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Insulin secretion and its association with physical activity, fitness and screen time in children

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Abstract

Objectives

To determine the independent associations of moderate to vigorous physical activity (MVPA), fitness, screen time, and adiposity with insulin secretion in children.

Design and Methods

Caucasian youth ($n = 423/630$), 8-10 years old, with at least one obese biological parent, were studied (QUALITY cohort). Insulin secretion was measured using HOMA2-%B, area under the curve (AUC) of insulin to glucose over the first 30 minutes (AUC I/G_{t30min}) of the OGTT and AUC I/G_{t120min} over 2 hours. Fitness was measured by VO_{2peak}; percent fat mass (PFM) by DXA; 7-day MVPA by accelerometry; self-reported screen time included television, video game, or computer use. Models were adjusted for age, sex, season, puberty, PFM, and insulin sensitivity [IS] (HOMA2-IS, Matsuda-ISI).

Results

PFM was strongly associated with insulin secretion, even after adjustment for IS: for every 1% increase in PFM, insulin secretion increased from 0.3% to 0.8% across indices. MVPA was negatively associated with HOMA2-%B ($P < 0.05$), but not with OGTT-derived measures. Fitness was negatively associated with AUC I/G_{t120min} ($P < 0.05$). Screen time showed a trend toward higher HOMA2-%B in girls ($P = 0.060$).

Conclusions

In children with an obese parent, lower insulin secretion is associated with lower adiposity, higher MVPA, better fitness, and possibly reduced screen time.

Introduction

Impairment of beta-cell response to chronic fuel excess was recently invoked as the initial mechanism leading to insulin resistance in adults [1], suggesting that dysregulated insulin secretion plays a leading role in the initiation of type 2 diabetes mellitus (DM2). While not yet fully elucidated, several mechanisms are thought to link physical activity to insulin secretion. Specifically, physical activity is thought to enhance beta-cell function by up-regulating cellular insulin signaling pathways, while concomitantly increasing beta-cell mass, preserving beta-cell proliferation, and potentially decreasing beta-cell apoptosis [2]. Similarly, improved cardiorespiratory fitness is thought to have beneficial effects on insulin homeostasis through morphological, metabolic, and gene regulating adaptations in skeletal muscle [3, 4], including increases in muscle respiratory capacity, improved mitochondrial respiratory chain function, increases in ATP synthase and enzymes of both the Krebs's cycle and beta-oxidation pathways [4]. Nevertheless, the pediatric literature remains undecided regarding the role of physical activity and fitness on insulin secretion [5-7].

Sedentary behavior, recently considered distinct from physical inactivity [8], is negatively associated with insulin sensitivity in youth [9], but its association with insulin secretion remains unstudied.

Given the ubiquity of screens [10], and overall low levels of physical activity [11], understanding the independent impacts of physical activity, fitness, sedentary behavior, and adiposity on insulin secretion is essential to further understand the pathophysiology of DM2 and to the development of effective preventive strategies. We pursued this aim using the baseline evaluation (2005-2008) of the Quebec Adipose and Lifestyle Investigation in Youth (QUALITY) cohort [12].

Methods

QUALITY is an ongoing longitudinal study of Caucasian youth 8-10 years of age with a history of obesity in one or both biological parents. Parental obesity was defined as a body mass index (BMI) $> 30 \text{ kg/m}^2$ or an elevated waist circumference [$>102 \text{ cm}$ in males and $>88 \text{ cm}$ in females [13]]. Children with a history of type 1 or type 2 diabetes or other chronic diseases, taking medication that alter carbohydrate metabolism, on severe caloric intake restriction ($<600 \text{ kcal/day}$) or with serious cognitive or psychological dysfunction were deemed ineligible.

Recruitment was school based, targeting second, third, fourth, and fifth grade students around three major urban centers of Quebec (Canada) [12]. Data on 630 families were available for the present study. All participants underwent the following assessments: blood samples, anthropometric measures, assessment of sexual maturity stage, questionnaires on lifestyle habits, and measurement of physical activity using accelerometers. 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.

