wear time of 10 h per day for a minimum of 4 days. There were no statistically significant differences between participants retained and those excluded because they did not meet the accelerometer wear time criterion according to age, sex, or BMI z score (data not shown). The other 111 subjects were excluded because they did not attain a maximal fitness test. There were no statistically significant differences between these participants and those included in the analyses

in terms of sex and BMI z score (data not shown). Participants with a submaximal fitness test, however, were slightly younger (mean age = 9.2 vs. 9.7 years) than those included in the analyses (t statistic = −5.69, $P < 0.0001$). Difficulty attaining a respiratory exchange ratio greater than 1.0 (current recommended criterion for maximal fitness testing in children) has been previously reported (36) in youth. Younger children may have more difficulty meeting the strenuous demands of a cycling test, such as pedaling against an increasing workload while following an imposed rhythm. Selected characteristics of the 424 participants retained for analysis are presented in Table 1. The average age of both boys and girls was 9.7 years. Over 50% of participants were of normal weight for their age and sex, approximately 20% were overweight, and 25% were obese. Baseline indices of glucose homeostasis and IS are detailed in Table 2.

The Spearman rank correlation between SBst and SBacc was 0.16 (95% CI 0.07–0.25). The correlation between MVPA and SBst was 0.03 (−0.07 to 0.12), whereas it was −0.47 (−0.54 to −0.39) with SBacc. MVPA, fitness, SBst, and SBacc were each univariately associated with all measures of IS (Table 3).

We then examined the independent associations of physical activity, fitness,

and SBst with IS, adjusting for percent body fat (Table 4).When all three variables (MVPA, fitness, and SBst) were included in a multivariable model, MVPA and SBst were independently associated with all three measures of IS after accounting for sex, age, pubertal development, and season, whereas fitness was not (Table 4).

When replacing SBst with SBacc, results were comparable. When all three exposure variables (MVPA, fitness, and SBacc) were included in a multivariable model, only MVPA and SBacc were independently associated with fasting-based measures of IS after controlling for age, sex, pubertal development, and season. It is noteworthy that MVPA, SBacc, and fitness were independent correlates of the OGTT-derived measure of IS (Matsuda-ISI) when included within the same model, even after adjusting for age, sex, pubertal development, and season (Table 4). We found no statistically significant interaction between fitness and PA in any of the above models.

We then examined the effect of adding adiposity to the previous models. The association between MVPA and IS was attenuated and no longer statistically significant once PFM was included in the models, regardless of the measure of SB used (Table 4). The one exception to this

Table 1—*Baseline characteristics of participants aged 8–10 years, according to sex (QUALITY cohort)*

	Boys (n = 222)	Girls (n = 202)
Age (years), mean (SD)	9.7 (0.9)	9.7 (0.9)
BMI (kg/m²), mean (SD)	19.3 (4.1)	19.9 (4.5)
BMI z score, mean (range)	0.7 (−1.8 to 2.6)	0.8 (−3.2 to 2.6)
BMI category, % (n)*		
Underweight	1.8 (4)	2.0 (4)
Normal weight	56.8 (126)	54.5 (110)
Overweight	21.2 (47)	17.8 (36)
Obese	20.3 (45)	25.7 (52)
Tanner stage, % (n)		
Prepubertal	88.7 (197)	61.4 (124)
Pubertal	11.3 (25)	38.6 (78)
Total fat mass (kg/m²), mean (SD)	4.9 (3.4)	6.3 (3.5)
Lean body mass (kg/m²), mean (SD)	13.5 (1.0)	12.7 (1.2)
PFM (%), mean (SD)	23.7 (10.9)	30.2 (10.3)
MVPA (min/day), mean (SD)	58.7 (27.2)	40.8 (18.9)
SB accelerometer (min/day), mean (SD)	367.1 (74.2)	367.2 (63.2)
Screen time (h/day), median (range)	2.6 (0.08–13.4)	1.7 (0.03–10.1)
$V_{O_{2peak}}$ (mL · kg LBM^{-1} · min^{-1}), mean (SD)	60.6 (5.9)	57.3 (6.0)

n = number of participants. LBM, lean body mass. *BMI <5th percentile = underweight; BMI ≥5th percentile but <85th percentile for age and sex = normal weight; BMI ≥85th percentile but <95th percentile for age and sex = overweight; BMI ≥95th percentile for age and sex = obese.

