Temporal Relationship Between Insulin Sensitivity and the Pubertal Decline in Physical Activity in Peripubertal Hispanic and African American Females

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OBJECTIVE—Little attention has been paid to possible intrinsic biological mechanisms for the decline in physical activity that occurs during puberty. This longitudinal observational study examined the association between baseline insulin sensitivity (SI) and declines in physical activity and increases in sedentary behavior in peripubertal minority females over a year.

RESEARCH DESIGN AND METHODS—Participants were Hispanic and African American girls (n = 55; 76% Hispanic; mean age 9.4 years; 36% obese). SI and other insulin indices were measured at baseline using the frequently sampled intravenous glucose tolerance test. Physical activity was measured on a quarterly basis by accelerometry and self-report.

RESULTS—Physical activity declined by 25% and time spent in sedentary behaviors increased by ~13% over 1 year. Lower baseline SI predicted the decline in physical activity measured by accelerometry, whereas higher baseline acute insulin response to glucose predicted the decline in physical activity measured by self-report. Time spent in sedentary behavior increased by ~13% over 1 year, and this was predicted by lower baseline SI. All models controlled for adiposity, age, pubertal stage, and ethnicity.

CONCLUSIONS—When evaluated using a longitudinal design with strong outcome measures, this study suggests that lower baseline SI predicts a greater decline in physical activity in peripubertal minority females.

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Although the health benefits of lifetime physical activity for girls and women are well defined, physical activity declines precipitously during puberty (1). This steep pubertal decline in physical activity has been noted in both girls and boys (2); however, girls accrue approximately 30 min per day less physical activity than boys at all ages and stages of maturity (3) and therefore cross below the recommended daily 60 min of physical activity 1.7 years earlier than do boys (2,4). Furthermore, the pubertal decline in physical activity is most pronounced in minority girls (5), putting them at higher risk for obesity and related disorders. This decline tracks into adulthood, leading to lifelong habitual physical inactivity (6). Current high levels of childhood obesity, insulin resistance, and other related diseases place the pubertal decline in physical activity in direct conflict with current public health goals.

The pubertal decline in physical activity is not well understood. Sharp declines in physical activity consistently occur during childhood across sex and ethnic groups in multiple countries (7). Animal studies reveal a similar phenomenon in many species, ranging from insects and rodents to monkeys (8). The striking similarities between human and animal studies suggest strong evidence that this decline in physical activity is driven, at least in part, by intrinsic biological mechanisms (7,8). Nonetheless, most research on the pubertal decline in physical activity has focused on environmental and psychosocial influences, while the probable role of biological mechanisms in the regulation of physical activity has received less attention (9).

Insulin sensitivity (SI) declines during puberty, with the lowest point at Tanner pubertal stage 3, and returning to near normal levels at Tanner pubertal stage 5, independent of body fat (10). In early maturation, and particularly in females, the decrease in SI is compensated by an increase in first-phase insulin response, as measured by the acute insulin response to glucose (AIRg) (11). It has been suggested that pubertal changes in insulin dynamics may serve to promote growth during pubertal development, perhaps by preserving energy (10). Several studies have identified sharp physical activity declines from age 12 (12,13), the average age at which girls reach Tanner stage 3 and demonstrate peak pubertal insulin resistance, which suggests that pubertal insulin resistance may trigger a decline in physical activity. That insulin resistance may begin earlier than the decline in physical activity, especially in girls

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(14), suggests that pubertal insulin resistance may *precede* the pubertal decline in physical activity. It is thus possible that decreasing SI and the resultant increases in AIRg during puberty *inhibits* physical activity, suggesting a mechanism that places peripubertal girls in a vicious cycle of insulin resistance, physical inactivity, and accumulation of body fat. The longitudinal study presented here, the TRANSITIONS study, followed Hispanic and African American girls through the early stages of puberty (15). We hypothesized that lower SI and/or related higher AIRg during early puberty would precede the drop in physical activity, such that lower SI and/or higher AIRg at baseline would predict a greater magnitude of decline in physical activity over a year in the lives in minority peripubertal girls.