Physical activity was assessed over a 7-day period using an Actigraph LS 7164 activity monitor (Actigraph LLC, Pensacola, Florida) that captures vertical accelerations and

converts them into activity counts. Accelerometry data were downloaded as 1-min epochs and underwent standardized quality control and data reduction procedures [14]. The recordings of a given day were considered valid when the accelerometer was worn for a minimum of 10 hours; respondents with four or more valid days were retained for analyses [14]. Wear time was determined by subtracting nonwear time from 24 hours. Nonwear time was defined as any period of 60 minutes or more of 0 counts, allowing for one interruption (1-minute duration) or two consecutive interruptions (2 consecutive minutes). An interruption was any minute where count values are > 0 and ≤ 100 [14]. The average time spent daily in sedentary, light, moderate, and vigorous physical activity was computed for each participant using validated pediatric cut-points [15]. Moderate to vigorous physical activity (MVPA) was computed by adding the total minutes spent daily in moderate and in vigorous physical activity and averaging over the total number of valid days of wear. This method of physical activity assessment has been shown to be valid and provide reliable estimates of physical activity in youth [15]. Screen time was assessed using an interviewer-administered questionnaire, documenting self-reported habitual daily hours of television viewing and leisure computer/video game use. Weekdays and weekends were addressed separately, and average daily hours of leisure screen time were computed. Accelerometer-measured sedentary time was estimated using the average daily minutes at < 100 counts based on accelerometer data [15]. Fitness was estimated using peak oxygen consumption (VO_2 peak), the gold standard in youth. VO_2 peak was determined during an adapted standard incremental exercise test [16], on an electromagnetic bicycle to volitional exhaustion with indirect calorimetry measurements throughout the test. VO_2 peak was considered as a true maximum value if one of the following two criteria was attained: (i) a respiratory exchange ratio (VCO_2/VO_2) greater than 1.0; and (ii) a heart rate at or above 185 beats per minute [17]. VO_2 peak was expressed in $\text{ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$. After a 12-hour overnight fast, participants underwent a 2-hour oral glucose tolerance test (OGTT). Blood samples were collected in tubes containing 1 g $\text{K}_2\text{EDTA/L}$ 30, 60, 90, and 120 minutes after an oral glucose dose of 1.75 g/kg body weight (maximum of 75 g). Plasma insulin was measured using the ultrasensitive Access[®] immunoassay system (Beckman Coulter), that has no cross-reactivity with proinsulin or C-peptide [18]. Plasma glucose concentrations were computed on the Beckman Coulter Synchron LX[®]20 automat using the glucose oxidase method. Analyses were performed in batches at a single site (CHU Sainte-Justine Clinical Biochemistry laboratory) twice monthly. We used both OGTT-derived indices and fasting-based indices of insulin secretion. The updated computer version of the Homeostatic Model Assessment (HOMA) was used as a measure of fasting insulin secretion (HOMA2-\%B). This measure correlated well with the acute insulin response to glucose (AIRg) derived from a frequently sampled intravenous glucose tolerance test (FSIVGTT) [19] in healthy children. HOMA2-\%B , as well as the corresponding fasting based measure of insulin sensitivity (HOMA2-IS), were calculated using the HOMA2 calculator v2.2 available at <http://www.dtu.ox.ac.uk/homa>. OGTT-derived measures of insulin secretion included the ratio of the area under the curve (AUC) of insulin to the AUC of glucose over the first 30 minutes ($\text{AUC I/G}_{\text{t30min}}$) of the OGTT (first-phase insulin secretion) and the AUC insulin to AUC glucose over the full 2 hours ($\text{AUC I/G}_{\text{t120min}}$) of the OGTT (second-phase insulin secretion). The $\text{AUC I/G}_{\text{t30min}}$ correlated well with the AIRg in healthy children [19]. Given that insulin

secretion is closely associated with insulin sensitivity, we adjusted for insulin sensitivity to investigate the direct and specific effect of lifestyle habits on insulin secretion, independent of the effect of insulin resistance. We used the Matsuda insulin sensitivity index (Matsuda-ISI) as an OGTT-derived measure of insulin sensitivity. ISI-Matsuda is computed as $10,000 / \text{square root} [(fasting\ glucose \times fasting\ insulin) \times (mean\ OGTT\ glucose \times mean\ OGTT\ insulin)]$ [20], and has been validated against the gold standard method of estimating insulin sensitivity in children [21]. Body composition was determined with dual energy X-ray absorptiometry (DXA) (Prodigy Bone Densitometer System, DF+14664, GE Lunar Corporation) [22]. Percent fat mass was used as the measure of adiposity. Age- and sex-adjusted BMI *z*-scores were calculated based on the United States Centers for Disease Control and Prevention growth charts [23]. A trained nurse evaluated children's stage of pubertal development according to Tanner stages [24, 25].

