

# Insulin Sensitivity, Depression/Anxiety, and Physical Fitness in At-Risk Adolescents



## Authors

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## ABSTRACT

Poor physical fitness contributes to the early progression of cardiometabolic disease, yet the physiological and psychological factors underpinning poor fitness in at-risk adolescents are not well understood. In this study, we sought to determine the relationship of physical fitness with two developmental phenomena of adolescence, insulin resistance and depression/anxiety symptoms among at-risk youth. We conducted secondary data analyses of 241 overweight or obese adolescents (12–17 years), drawn from two study cohorts. Insulin sensitivity index was derived from oral glucose tolerance tests. Adolescents self-reported depressive symptoms and anxiety symptoms on validated surveys. A walk/run test was administered to determine perceived exertion and physical fitness (distance traveled). Insulin sensitivity was positively associated with walk/run distance ( $b = 0.16$ ,  $P < 0.01$ ), even after accounting for all covariates. Anxiety symptoms were inversely related to perceived exertion ( $b = -0.11$ ,  $P < 0.05$ ), adjusting for covariates. These findings suggest that insulin resistance and anxiety symptoms are associated with different dimensions of physical fitness in overweight or obese adolescents and could both potentially contribute to declining fitness and worsening metabolic outcomes in at-risk youth.

The progressively earlier onset of preventable lifestyle-related diseases has become an alarming public health issue among adolescents in the United States. In particular, type 2 diabetes is increasingly prevalent in adolescents, especially adolescent females from

historically disadvantaged racial/ethnic groups [4]. Early onset of type 2 diabetes is associated with a more severe and aggressive disease course, necessitating a better understanding of the potentially modifiable precursors to cardiometabolic disease [23].

A modifiable risk factor, poor physical fitness, caused by insufficient moderate-to-vigorous physical activity and high amounts of sedentary behavior [8], is correlated with reduced insulin sensitivity in adolescents, above and beyond the effects of adiposity and body mass index (BMI; kg/m<sup>2</sup>) [1]. Adolescence is marked by a notable decrease in moderate-to-vigorous physical activity and an increase in sedentary behavior, especially in girls from historically disadvantaged racial/ethnic groups [15, 24], potentially exacerbating the pubertal increases in insulin resistance [14]. Conversely, the decreases in insulin sensitivity accompanying puberty also have been posited to lead to fatigue, triggering adolescents' withdrawal from physical activity and subsequently, poorer fitness [3].

In addition, adolescence is notable for a rise in affective disturbances, including internalizing symptoms of depression and anxiety [18], which may contribute to declining physical activity and fitness during this stage of development [24]. In adults, symptoms of depression and anxiety have been associated with obesity, physical inactivity, poor physical fitness, and type 2 diabetes [19, 28, 34]. Although there is a smaller body of literature examining these associations among adolescents, existing data suggest that adolescent depressive symptoms relate to less reported physical activity over time, possibly due to the vegetative symptoms of depression such as fatigue and psychomotor retardation [13]. Social isolation, which frequently accompanies depression and anxiety symptoms, also may play a role [9].

In the current study, we sought to evaluate how both insulin sensitivity and symptoms of depression and anxiety were associated cross-sectionally with objectively-measured physical fitness during walk/run testing in adolescents at heightened risk for cardiometabolic disease. We hypothesized that insulin sensitivity would be positively associated with physical fitness, whereas depression and anxiety symptoms would be inversely associated with fitness. We anticipated that these associations would exist independently of current adiposity. We examined these aims and hypotheses in two adolescent cohorts; one was a group of overweight/obese females with elevated depression symptoms and a family history of type 2 diabetes, and the other was a group of males and females with obesity and obesity-related health comorbidities. Despite some expected descriptive differences between the samples by study design (e. g., depression level and degree of obesity/BMI standard score), we anticipated that the relations of insulin sensitivity and internalizing symptoms with physical fitness would be similar across cohorts.

## Materials and Methods

### Study participants

This study represents a secondary data analysis of two convenience samples used to address the current research questions.