Table 2—Mean or median values of glucose homeostasis indices in children aged 8–10 years (QUALITY cohort)

Indices	Boys (n = 222)	Girls (n = 202)
FPG (mmol/L), mean (SD)	5.0 (0.4)	4.9 (0.4)
Fasting insulin (pmol/L), median (range)	25.4 (6.9–90.1)	32.0 (7.0–139.6)
Glucose 2-h postload (mmol/L), mean (SD)	6.4 (1.0)	6.5 (1.4)
Insulin 2-h postload (pmol/L), median (range)	143.7 (24.6–2,005.0)	210.3 (12.2–1,554.3)
HOMA-IR, median (range)	0.8 (0.2–2.9)	1.0 (0.2–4.5)
Matsuda-ISI, median (range)	10.1 (1.8–31.0)	8.1 (1.6–45.1)

FPG, fasting plasma glucose.

was the association between MVPA with fasting insulin when adjusting for fitness, PFM, SBst, and covariates. MVPA remained an independent correlate of fasting insulin: for every additional 10 min of MVPA daily, fasting insulin decreased by 1.8%.

The association between SBst and IS, after accounting for adiposity, differed by sex. Although SBst was not an independent correlate of IS (after accounting for adiposity and other covariates) in boys, it remained strongly associated with IS (across all measures) in girls: for every additional 10 min of SBst daily in which the girls were engaged, their IS decreased by 4.6–5.6%, even after adjusting for adiposity (Table 4). These findings suggest that the influence of screen time on IS in girls is not completely explained by adiposity. Overall, this did not hold true for the other measure of SB; the association between SBacc and IS was attenuated and no longer statistically significant when adiposity was taken into account (except when looking at HOMA-IR, where it just attained statistical significance) (Table 4). We did not observe any differences between boys and girls when considering SBacc in these associations, nor did we

observe a statistically significant interaction between fitness and PA in any of these analyses.

Although fitness was not an independent correlate of fasting-based measures of IS, it was independently associated with better IS measured by the OGTT when MVPA, SB (irrespective of the measure of SB considered), and adiposity were taken into account (Table 4).

Given the established higher metabolic risk in obese/overweight youth (37), we reanalyzed our data, stratifying the sample according to weight status as follows: 244 participants had an age- and sex-specific BMI percentile <85 (i.e., the normal weight), and 180 participants had an age- and sex-specific BMI percentile ≥85 (i.e., the overweight/obese). Overall, the relationship between PA, fitness, and SB with IS did not differ between groups based on weight status (results not shown). Artero et al. (37) also found persistent associations between fitness and metabolic risk in both normal weight and obese/overweight youth.

CONCLUSIONS—In this cross-sectional sample of children with a family history of obesity, we found that PA is a correlate

of both fasting-based and OGTT-derived IS indices independent of fitness and SB. However, this association was attenuated when adiposity was taken into account, suggesting that the influence of MVPA is at least partly mediated by its association with adiposity. In contrast, fitness remained a statistically significant correlate of OGTT-derived IS (after adjusting for PA, SB, and adiposity), suggesting that the negative association of excessive adiposity to IS may be minimized by better fitness. Results differed when using fasting-based measures of IS. This is in keeping with the fact that fasting indices measure primarily hepatic IS, whereas OGTT-derived indices measure total body IS within a dynamic context. Having a higher $V_{O_{2peak}}$ reflects an increased ability to use substrate (hence, consume oxygen) by muscles, which may be associated with improved total body IS.

We also found that the association between SB and IS differs across sex, as well as how SB is measured. In girls, screen time is negatively associated with IS, even when controlling for adiposity. We found no such association in boys. Thus, although adiposity may partly explain the association between screen time and IS in girls, it does not account for it entirely, suggesting that other factors intrinsic to screen time may be involved. We hypothesize that dietary habits linked to screen time, and in particular the consumption of high-fructose beverages, may explain the detrimental effect of screen time on IS. Indeed, screen time is associated with several unhealthy dietary habits in children and adults, notably with the increased consumption of sugar-sweetened beverages (SSB) (38). Fructose, a predominant sweetener in SSB, has been linked to an increased risk of type 2 diabetes (39). An

Table 3—β-Coefficients and 95% CIs obtained from univariable linear regressions for the associations among PA, fitness, and SB and IS in children (QUALITY cohort)