Data analysis

We used univariable and multivariable linear regressions to examine the associations between physical activity, fitness, sedentary behavior, and insulin secretion. Given that the association between insulin secretion and insulin sensitivity was statistically significantly nonlinear, we modeled this association using a nonparametric smoothing spline with four degrees of freedom in which the shape of the association was estimated directly from the data, using generalized additive models [26]. We defined two timeframes: “winter” (November-March) and “nonwinter” (April-October), and adjusted for seasonal variation in physical activity [27]. Potential confounders included sex, age, stage of pubertal development (Tanner stage) and percent fat mass. Outcome variables had nonsymmetric distributions and were log transformed using $100 \times \ln$ of the variable [28]. Interaction terms were introduced one at a time into the models to examine if the association between each of physical activity, fitness, and screen time with insulin secretion varied as a function of sex. A 2-tailed *P* value less than 0.05 defined statistical significance. All analyses were performed using SAS 9.2 (SAS Institute Incorporated).

Results

Of the 630 participants, 206 were excluded because of inadequate accelerometer or fitness testing data. Ninety five of these 206 were excluded because they did not have a minimum accelerometer wear time of 10 hours per day, for a minimum of 4 days, but these were similar to participants retained for analysis 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. These 111 subjects were also similar to those included in the analyses in terms of sex and BMI *z*-score (data not shown), but were slightly younger (mean age = 9.2 years versus 9.7 years; $P < 0.0001$). One subject was excluded because of absent DEXA data. Difficulty attaining the current recommended criterion for maximal fitness testing in children (a respiratory exchange ratio greater than 1.0) has been reported [29]. Younger children may have more trouble meeting the strenuous demands of a

cycling test, such as pedaling against an increasing workload while following an imposed rhythm. Selected characteristics of the 423 participants retained are presented in Table 1. More than half were of normal weight for their age and sex; approximately 20% were overweight, whereas 20% of boys and 26% of girls were obese. Baseline indices of glucose homeostasis and insulin secretion are reported in Table 2. Girls had higher insulin secretion and lower insulin sensitivity measures overall compared to boys.

Table 1. Participant characteristics of children in the QUALITY cohort by sex

	Boys	Girls	Pvalue ^a
	(n = 222)	(n = 201)	
<p>1. Note: <i>n</i>, number of participants; SD, standard deviation; BMI, body mass index; MVPA, moderate to vigorous physical activity (Activity counts greater than 100 but less than 2296 per minute defined light physical activity; counts greater than or equal to 2296 but less than 4012 defined moderate physical activity; vigorous physical activity was defined as counts greater than or equal to 4012 per minute); VO₂ peak = peak oxygen consumption.</p> <p>2. a The <i>P</i> value indicates the statistical significance of a <i>t</i>-test comparing mean values between boys and girls for normally distributed variables, or a Mann-Whitney <i>U</i> test for variables with a skewed distribution.</p> <p>3. b BMI < 5th percentile = underweight; BMI ≥ 5th percentile but < 85th percentile for age and gender = normal weight; BMI ≥ 85th percentile but < 95th percentile for age and gender = overweight; BMI ≥ 95th percentile for age and gender = obese.</p>			
Age (years), mean (SD)	9.7 (0.9)	9.7 (0.9)	0.384
BMI (kg/m ²), mean (SD)	19.3 (4.1)	20.0 (4.5)	0.132
BMI z-score, mean (range)	0.7 (−1.8, 2.6)	0.8 (−3.2, 2.6)	0.412

	Boys	Girls	<i>P</i> value ^{a}
	(<i>n</i> = 222)	(<i>n</i> = 201)	
BMI category,^{b} % (n)			
Underweight	1.8 (4)	2.0 (4)	
Normal weight	56.8 (126)	54.2 (109)	
Overweight	21.2 (47)	17.9 (36)	
Obese	20.3 (45)	25.8 (52)	
Tanner stage, % (n)			
Prepubertal	88.7 (197)	61.2 (123)	
Pubertal	11.3 (25)	38.8 (78)	
Total fat mass (kg/m²), mean (SD)	4.9 (3.4)	6.3 (3.5)	<0.0001
Percent fat mass (%), mean (SD)	23.7 (10.9)	30.2 (10.3)	<0.0001

	Boys	Girls	Pvalue ^a
	(n = 222)	(n = 201)	
MVPA (min/day), mean (SD)	58.7 (27.2)	40.8 (18.9)	<0.0001
Accelerometer-measured sedentary time (min/day), mean (SD)	367.1 (74.2)	367.4 (63.3)	0.967
Screen time (hrs/day), median (range)	2.6 (0.08-13.4)	1.8 (0.03-10.1)	<0.0001
VO2 peak(ml·kg LBM⁻¹·min⁻¹), mean (SD)	60.6 (5.9)	57.3 (6.0)	<0.0001

Table 2. Mean or median values of glucose homeostasis indices among children studied in the QUALITY cohort