#### Cohort 1

Cohort 1 participants were recruited to take part in a behavioral trial for the prevention of type 2 diabetes (NCT 01425905); the main outcomes have been reported [29, 30]. Participants were adolescent girls ages 12–17 years who were in good general health,

other than being overweight or obese (BMI  $\geq$  85<sup>th</sup> percentile for age and sex) and all reported a family history of diabetes. Adolescents reported mild-to-moderate depressive symptoms, determined as a total score  $\geq$  16 on the Centers for Epidemiologic Studies Depression Scale [26]. Volunteers were excluded if they had current psychiatric symptoms requiring treatment; fasting glucose  $>$  126 mg/dL; 2-hour glucose  $>$  200 mg/dL; pregnancy; use of medication affecting insulin sensitivity, weight, or mood; and/or were involved in current psychotherapy or weight loss treatment. The present analysis uses data only from the baseline assessment.

#### Cohort 2

Cohort 2 participants were recruited for a medication trial for the treatment of obesity (NCT00001723). Other exercise-related outcomes have been reported elsewhere [6, 25, 27, 31]. Participants were non-Hispanic Black and White adolescent boys and girls 12–17 years with obesity (BMI  $\geq$  95<sup>th</sup> percentile for age and sex) and  $\geq$  1 obesity-related health co-morbidity, including hypertension, hyperlipidemia, sleep apnea, hepatic steatosis, insulin resistance, impaired glucose tolerance, and/or type 2 diabetes. Volunteers were excluded for current or past medical problems that would impair exercise testing performance, medication use for weight loss, psychiatric symptoms that necessitated a referral and would impede compliance, and pregnancy or nursing in females. In the present analysis, we included data only from the baseline assessment.

### Procedures and measures

Unless otherwise noted, the same method was used in both samples. All assessments took place in the Mark O. Hatfield Clinical Research Center of the National Institutes of Health. Procedures were approved by the Institutional Review Board of the Eunice Kennedy Shriver National Institute of Child Health and Human Development and were consistent with the ethical standards of Sports Medicine International Open [11]. Parents/guardians provided written informed consent, and adolescents provided assent to participate.

#### Anthropometric measurements

Height was measured in triplicate by stadiometer and averaged. Fasting weight was assessed using a calibrated digital scale. Height and weight were used to compute BMI (kg/m<sup>2</sup>), BMI standard score (z), and BMI percentile for age and sex. Fat and lean mass (kg) were measured using dual-energy x-ray absorptiometry using either a Hologic QDR-4500A instrument (Hologic Inc., Waltham, MA, USA) or iDXA (GE Healthcare, Madison, WI, USA).

#### Puberty

Pubertal development was determined from physical examination by an endocrinologist or nurse practitioner using Tanner staging derived from breast development in females and testicular volume in males [20, 21].

#### Physical fitness and perceived exertion

Physical fitness was measured using an individual 12-minute walk/run shuttle test, running back and forth in a hallway, that has been shown to correlate with cardiorespiratory fitness as measured dur-

ing a maximal cycle ergometry test in adolescents with obesity [6]. Participants were instructed to give their best effort by covering as much distance as possible in 12 min. Total distance traveled was measured with a measurement wheel. Perceived exertion, referring to adolescents' perceptions of degree of effort and intensity level of their physical activity, was assessed upon completion of the fitness test with the 20-point Borg Rating of Perceived Exertion Scale (range = 6–20) [2]. Participants were shown a diagram to familiarize themselves with the rating of perceived exertion scale.

### Depression and anxiety symptoms

Adolescents completed widely-used, validated survey instruments to assess depression and anxiety symptoms in this age group. Adolescents completed questionnaires in a private room and were instructed that surveys would ask about their feelings and behavior. Depressive symptoms were determined using adolescents' reports on the reliable and well-validated Children's Depression Inventory, a 27-item survey with the total score calculated as the sum of all items (range = 0–54) [16]. Anxiety symptoms were measured using youth's report on the 20-item State-Trait Anxiety Inventory for Children (STAI-C)-Trait Version, a widely used reliable and valid measure, calculated as the sum of all items (range = 20–60) [32].

### Insulin sensitivity

Testing to assess insulin sensitivity was performed in a pediatric research clinic in the morning following an overnight fast, in which adolescents were asked to refrain from food or drink other than water, after 10:00 pm the evening before the visit. A 2-hour oral glucose tolerance test (OGTT) was used to determine insulin sensitivity, calculated as Insulin Sensitivity Index (ISI) using reduced time points of insulin and glucose at 0 and 120 min [5]. Using only fasting samples, we also determined insulin sensitivity with quantitative insulin sensitivity check index (QUICKI) [10] and insulin resistance with the homeostasis model assessment of insulin resistance (HOMA-IR) formulae [22].