Models	HOMA-IR (n = 420)†		Fasting insulin (n = 420)†		Matsuda (n = 397)†	
	β (95% CI)	P value*	β (95% CI)	P value*	β (95% CI)	P value*
MVPA (10 min/day)	−6.5 (−8.7 to −4.3)	<0.0001	−6.7 (−8.8 to −4.6)	<0.0001	6.8 (4.6–9.0)	<0.0001
$V_{O_{2peak}}$ (mL · kg LBM^{-1} · min^{-1})	−1.0 (−1.9 to −0.03)	0.043	−1.0 (−1.9 to −0.1)	0.026	1.5 (0.5–2.4)	0.002
SBst (h/day)	4.7 (1.8–7.7)	0.001	4.2 (1.5–7.0)	0.003	−4.9 (−7.8 to −2.0)	0.0009
SBacc (10 min/day)	2.3 (1.4–3.1)	<0.0001	2.2 (1.4–2.9)	<0.0001	−2.0 (−2.8 to −1.2)	<0.0001
PFM (%)	3.6 (3.2–4.0)	<0.0001	3.5 (3.1–3.9)	<0.0001	−3.7 (−4.1 to −3.3)	<0.0001

LBM, lean body mass. *Statistically significant (P value < 0.05). MVPA and SBacc can be interpreted as follows: for every 10-min increase in MVPA or SBacc, β represents the % change in the outcome of interest. †Of the 424 participants under study, three subjects did not have fasting insulin and HOMA-IR values, one subject did not have DXA values of adiposity, and 26 subjects did not have Matsuda-ISI values.

Table 4—β-Coefficients and 95% CIs obtained from multivariable linear regression models examining the associations among PA, fitness, SB, and IS in youth (QUALITY cohort), with and without PFM

	HOMA-IR ($n = 420$)§		Fasting insulin ($n = 420$)§		Matsuda ($n = 397$)§	
	β (95% CI)	P value*	β (95% CI)	P value*	β (95% CI)	P value*
Models including screen time as the measure of SB						
Model 1†						
MVPA (10 min/day)	−4.0 (−6.4 to −1.7)	0.0009	−4.2 (−6.4 to −1.9)	0.0003	3.8 (1.5–6.2)	0.001
$V_{O_{2peak}}$ (mL · kg LBM^{-1} · min^{-1})	−0.4 (−1.3 to 0.6)	0.425	−0.4 (−1.2 to 0.5)	0.410	0.8 (−0.08 to 1.8)	0.075
SBst (h/day)	4.5 (1.7–7.3)	0.002	4.1 (1.5–6.7)	0.002	−4.6 (−7.4 to −1.9)	0.0009
Adjusted R^2	0.16		0.18		0.19	
Model 2‡						
MVPA (10 min/day)	−1.6 (−3.5 to 0.4)	0.117	−1.8 (−3.7 to −0.001)	0.049	1.4 (−0.4 to 3.3)	0.126
$V_{O_{2peak}}$ (mL · kg LBM^{-1} · min^{-1})	−0.5 (−1.3 to 0.2)	0.170	−0.5 (−1.2 to 0.2)	0.153	0.9 (0.2–1.6)	0.015
SBst (h/day)	−0.07 (−3.0 to 2.9)	0.962	−0.4 (−3.1 to 2.3)	0.755	0.5 (−2.2 to 3.3)	0.693
PFM (%)	3.2 (2.7–3.6)	<0.0001	3.0 (2.6–3.4)	<0.0001	−3.2 (−3.6 to −2.8)	<0.0001
Sex*ST	4.7 (0.1–9.3)	0.044	4.9 (0.7–9.2)	0.024	−6.1 (−10.4 to −1.8)	0.006
Adjusted R^2	0.45		0.48		0.51	
Models including accelerometer-measured SB						
Model 3†						
MVPA (10 min/day)	−2.8 (−5.5 to −0.2)	0.037	−3.1 (−5.6 to −0.6)	0.015	3.1 (0.5–3.7)	0.019
$V_{O_{2peak}}$ (mL · kg LBM^{-1} · min^{-1})	−0.6 (−1.5 to 0.4)	0.225	−0.5 (−1.4 to 0.3)	0.219	1.0 (0.09–1.9)	0.031
SBacc (10 min/day)	1.1 (0.2–2.0)	0.021	1.0 (0.1–1.9)	0.027	−0.7 (−1.6 to 0.2)	0.117
Adjusted R^2	0.15		0.17		0.18	
Model 4‡						
MVPA (10 min/day)	−0.5 (−2.7 to 1.7)	0.663	−0.8 (−2.9 to 1.2)	0.411	0.7 (−1.3 to 2.7)	0.479
$V_{O_{2peak}}$ (mL · kg LBM^{-1} · min^{-1})	−0.6 (−1.4 to 0.1)	0.105	−0.6 (−1.3 to 0.1)	0.097	1.0 (0.3–1.7)	0.008
SBacc (10 min/day)	0.8 (0.002–1.5)	0.050	0.7 (−0.03 to 1.4)	0.062	−0.4 (−1.1 to 0.3)	0.260
PFM (%)	3.3 (2.8–3.7)	<0.0001	3.1 (2.7–3.5)	<0.0001	−3.3 (−3.7 to −2.9)	< 0.0001
Adjusted R^2	0.45		0.47		0.50	