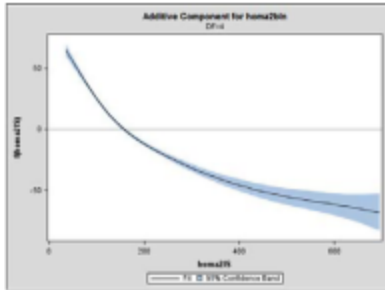
Indices	Boys	Girls	P value ^a
	(n = 222)	(n = 201)	
<p>1. Note: FPG, fasting plasma glucose; HOMA2-IS, homeostatic model assessment version 2 index of insulin sensitivity; Matsuda-ISI, Matsuda-insulin sensitivity index; AUC I/G_{t30min}, area under the curve insulin/glucose _{t30min}; AUC I/G_{t120min}, area under the curve insulin/glucose _{t120min}.</p> <p>2. a</p>			

Indices	Boys	Girls	P value ^a
	(n = 222)	(n = 201)	
<p>The <i>P</i> value indicates the statistical significance of a <i>t</i>-test comparing mean values between boys and girls for normally distributed variables, or a Mann-Whitney <i>U</i> test for variables with a skewed distribution.</p>			
FPG (mmol/l), median (range)	5.0 (3.4, 7.4)	4.9 (3.8, 6.3)	0.002
Fasting insulin (pmol/l), median (range)	25.4 (6.9, 90.1)	32.2 (7.0, 139.6)	<0.0001
Glucose 2-hour postload (mmol/l), median (range)	6.4 (3.7, 9.8)	6.5 (4.1, 15.9)	0.674
Insulin 2-hour postload (pmol/l), median (range)	143.7 (24.6, 2005.0)	211.4 (35.3, 1554.3)	<0.0001
HOMA2-IS, median (range)	181.7 (52.0, 694.5)	143.0 (34.8, 664.5)	<0.0001
Matsuda-ISI, median (range)	10.1 (1.8, 31.0)	8.1 (1.6, 45.1)	<0.0001

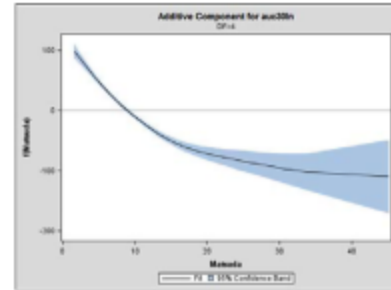
Indices	Boys	Girls	<i>P</i> value ^a
	(<i>n</i> = 222)	(<i>n</i> = 201)	
HOMA2-%B, median (range)	62.8 (29.6, 167.4)	76.7 (29.2, 216.0)	<0.0001
AUC I/G_{t30min}, median (range)	23.5 (6.2, 116.0)	31.3 (6.4, 156.3)	<0.0001
AUC I/G_{t120min}, median (range)	24.1 (6.1, 129.5)	33.4 (5.2, 172.4)	<0.0001

Insulin sensitivity was, as expected, highly associated with insulin secretion across all indices in a nonlinear fashion. Figure 1 illustrates the hyperbolic association noted between HOMA2-%B and HOMA2-IS, as well as Matsuda-ISI and AUC I/G_{t30min} and AUC I/G_{t120min}. Table 3 illustrates the association between each exposure variable and measures of insulin secretion, adjusted for insulin sensitivity only (“univariable models”), and then in a multivariable model. Interestingly, percent fat mass was associated with insulin secretion, even after controlling for insulin sensitivity: for every 1% increase in percent fat mass, insulin secretion increased by 0.4% to 0.7% (Table 3). While associations were not consistently statistically significant, both MVPA and fitness were inversely associated with insulin secretion after adjustment for insulin sensitivity. Screen time was negatively associated with both fasting insulin secretion and second-phase insulin secretion as measured by AUC I/G_{t120min}, but positively associated with first-phase insulin secretion (AUC I/G_{t30min}). Screen time and insulin secretion were no longer associated after controlling for sex.

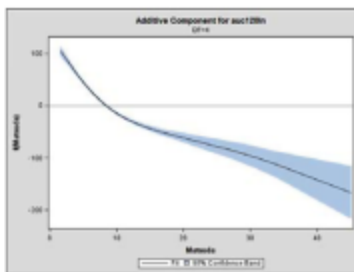
a) Association between HOMA2%-beta and HOMA2-IS ($p < 0.0001$)



b) Association between AUC I/G_{t30min} and Matsuda-ISI ($p < 0.0001$)



1c) Association between AUC I/G_{t120min} and Matsuda-ISI ($p < 0.0001$)



Note: The shaded areas indicate the 95% confidence interval.