### Statistical analyses

Analyses were conducted with SPSS version 23. Data were cleaned by winsorizing outliers to fall 1.5 times the interquartile range below the 25<sup>th</sup> percentile or above the 75<sup>th</sup> percentile. Characteristics of cohorts 1 and 2 were compared using chi-square for categorical variables and independent samples t-tests for continuous variables. Multiple hierarchical regression models using listwise deletion to handle missing data (0.6%) were used to examine the associations of insulin sensitivity, depressive symptoms, and anxiety symptoms (independent variables) with physical fitness, including perceived exertion and total distance traveled (dependent variables). We included the following covariates in step 1 of the models: race/ethnicity, age, puberty, height, lean mass, percent adiposity, sex, and study cohort. In step 2, ISI, QUICKI, or HOMA-IR were entered in separate models. In step 3, depression and anxiety symptoms were added. We combined cohorts 1 and 2 in the analyses; however, given demographic differences in the cohorts, by design, we also analyzed the models separately, stratified by study cohort. Significance was determined as a  $P < 0.05$ . Effect sizes were estimated with Cohen's  $d$  (~0.20: small, ~0.50: medium,  $\geq 0.80$ : large).

## Results

### Sample

Characteristics of the total sample ( $N = 241$ ), as well as differences between cohort 1 ( $n = 100$ ) and cohort 2 ( $n = 141$ ), are displayed in ► **Table 1**. Average (SD) age of participants was 14.67 (1.46) years, with no age difference between samples ( $P = 0.15$ ).

### Perceived exertion

► **Table 2** displays a summary of regression analyses for perceived exertion during walk/run fitness testing. Within the combined cohort, anxiety symptoms were negatively associated with perceived exertion ( $P = 0.02$ ; Cohen's  $d = 0.10$ ), after accounting for all covariates. When the analyses were stratified by cohort, anxiety symptoms remained significant in the model including cohort 1 ( $P < 0.05$ ; Cohen's  $d = 0.23$ ).

### Walk/run distance

► **Table 3** summarizes the results for the regression models for walk/run distance traveled. Accounting for all covariates, insulin sensitivity by ISI was significantly, positively associated with walk/run distance ( $P < 0.01$ ; Cohen's  $d = 0.16$ ). ISI explained 2% of the unique variance in walk/run distance ( $P < 0.01$ ), after accounting for covariates. Parallel effects were observed for insulin sensitivity measured via QUICKI (Cohen's  $d = 0.23$ ) and insulin resistance estimated with HOMA-IR (Cohen's  $d = 0.25$ ). When we also explored controlling for perceived exertion in these models predicting walk/run distance, the effects of insulin sensitivity/resistance remained significant.

When analyses were stratified by study cohort, results were similar. In cohort 1, the associations of QUICKI (Cohen's  $d = 0.25$ ) and HOMA-IR (Cohen's  $d = 0.31$ ) remained significantly associated with walk/run distance ( $P \leq 0.01$ ), but the association of ISI with walk/run distance was attenuated ( $P = 0.13$ ; Cohen's  $d = 0.14$ ). In cohort 2, the effects for all three indices of insulin sensitivity/resistance remained significant predictors of walk/run distance ( $P < 0.01$ ; Cohen's  $d = 0.17$ – $0.23$ ).

In addition, after including covariates and insulin sensitivity in the model, depressive symptoms were significantly, inversely associated with walk/run distance in cohort 2 only ( $P < 0.05$ ; Cohen's  $d = 0.19$ ).

## Discussion

In the current paper, we conducted a secondary cross-sectional data analysis of two adolescent cohorts at heightened risk for cardiometabolic disease. The aim was to determine the relationship of two developmental phenomena of adolescence – reduced insulin sensitivity and increased depression and anxiety symptoms – to physical fitness, measured during walk/run testing. In the total combined sample, anxiety symptoms related to less perceived exertion, and insulin resistance related to less distance traveled, with some slight, but potentially meaningful, differences by cohort.

An inverse association of anxiety symptoms with adolescents' perceived effort during physical activity was apparent in cohort 1, the female-only cohort. These participants had more elevated symptoms of depression and anxiety compared to cohort 2. Our results are con-

► **Table 1** Characteristics of the total sample and differences in characteristics between cohorts 1 and 2.