RESEARCH DESIGN AND METHODS

Participants

Participants (paid volunteers) were recruited from participating clinics, churches, schools, and community centers in the Los Angeles area (15). The longitudinal study assessed insulin dynamics, body composition, and pubertal stage each year during annual overnight visits to the University of Southern California General Clinical Research Center (GCRC). In addition, physical activity and sedentary behavior were assessed every 3 months during quarterly home visits. Data presented here are from five assessment points (visits 1 through 5) conducted in the first 2 years of the study. Visit 1 is the baseline GCRC annual assessment, which also includes physical activity assessments. Quarterly visits 2 through 5 include physical activity measurement.

The inclusion criteria were nonmenstruating females between the ages of 8 to 11 at baseline, of Hispanic or African American ethnicity, who were at pubertal Tanner breast stage 1 or 2 (16). Additional inclusion criteria were determined at a preliminary screening visit conducted at the GCRC. These criteria were child classification as overweight or obese (BMI ≥85th percentile) or child classification as normal weight (BMI in 5th to 85th percentile), with at least one parent meeting adult criteria for overweight (BMI ≥25) or being diagnosed with type 2 diabetes. Participants were excluded from the study if they had diabetes at the screening visit (defined as fasting plasma glucose ≥126 mg/dL) or otherwise met diagnostic criteria for diabetes (i.e., symptoms of diabetes with random glucose >200 mg/dL). Subjects also were excluded if they were *1*) taking any medications known to influence body composition, insulin action, or insulin secretion (e.g., prednisone, Ritalin, growth hormone); 2) diagnosed with syndromes or diseases that may influence insulin action and secretion (e.g., maturity-onset diabetes of the young, lipoatrophic diabetes, cystic fibrosis) or body composition and fat distribution (e.g., Cushing syndrome, Down syndrome); or, *3*) previously diagnosed with any major illness since birth (e.g., severe intrauterine growth retardation, birth asphyxia, cancer) or a condition that could affect body composition, fat distribution, or insulin action or secretion. Informed written parental consent and participant assent were obtained. All study procedures were approved by the institutional review board of the University of Southern California.

Procedures

At the annual overnight visits, participants arrived at the GCRC in the afternoon on day 1. Participants completed anthropometric measures and received a complete medical examination, including determination of Tanner pubertal stage of development (16) and a health history conducted by a licensed pediatric health care provider. Participants were given a standard meal and snack before 2000 h, after which they were restricted to water. After an overnight stay, on day 2 a frequently sampled intravenous glucose tolerance test (FSIVGTT) was performed over the course of 3 h to assess SI, after which participants were given lunch and discharged from the GCRC. Participants were instructed to wear an accelerometer for the week after the inpatient visit, and a study team member contacted the participant to retrieve the accelerometer and complete the physical activity recall (PAR).

In between the annual GCRC visits, quarterly home visits were conducted approximately every 3 months. At these visits, a study team member provided the participant with an accelerometer and the 3-day PAR to be completed during the subsequent week; the study team member then retrieved the accelerometer and 3-day PAR after 7 days.

Measures

Demographics and anthropometry. Baseline pubertal Tanner stage was assessed by the licensed pediatric medical care provider. Fat mass and lean mass were measured by air displacement plethysmography (Bod Pod; Life Measurement Instruments, Concord, CA), using computerized pressure sensors to determine body volume and body density through air displacement. The BodPod provides an accurate measure of body fat and lean body mass in children without discomfort to the participant and has been validated in children against hydrostatic weighing, dual energy X-ray absorptiometry, and multicompartment models (17).