Figure 1.

Nonlinear association between measures of insulin sensitivity and insulin secretion in youth (QUALITY cohort) modeled using smoothing splines with four degrees of freedom in generalized additive models. (a) Association between HOMA2%-beta and HOMA2-IS ($P < 0.0001$). (b) Association between AUC I/G_{t30min} and Matsuda-IS ($P < 0.0001$).

Table 3. Beta coefficients and 95% confidence intervals (obtained from generalized additive models using nonparametric splines to adjust for insulin sensitivity) for the associations among physical activity, fitness, and screen time in youth (QUALITY cohort)

Models	HOMA2-%B (<i>n</i> = 420) ^a		AUC I/G _{t30min} (<i>n</i> = 397) ^a		AUC I/G _{t120min} (<i>n</i> = 397) ^a	
	β (95% CI)	<i>P</i> value	β (95% CI)	<i>P</i> value	β (95% CI)	<i>P</i> value

1. Note: MVPA, moderate to vigorous physical activity; min/d, minutes per day; VO₂ peak, peak oxygen

Models	HOMA2-%B (n = 420) a		AUC I/G _{t30min} (n = 397) a		AUC I/G _{t120min} (n = 397) a	
	β (95% CI)	Pvalue	β (95% CI)	Pvalue	β (95% CI)	Pvalue

consumption; 95% CI, 95% confidence interval. Beta coefficients represent the % change in the outcome associated with a 1 unit increase in the exposure variable. MVPA can be interpreted as follows: for every 10% increase in MVPA, β represents the % change in the outcome of interest. The measure of insulin sensitivity used as covariate varied according to the measure of insulin secretion in the models: for HOMA2%beta, the measure of insulin sensitivity used was HOMA2IS, while the measure used for OGTT-derived measures of insulin secretion was the Matsuda-ISI.

2. a

Of the 423 participants under study, three subjects did not have fasting insulin and HOMA-IR values; 26 subjects did not have Matsuda-ISI values.

Model 1—adjusted for insulin sensitivity only

MVPA (10 min/d)	-1.3 (-1.9, -0.7)	<0.0001	-0.3 (-1.7, 1.1)	0.710	-0.9 (-2.1, 0.3)	0.0001
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Model 2—adjusted for insulin sensitivity only

VO2 peak (ml·kgLBM ⁻¹ ·min ⁻¹)	-0.22 (-0.46, 0.02)	0.065	-0.4 (-1.0, 0.2)	0.171	-0.6 (-1.1, -0.1)	0.0001
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Model 3—adjusted for insulin sensitivity only

Models	HOMA2-%B (<i>n</i> = 420) a		AUC I/G _{t30min} (<i>n</i> = 397) a		AUC I/G _{t120min} (<i>n</i> = 397) a	
	β (95% CI)	<i>P</i> value	β (95% CI)	<i>P</i> value	β (95% CI)	<i>P</i> value
Screen time (hours/day)	−0.67 (−1.4, 0.05)	0.072	1.5 (−0.2, 3.2)	0.093	−1.5 (−2.9, −0.05)	0.0003
Model 4— adjusted for insulin sensitivity only						
Fat mass (%)	0.38 (0.22, 0.54)	<0.0001	0.7 (0.3, 1.1)	0.0003	0.6 (0.3, 0.9)	0.0003
Model 5—Multivariable model						
MVPA (10 min/d)	−0.8 (−1.4, −0.2)	0.009	−0.02 (−1.5, 1.5)	0.979	0.1 (−1.2, 1.4)	0.867
VO ₂ peak (ml·kg LBM ^{−1} ·min ^{−1})	−0.05 (−0.3, 0.2)	0.661	−0.3 (−0.9, 0.3)	0.258	−0.5 (−1.0, −0.001)	0.0003
ST(hours/day)	−0.9 (−1.8, 0.03)	0.066	1.5 (−0.3, 3.3)	0.097	−1.1 (−2.6, 0.4)	0.0003

Models	HOMA2-%B (<i>n</i> = 420) a		AUC I/G _{t30min} (<i>n</i> = 397) a		AUC I/G _{t120min} (<i>n</i> = 397) a	
	β (95% CI)	<i>P</i> value	β (95% CI)	<i>P</i> value	β (95% CI)	<i>P</i> value
Fat mass (%)	0.3 (0.1, 0.5)	0.002	0.7 (0.3, 1.1)	0.0004	0.5 (0.2, 0.8)	0.0004
Sex*SB_{ST}	1.4 (−0.06, 2.9)	0.060	-	N.S.	-	N.S.