Characteristic	Total Sample		Cohort 1		Cohort 2		P
	N = 241		n = 100		n = 141		
	M ± SD	n, %	M ± SD	n, %	M ± SD	n, %	
<b>Sex</b>							<0.001
Male		48, 19.9%		0, 0%		48, 34.0%	
Female		193, 80.1%		100, 100%		93, 66.0%	
<b>Race/ethnicity</b>							<0.001
Non-Hispanic Black		142, 58.9%		59, 59.0%		83, 58.9%	
Non-Hispanic White		76, 31.5%		18, 18.0%		58, 41.1%	
Hispanic		12, 5.0%		12, 12.0%		0, 0%	
Multiple or Other		11, 4.6%		11, 11.0%		0, 0%	
<b>Age, y</b>	14.67 ± 1.46		14.83 ± 1.50		14.56 ± 1.42		0.15
<b>BMI z score</b>	2.31 ± 0.47		1.99 ± 0.48		2.53 ± 0.32		<0.001
<b>Body fat, %</b>	46.35 ± 6.57		43.14 ± 5.76		48.63 ± 6.16		<0.001
<b>Internalizing symptoms</b>							
Depressive symptoms	9.87 ± 6.65		13.57 ± 6.10		7.24 ± 5.73		<0.001
Anxiety symptoms	35.03 ± 7.54		38.80 ± 6.69		32.35 ± 6.96		<0.001
<b>Insulin sensitivity</b>							
ISI	2.67 ± 1.71		2.80 ± 1.90		2.59 ± 1.57		0.36
QUICKI	0.30 ± 0.02		0.31 ± 0.03		0.31 ± 0.03		0.36
HOMA-IR	5.86 ± 3.30		0.30 ± 0.02		5.59 ± 3.26		0.28
<b>12-Min. Walk-Run Test</b>							
Distance, m	1 176.64 ± 208.20		1 220.29 ± 216.40		1 146.68 ± 197.25		0.01
Perceived exertion	11.05 ± 3.50		14.42 ± 2.02		8.31 ± 1.47		<0.001

Note: Abbreviations are: M ± SD = mean ± standard deviation; BMI z score = body mass index standard score for age and sex; ISI = insulin sensitivity index; QUICKI = quantitative insulin sensitivity check index; HOMA-IR = homeostasis model assessment of insulin resistance. For perceived exertion, N = 219 for the total sample, n = 98 for cohort 1, and n = 121 for cohort 2.

sistent with previous research suggesting that women with obesity experience lower energy and report less pleasure from exercise than women without obesity [7]. The current findings suggest that anxiety may be a barrier to engagement in physical activity in heavier adolescents, particularly in girls. Adolescence is notable for increases in anxiety and body dissatisfaction, and adolescent girls who are heavier report greater anxiety and more anxiety specific to body image and physique than females who are leaner [33]. Exertion relates to likelihood to achieve fitness, and declining physical fitness is a key contributor in the progressive course of cardiometabolic disease onset [1]; thus, strategies for directly addressing this distinct psychological barrier (e.g., altering the contextual features and/or type of delivery of physical activity interventions) warrant consideration.

In contrast, depression symptoms related to less distance traveled in cohort 2 only, the sample of adolescent girls and boys with obesity and obesity-related health co-morbidities. This effect is consistent with previous studies showing a relationship of depression to cardiorespiratory fitness and to prospective declines in physical activity over time in adolescents [13, 31]. In theory, the vegetative symptoms of depression, including fatigue, low energy, sleep disruption, appetite dysregulation, and anhedonia or lack of pleasure in daily activities, are proposed to contribute to withdrawal from physical activities, which, in turn, further worsens depressed mood [13]. Indeed, behavioral activation – scheduling and doing activities even when one does not feel like it – is an evidence-based interven-

tion for preventing and treating adolescent depression [12]. Addressing symptoms of depression may have the potential to encourage engagement in physical activity that leads to improvements in physical fitness, and in turn, lessens cardiometabolic risk independent of weight loss. In the current study, the lack of association of depressive symptoms with physical fitness in cohort 1 cannot be determined with certainty, but one likely explanation is that this null effect may be explained by the more restricted variability in depression symptoms in cohort 1, all of whom were girls reporting some degree of elevated affective disturbance.