All models adjusted for age, sex, pubertal stage, and season. MVPA and SBacc can be interpreted as follows: for every 10-min increase in MVPA or SBacc, β represents the % change in the outcome of interest. LBM, lean body mass. *Statistically significant (P value < 0.05). †Models 1 and 3 do not include PFM. ‡Models 2 and 4 include PFM. §Of the 424 participants under study, three subjects did not have fasting insulin and HOMA-IR values, one subject did not have DXA values of adiposity, and 26 subjects did not have Matsuda-ISI values.

increased consumption of SSB may mediate the detrimental impact of screen time on IS. Why these associations differ between boys and girls remains unclear. It may be that we have incompletely controlled for possible confounding factors such as physical activity. Alternatively, there may be physiological or behavioral differences that mediate these sex-specific differences. Further research is needed to enhance our understanding of how screen time influences IS across sexes. In contrast to self-report SB, SBacc was not associated with IS independent of PA, fitness, and adiposity. Screen time and accelerometer-measured SB appear to be distinct entities, with different cardiometabolic impacts. The low correlation between SBst and

SBacc observed in our study supports this distinction.

Substantial heterogeneity in methods—notably with respect to covariates—makes comparisons across studies investigating the determinants of cardiometabolic health difficult. The populations targeted in previous studies were generally different from ours (including older youth [5,9,37], exclusively obese youth [6,8,11], and those from differing ethnic backgrounds [7,11,12]). Moreover, using different indicators of fitness or of IS can lead to different conclusions (11). For example, fitness expressed as $V_{O_{2max}}$ in milliliters per minute per kilogram of body weight is a widely used method that inherently includes a measure of adiposity. We opted to express fitness as

$V_{O_{2peak}}$ in milliliters per minute per kilogram of lean body mass, allowing us to consider the oxidative capabilities of muscle mass, while controlling for a distinct measure of adiposity.

Despite the difficulty in comparing studies, the role of fitness and SB merits discussion. Although the positive association between PA and IS has been established in several studies (5,7,40), few studies have examined the concomitant influence of fitness. Likewise, studies have also found independent associations between screen time and HOMA-IR (13,14) and SBacc and HOMA-IR (40), without accounting for fitness. Measuring fitness is important, because fitness is associated with IS, at least in some studies

(8,9). Although others (11,12) found that fitness ($V_{O_{2max}}$) was not directly associated with IS, their findings suggest nevertheless an indirect effect, most likely as a function of body composition. Finally, although it remains difficult to disentangle the separate contributions of fitness, PA, SB, and body composition to IS given their strong interconnectedness, our analyses contribute substantially to this body of research because no other study has considered the joint, independent association among these four factors, and IS.

Major strengths of this study include the relatively large sample of children with a family history of obesity, the fact that we considered the independent association of fitness, PA, and SB on IS, and the high-quality measures, including numerous covariates. One exception to this may be the IS measure. We did not use the current gold standard measure, the HEC, since it is not feasible in large epidemiologic studies, particularly those involving children, given that it is invasive, costly, and time-consuming. Nevertheless, we used surrogate IS measures that have been validated in adults and children (25,27,29). Furthermore, OGTT-derived IS measures, in contrast to HEC, have the advantage of measuring IS in a dynamic context, which better mimics physiology, taking into consideration both the full spectrum of insulin concentrations and the impact of enteral hormone action, and assessing whole-body IS (including muscular and hepatic components). Finally, although generalizability of our findings may be restricted to white children with a parental history of obesity, this group comprises a large segment of the Canadian population and constitutes a relevant "at-risk" group.

In conclusion, our findings suggest that, in children with a parental history of obesity, increasing PA (specifically MVPA) may have a beneficial effect on IS, but the effect is mediated by body composition, specifically adiposity. Better fitness, on the other hand, is associated with higher total body IS (measured by the OGTT), independent of PA, SB, and adiposity. Finally, decreasing screen time in girls may have beneficial effects on IS, independent of body composition. These findings are useful to both clinicians and public health policymakers for the prevention of diabetes in youth. Longitudinal studies are required to examine how important the cumulative effects of these lifestyle factors are on IS over time in the pediatric population and whether interventions targeting these lifestyle habits lead to improved cardiometabolic health.

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