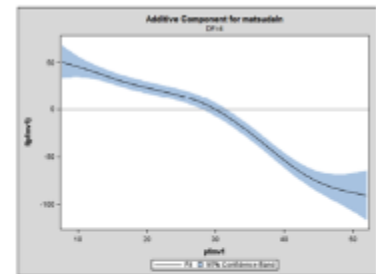
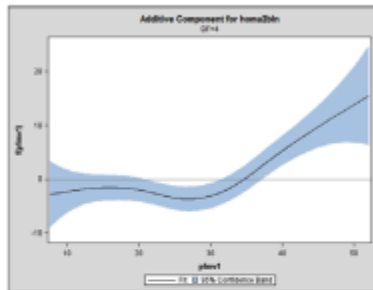
Percent fat mass remained strongly associated with all measures of insulin secretion in multivariable models, even after adjustment for insulin sensitivity (Table 3): for every 1% increase in fat mass, insulin secretion increased from 0.3% to 0.8% across indices. When including MVPA, fitness, adiposity, and screen time within the same model, MVPA was an independent correlate of HOMA2-%B, after accounting for covariates, but not of OGTT-derived measures of insulin secretion (Table 3). Every 10-minute increase in daily MVPA was associated with a decrease in HOMA2-%B of almost 1% (*P* = 0.01). Fitness was not associated with HOMA2-%B, or with first-phase insulin secretion as measured by AUC I/G_{t30min}. However, a one unit increase in VO₂ peak was associated with a 0.7% decrease in second-phase insulin secretion as measured by AUC I/G_{t120min} (Table 3).

Although not reaching statistical significance, screen time was negatively associated with HOMA2-%B in boys, but positively associated in girls: for every 1 hour increase in daily screen time, girls' HOMA2-%B increased by 0.5%. We found no other sex-specific difference in associations between our risk factors of interest and insulin secretion. Conversely, screen time tended to be positively associated with increased first-phase insulin secretion (*P* = 0.097), as measured by AUC I/G_{t30min}, for both boys and girls: for every 1 hour increase in daily screen time, first-phase insulin secretion increased by 1.5% across sexes (Table 3), after accounting for MVPA, fitness, and covariates. When stratifying by weight category, the association between MVPA and HOMA2-%B was strongest for obese youth, but overall conclusions were largely unchanged, despite

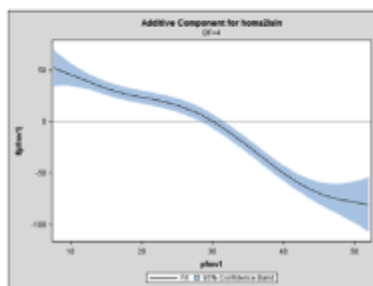
being under-powered. Accelerometer-measured sedentary time was not independently associated with insulin secretion.

Adiposity had a significantly nonlinear, attenuated U-shaped pattern with HOMA2-%B, but not AUC I/G_{t30min} or AUC I/G_{t120min}. This suggests that the findings regarding the associations between lifestyle habits and HOMA2-%B in Table 3 may in fact be an underestimate among overweight children, and an overestimate among normal weight children. We presented the results from the linear model given that the overall conclusions of the models were similar for both approaches and for ease of interpretability. The nonlinear pattern was equally present for adiposity with HOMA2-IS and Matsuda-ISI (Figure 2). Given that insulin sensitivity deteriorates with increasing adiposity, we wondered if metabolically atypical youth might be driving this U-shaped association. To explore this further, we defined the top quartile for HOMA2-%B, HOMA2-IS, and Matsuda-ISI across the entire sample of children, and applied these cut-points within the normal weight youth, thus identifying 20 children with deleterious HOMA2-%B levels, 19 youth with low HOMA2-IS and 27 youth with low Matsuda-ISI. We compared metabolic parameters between these children and the remaining normal weight youth (Table 4). Despite the small number of children with deleterious profiles of insulin sensitivity and secretion, their waist circumference was significantly larger across all outcomes compared to the remaining normal weight youth. Children with low insulin sensitivity as measured by Matsuda-ISI had significantly higher triglycerides, whereas those with low HOMA2-IS had significantly higher diastolic blood pressure. It appeared that the U-shape noted was driven by some normal weight children with low insulin sensitivity and high insulin secretion, akin to their obese counterparts. Moreover the normal weight youth with a deleterious HOMA2-%B profile had significantly higher systolic blood pressure compared with the remaining normal weight children.

a) Association HOMA2% beta (ln transformed) and fat mass (%) [p=0.022] b) Matsuda-ISI (ln transformed) and fat mass (%) [p <0.0001]



c) HOMA2-IS (ln transformed) and fat mass (%) [p=0.0001]



Note: Shaded area represents 95% confidence interval

Figure 2.