Insulin sensitivity, assessed across multiple indices (ISI, HOMA-IR, QUICKI), was positively associated with walk/run distance traveled. These associations were observed consistently in the combined sample and across both cohorts examined separately, notably after controlling for body composition and other possible confounds (with the exception that the relationship of ISI to walk/run distance was slightly attenuated in cohort 1). The relationship of insulin sensitivity and physical fitness may be explained by several possible underlying mechanisms. One possibility is that poorer physical fitness may worsen insulin sensitivity in youth independent of adiposity [1]. Youth with recent-onset T2D, for instance, have less moderate-to-vigorous activity and spend more time engaging in sedentary behaviors than youth with obesity but no T2D, suggesting a possible putative role for physical activity and fitness in T2D onset, regardless of degree of adiposity [17]. Alternatively, it is pos-

► **Table 2** Series of multiple hierarchical regressions for perceived exertion in the total sample and stratified by study cohort.

Model	Variable	Total Sample				Cohort 1				Cohort 2			
		$\beta$ [95% CI]	SE	b	$\beta$ [95% CI]	SE	b	$\beta$ [95% CI]	SE	b	$\beta$ [95% CI]	SE	b
1	Study cohort	-6.04 *** [-6.63, -5.45]	0.30	-0.86 ***	---	---	---	---	---	---	---	---	---
	Female	0.16 [-0.57, 0.89]	0.37	0.02	---	---	---	---	---	---	---	---	---
	Black	-0.18 [-0.70, 0.33]	0.26	-0.03	-0.41 [-1.24, 0.42]	0.42	-0.10	0.16 [-0.48, 0.79]	0.32	-0.10	0.16 [-0.48, 0.79]	0.32	-0.03
	Age, y	-0.11 [-0.30, 0.08]	0.10	-0.05	-0.20 [-0.50, 0.10]	0.15	-0.15	-0.01 [-0.24, 0.23]	0.12	-0.15	-0.01 [-0.24, 0.23]	0.12	-0.01
	Tanner 5	0.00 [-0.12, 0.12]	0.06	0.00	-0.10 [-0.30, 0.09]	0.10	-0.12	0.11 [-0.03, 0.26]	0.07	-0.12	0.11 [-0.03, 0.26]	0.07	0.19
	Height, cm	-0.04 * [-0.08, 0.00]	0.02	-0.10 *	-0.07 [-0.14, 0.01]	0.04	-0.24	-0.01 [-0.06, 0.03]	0.02	-0.24	-0.01 [-0.06, 0.03]	0.02	-0.07
	Lean mass, kg	0.02 [-0.01, 0.06]	0.02	0.07	0.05 [-0.02, 0.11]	0.03	0.20	-0.02 [-0.06, 0.03]	0.02	0.20	-0.02 [-0.06, 0.03]	0.02	-0.10
	Fat mass, %	-0.02 [-0.06, 0.02]	0.02	-0.04	-0.05 [-0.13, 0.02]	0.04	-0.15	0.00 [-0.04, 0.05]	0.02	-0.15	0.00 [-0.04, 0.05]	0.02	0.02
			$R^2=0.75$ ***			$R^2=0.12$						$R^2=0.05$	
			$\Delta R^2=0.75$ ***			$\Delta R^2=0.12$						$\Delta R^2=0.05$	
Step	ISI	0.11 [-0.04, 0.26]	0.08	0.05	0.00 [-0.25, 0.26]	0.13	0.00	0.18 [0.00, 0.36]	0.09	0.00	0.18 [0.00, 0.36]	0.09	0.19
			$R^2=0.75$ ***			$R^2=0.12$						$R^2=0.08$	
Step	QUICKI	6.48 [-4.66, 17.61]	5.65	0.05	3.09 [-17.98, 24.16]	10.61	0.04	8.27 [-4.08, 20.62]	6.23	0.04	8.27 [-4.08, 20.62]	6.23	0.13
			$\Delta R^2=0.00$			$\Delta R^2=0.00$						$\Delta R^2=0.03$	
Step	HOMA-IR	-0.02 [-0.11, 0.06]	0.04	-0.02	-0.03 [-0.20, 0.15]	0.09	-0.04	-0.02 [-0.11, 0.07]	0.04	-0.04	-0.02 [-0.11, 0.07]	0.04	-0.04
			$R^2=0.75$ ***			$R^2=0.12$						$R^2=0.08$	
Step	Depression	0.03 [-0.02, 0.08]	0.02	0.06	0.02 [-0.06, 0.09]	0.04	0.05	0.03 [-0.04, 0.09]	0.03	0.05	0.03 [-0.04, 0.09]	0.03	0.10
	Anxiety	-0.05 [-0.09, -0.01]	0.02	-0.11 *	-0.07 * [-0.14, 0.00]	0.03	-0.23 *	-0.03 [-0.08, 0.02]	0.03	-0.23 *	-0.03 [-0.08, 0.02]	0.03	-0.14
Step			$R^2=0.76$			$R^2=0.16$						$R^2=0.09$	
			$\Delta R^2=0.01$			$\Delta R^2=0.04$						$\Delta R^2=0.01$	