Shape of associations between adiposity and measures of insulin sensitivity and secretion. (a) Association between HOMA2%-beta (in transformed) and fat mass (%) ($P = 0.022$). (b) Matsuda-ISI (in transformed) and fat mass (%) ($P < 0.0001$). (c) HOMA2-IS (in transformed) and fat mass (%) ($P = 0.0001$).

Table 4. *T*-tests comparing mean values of metabolic risk factors among normal weight youth across various indices of insulin sensitivity and secretion

Risk factors	Unfavorable profile	Favorable profile	<i>P</i> -value
1. Note: All data presented as means (standard deviation). LDL, low-density lipoprotein; HDL, high-density lipoprotein; SBP-z, systolic blood pressure age and sex-adjusted z-score; DBP-z, diastolic blood pressure age and sex-adjusted z-score; WC, waist circumference.			
	Hi HOMA2-%B (n = 20)	Low HOMA2-%B (n = 213)	

Risk factors	Unfavorable profile	Favorable profile	<i>P</i> -value
Triglycerides	0.82 (0.4)	0.68 (0.2)	0.120
LDL	2.39 (0.6)	2.31 (0.6)	0.634
HDL	1.17 (0.2)	1.26 (0.3)	0.062
SBP-z	−0.37 (0.9)	−0.92 (0.7)	0.016
DBP-z	−1.05 (0.5)	−1.18 (0.4)	0.260
WC	62.3 (5.6)	59.6 (4.3)	0.048
	Low HOMA2-IS (n = 19)	Hi HOMA2-IS (n = 216)	P-value
Triglycerides	0.84 (0.4)	0.68 (0.2)	0.134
LDL	2.36 (0.7)	2.32 (0.6)	0.800
HDL	1.23 (0.2)	1.25 (0.3)	0.666
SBP-z	−0.52 (0.8)	−0.91 (0.7)	0.065

Risk factors	Unfavorable profile	Favorable profile	P-value
DBP-z	−0.96 (0.4)	−1.19 (0.4)	0.041
WC	63.18 (4.2)	59.56 (4.4)	0.002
	Low Matsuda (n = 27)	Hi Matsuda (n = 208)	P-value
Triglycerides	0.84 (0.3)	0.67 (0.2)	0.027
LDL	2.55 (0.6)	2.29 (0.6)	0.061
HDL	1.29 (0.3)	1.25 (0.3)	0.441
SBP-z	−0.60 (0.8)	−0.91 (0.7)	0.073
DBP-z	−1.05 (0.5)	−1.19 (0.4)	0.185
WC	62.85 (4.8)	59.46 (4.3)	0.002

Discussion

In this cross-sectional sample of children with a family history of obesity, we found that adiposity is strongly associated with insulin secretion across all indices, even after controlling for insulin sensitivity. Furthermore, physical activity is negatively associated with HOMA2-%beta, while fitness is negatively associated with second-phase insulin

secretion. Finally, screen time tends to be positively associated with fasting insulin secretion in girls, and first-phase insulin secretion in both boys and girls.

In Lee et al.'s study examining the relationship between cardiorespiratory fitness and insulin secretion in 122 healthy African-American ($n = 65$) and white ($n = 57$) children of 8-17 years, race, pubertal status, and percent body fat were significantly associated with first-phase insulin secretion (measured by the hyperglycemic clamp), whereas pubertal status, VO_2 peak, and percent body fat were independently associated with second-phase insulin secretion [6]. Physical activity and sedentary behavior were not measured, however, nor was insulin sensitivity controlled for. In contrast, Ball et al. found that fitness (VO_2 max) and physical activity were not associated with insulin secretion in a group of obese Hispanic children with a family history of diabetes, controlling for sex, Tanner stage, and body composition (including total fat mass and lean body mass) [7]. They measured insulin secretion using the AIRg from a FSIVGTT, and physical activity was measured by interviewer-administered questionnaire. The authors concluded that the effect of fitness on insulin secretion is indirect and likely a function of body composition [7]. Cross-study comparisons are difficult, however, given the differences related to methodology and the populations under study.