Note: \*  $P < 0.05$ ; \*\*  $P < 0.01$ ; \*\*\*  $P < 0.001$ . Study cohort coded 1 = Cohort 1 and 2 = Cohort 2. Estimates are from entry into the model. Models 2a, 2b, and 2c reflect separate regressions; model 3 estimates are after accounting for models 1 and 2a variables. Abbreviations are:  $\beta$  = unstandardized regression coefficient; 95% CI = 95% confidence interval; SE = standard error; b = standardized regression coefficient;  $R^2$  = percentage of variance accounted for in the dependent variable; ISI = insulin sensitivity index; QUICKI = quantitative insulin sensitivity check index; HOMA-IR = homeostasis model assessment of insulin resistance. N = 219 for the total sample, n = 98 for cohort 1, and n = 121 for cohort 2.

► **Table 3** Series of multiple hierarchical regressions predicting walk/run distance (m) in the total sample and stratified by study cohort.

Model	Variable	Total Sample				Cohort 1				Cohort 2			
		$\beta$ [95% CI]	SE	b	$\beta$ [95% CI]	SE	b	$\beta$ [95% CI]	SE	b	$\beta$ [95% CI]	SE	b
Step 1	Study cohort	52.66* [0.79, 104.53]	26.33	0.13*	---	---	---	---	---	---	---	---	---
	Female	-17.87 [-80.78, 45.04]	31.93	-0.03	---	---	---	---	---	---	---	---	-0.08
	Black	-100.75*** [-145.73, -55.77]	22.83	-0.24***	-172.05*** [-239.29, -104.81]	33.86	-0.39***	-36.65 [-96.02, 22.72]	30.01	-0.09			
	Age, y	11.29 [-5.35, 27.93]	8.44	0.08	-6.20 [-30.71, 18.30]	12.34	-0.04	27.22* [5.08, 49.35]	11.19	0.20*			
	Tanner 5	-5.52 [-15.94, 4.91]	5.29	-0.06	-5.39 [-21.24, 10.47]	7.98	-0.06	-4.26 [-18.07, 9.55]	6.98	-0.05			
	Height, cm	6.06** [2.42, 9.70]	1.85	0.21**	4.08 [-1.66, 9.82]	2.89	0.14	8.99*** [4.26, 13.72]	2.39	0.34***			
	Lean mass, kg	-6.45*** [-9.45, -3.44]	1.53	-0.32***	-4.68 [-9.89, 0.53]	2.62	-0.18	-9.05*** [-12.84, -5.27]	1.92	-0.45***			
	Fat mass, %	-16.17*** [-19.70, -12.65]	1.79	-0.51***	-18.39*** [-24.38, -12.41]	3.02	-0.49***	-14.16*** [-18.49, -9.82]	2.19	-0.44***			
				R <sup>2</sup> =0.44***				R <sup>2</sup> =0.49***					
				$\Delta R^2=0.44***$				$\Delta R^2=0.49***$					
Step 2a	ISI	19.49** [6.85, 32.13]	6.41	0.16**	15.82 [-4.35, 35.98]	10.15	0.14	20.93* [3.88, 37.97]	8.62	0.17*			
				R <sup>2</sup> =0.46**				R <sup>2</sup> =0.45***					
				$\Delta R^2=0.02**$				$\Delta R^2=0.02*$					
Step 2b	QUICKI	1937.54*** [978.03, 2897.05]	486.99	0.23***	2152.89** [518.64, 3787.13]	822.85	0.25**	1727.00** [530.35, 2923.66]	604.95	0.20**			
				R <sup>2</sup> =0.47***				R <sup>2</sup> =0.46***					
				$\Delta R^2=0.03***$				$\Delta R^2=0.03**$					
Step 2c	HOMA-IR	-15.89*** [-22.88, -8.91]	3.54	-0.25***	-20.47** [-33.64, -7.31]	6.63	-0.31**	-13.39** [-21.62, -5.16]	4.16	-0.23**			
				R <sup>2</sup> =0.48***				R <sup>2</sup> =0.47***					
				$\Delta R^2=0.04***$				$\Delta R^2=0.04**$					
Step 3	Depression	-1.03 [-5.23, 3.17]	2.32	-0.03	3.92 [-2.05, 9.90]	3.01	0.11	-6.64* [-12.63, -0.65]	3.03	-0.19*			
	Anxiety	0.38 [-3.25, 4.01]	1.84	0.01	-2.05 [-7.47, 3.38]	2.73	-0.06	3.70 [-1.20, 8.59]	2.47	0.13			
				R <sup>2</sup> =0.46***				R <sup>2</sup> =0.47***					
				$\Delta R^2=0.00$				$\Delta R^2=0.02$					

Note: \* P<0.05; \*\* P<0.01; \*\*\* P<0.001. Study cohort coded 1 = Cohort 1 and 2 = Cohort 2. Estimates are from entry into the model. Models 2a, 2b, and 2c reflect separate regressions; model 3 estimates are after accounting for models 1 and 2a variables. Abbreviations are:  $\beta$  = unstandardized regression coefficient; 95% CI = 95% confidence interval; SE = standard error; b = standardized regression coefficient; R<sup>2</sup> = percentage of variance accounted for in the dependent variable; |SI| = insulin sensitivity index; QUICKI = quantitative insulin sensitivity check index; HOMA-IR = homeostasis model assessment of insulin resistance. N = 241 for the total sample, n = 100 for cohort 1, and n = 141 for cohort 2.

sible that poor insulin sensitivity may contribute to less physical activity due to physiological consequences such as fatigue [3]. If the insulin sensitivity-physical fitness connection represents a bidirectional relationship, then theoretically, intervening to improve insulin sensitivity (e. g., through pharmacological agents) might enhance adolescent's willingness to engage in physical activity, thereby improving their fitness, just as improving fitness would be anticipated to improve insulin resistance. These alternative hypotheses require experimental testing in future research.

Limitations to the present study include the cross-sectional and correlational design, making it impossible to determine the causal direction of effects. All of the effects we did observe for the relationships of psychological symptoms and insulin sensitivity with perceived exertion or walk/run distance were small, underscoring the multitude of factors that are associated with physical activity in overweight or obese adolescents. Generalizability of the observed effects are limited to adolescents at-risk for cardiometabolic disease and may or may not apply to adolescents with lower risk of disease. Non-Hispanic Black and non-Hispanic White adolescents were also disproportionately sampled and there was limited representation of Hispanic adolescents or other racial/ethnic groups at heightened risk for obesity and metabolic disorders. Similarly, the cohorts did not include younger adolescents at a less advanced pubertal stage. This feature made the participants largely homogenous for the late pubertal stage, and thus, we could not ascertain or isolate the distinctive association of pubertal development or timing with the variables of interest examined in this study. Though walk/run testing relates to cardiorespiratory fitness [6], an important risk factor for cardiometabolic disease, we did not evaluate habitual physical activity. Future work should consider ambulatory physical activity monitoring in relation to insulin sensitivity and depression/anxiety symptoms to determine whether the observed associations apply to physical activity.

The current study supports a role for both insulin sensitivity and affective disturbance in dimensions of physical fitness among adolescents at high-risk for cardiometabolic disease. Most adolescents, and particularly those who are overweight or obese, do not achieve the recommended 60 min per day of moderate-to-vigorous physical activity [35]. Considering developmentally-sensitive factors may be relevant in the design of more effective interventions to address a strong need for increased physical activity and physical fitness in at-risk adolescents.

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## Conflict of Interest

None of the authors has a conflict of interest. J. A. Yanovski and B.E. Drinkard are Commissioned Officers in the U.S. Public Health Service. The opinions and assertions expressed herein are those of the authors

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