Our finding of the strong association between adiposity and insulin secretion, even after adjusting for insulin sensitivity, confirms reports by Lee et al. [6], although without insulin sensitivity in their models, their association (between fat and insulin secretion) could be because of the confounding effect of insulin sensitivity. While adipose tissue was traditionally regarded as an inert substance, research over the past 10-15 years has shown that it is extremely active hormonally. Several adipocyte-derived hormones have been found to play an important role in insulin sensitivity [30]. The relationship between adipokines and insulin secretion, however, is complex and somewhat less established [31]. Nonetheless, several adipocyte-derived hormones, including leptin [31, 32], adiponectin [31, 32], $TNF-\alpha$ [31], and interleukin-6 [31, 34] are postulated to play a role in beta-cell function and survival. Further research is needed to define the exact mechanisms underlying the role of adiposity, and more precisely of adipokines, on insulin secretion. Even so, our findings suggest that higher levels of physical activity and better fitness may offset the negative impact of adiposity on insulin secretion. This work is complementary to and consistent with our previous work examining the associations between lifestyle habits and insulin sensitivity in youth [35]. Notably, fitness was associated with the OGTT-derived measure of insulin secretion, specifically AUC I/Gt120 minutes. Similarly, fitness was associated with the OGTT-derived measure (Matsuda-ISI) of insulin sensitivity. Having a higher VO_{2peak} reflects an increased ability to use substrate (hence consume oxygen) by muscles, which may be associated with both improved total body insulin sensitivity, but also the body's ability to actively produce insulin after an oral challenge (which AUC I/G t120 minutes measures). Moreover, while the association between MVPA and insulin sensitivity was mediated by adiposity, in this work, MVPA was *independently* associated with insulin secretion, at least in the fasted state. Further research is required to better understand the effects of physical activity across intensities on beta-cell function in both the fasted and fed states, beta-cell mass, and mechanisms of beta-cell proliferation and apoptosis [2]. We also found that

associations between screen time and insulin secretion differed by sex. The reasons for these differences remain unclear. One potential explanation relates to physiological or behavioral differences that mediate sex-specific differences. For example, boys and girls may engage in different forms of screen time, each having different cardiometabolic impacts. There is emerging interest in active-gaming as a method of enhancing physical activity in youth [36]. Alternately, we may have incompletely controlled for confounding factors such as physical activity. Studies specifically comparing different types of screen time and their association with cardiometabolic health would be particularly relevant given the large amount of time children currently spend engaged in screen time [10]. Also noteworthy is that accelerometer-measured sedentary time was not independently associated with any measure of insulin secretion. This is in keeping with our previous work [35] that showed no association with insulin sensitivity when adjusting for adiposity. Why screen time and accelerometer-measured sedentary time appear to have different impacts on cardiometabolic health in children remains unknown. Given that in adults, higher numbers of breaks in sedentary behavior are associated with lower metabolic risk [37], one hypothesis is that the pattern in which sedentary behavior is accumulated is more important to metabolic health than the total quantity. Colley et al., however, found no association between patterns in accelerometer-measured sedentary time and metabolic health in children [38]. Data reduction procedures used to analyze accelerometer data, developed to accurately measure MVPA, might not be appropriate to capture sedentary behavior [38]. Alternatively, screen time might be poorly measured using self-report and/or is a marker for unhealthy lifestyle habits in general, including adverse dietary habits. Further research is needed to identify what specific forms of sedentary behavior are detrimental to metabolic health.

The non-linear, somewhat U-shaped pattern we noted between adiposity and insulin secretion and insulin sensitivity was partially explained by a distinct sub-group of normal weight youth with an atypical metabolic profile. The principal idiosyncrasy in this group appeared to be a higher waist circumference despite their normal weight. Growing evidence supports the fact that visceral or intra-abdominal adipose tissue is more closely linked to the pathophysiology of DM2 and cardiovascular disease risk than subcutaneous fat [39]. The identification of metabolically obese but normal weight (MONW) youth remains tentative at best as there is no accepted definition for this phenotype in children. Nonetheless, efforts to better define this subpopulation are required, given that adult MONW individuals have been shown to be at higher risk of DM2 and cardiovascular disease [40].

The major strengths of this study are the large sample of children, the high quality measures including numerous covariates, and the emphasis on the independent association of fitness, physical activity, and screen time on insulin secretion. The cross-sectional nature of the analysis limits causal inference. While our findings are generalizable only to Caucasian youth 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, adiposity is highly positively associated with insulin secretion, above and beyond its established association with insulin sensitivity. Higher physical activity levels (specifically MVPA) may have a beneficial effect on fasting insulin secretion, even after accounting for adiposity. Similarly, better fitness levels are associated with lower second-phase insulin secretion requirements. Longitudinal studies are required to examine how important the cumulative effect of these lifestyle factors is on insulin secretion and how this relates to the development of DM2. Finally, there is a pressing need to better define and characterize the metabolically obese normal weight phenotype in youth.

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