Insulin indices. A fasting blood draw was completed at 0800 h followed by the initiation of the FSIVGTT. Blood samples were collected at time points −15, −5, 2, 4, 8, 19, 22, 30, 40, 50, 70, 100, and 180 min. At time 0, glucose (25% dextrose, 0.3 g/kg body weight) was administered intravenously. Insulin (0.02 units/kg body weight, Humulin R [regular insulin for human injection; Eli Lilly, Indianapolis, IN]) was injected intravenously at 20 min (10,18,19). SI and AIRg were calculated using the minimal model from the FSIVGTT results (20) (MINMOD MILLENIUM 2002 computer program, version 5.16; Richard Bergman, Los Angeles, CA [21]). AIRg characterizes the first phase of insulin secretion after glucose administration.

Physical activity. Because device-based and self-reported measures tend to capture different aspects of physical activity (22,23), physical activity and sedentary behavior were assessed with both accelerometers and 3-day PAR measures at all five visits. The participants wore a uniaxial Actigraph GT1M accelerometer on the right iliac crest using an elastic belt for at least 10 h on 4 days. The monitor was programmed to collect data in 15-s epochs. The data then were compounded into 60-s epochs for use with the current activity cut points. The data were processed using an adaptation of the SAS code developed by the National Cancer Institute for use with National Health and Nutrition Examination Survey data (available at: http://riskfactor.cancer.gov/tools/nhanes_pam). Time spent in the activity levels was calculated by summing each minute spent above the user-defined thresholds for moderate to vigorous physical activity (MVPA) and below the user-defined threshold for sedentary activity. The cut points for moderate (4 METs) and vigorous (7 METs) activity were adjusted for age using the criteria from Freedson et al. (24). The sedentary cut

point of 100 counts was previously defined by Matthews et al. (25).

A modified 3-day PAR was used to assess self-reported physical activity and sedentary behavior (26). Participants identified different activities (from a list of 71 activities provided) to describe their daily activity in half-hour intervals from 0700 to 1200 h for 3 days (two weekdays and one weekend day). Data reduction procedures for this measure were carried out as specified by the developers of the measure (27) and have been described earlier (28). Minutes per day spent in MVPA (at an intensity of ≥4 METs) was created to complement the variable extracted from the accelerometer measure. Leisure-time sedentary behaviors were coded as half-hour blocks spent watching television/movies, playing video games/surfing the Internet, and talking on the phone. Mean minutes per day spent in MVPA and leisure-time sedentary behavior were obtained by averaging total minutes in either activity level across 3 days.

Statistical analysis. The analysis examined the influence of baseline insulin dynamics as predictors of physical activity and sedentary behavior change over 1 year in minority female youth. Separate models were run for physical activity and sedentary behavior according to measure type (accelerometer or 3-day PAR).

First, we examined the change in physical activity and sedentary behavior over the five visits. The physical activity and sedentary behavior data were collected four times per year, thereby providing an estimate of true activity levels independent of the effects of seasonality. We calculated mean time spent in activity levels for both measures. *t* Tests assessed mean differences in activity levels for each time point. Second, linear mixed models were run to determine the ability of baseline SI and AIRg to predict change in MVPA and sedentary behavior (dependent variables) for each measurement type. The selected time-invariant covariates included in these models were baseline age, ethnicity, pubertal Tanner stage, fat mass, and lean mass. Visit (time), ethnicity, and pubertal Tanner stage were included as categorical variables. The models used all available data for each participant and were repeated-measure models to account for within-subject correlations over time. Variance components were estimated using the restricted maximum likelihood method with an unstructured covariance matrix. All analyses were conducted in SAS version 9.2 (SAS Institute, Cary, NC). Because the hypothesis was one sided, α was set at 0.025.

RESULTS—Figure 1 provides a consort diagram of recruitment, exclusion, and final inclusion in the first 2 years of the TRANSITIONS study. The reasons for exclusion included not of Hispanic or African American ethnicity (defined by self-report of both parents and all four grandparents of the same ethnic group as the child in the study (19) or menstruating.

The baseline participant characteristics are presented in Table 1. The sample was approximately split between Tanner stages, and 36% were obese (i.e., >95th percentile for age- and sex-specific BMI per the Centers for Disease Control and Prevention).

Changes in MVPA and sedentary behavior over time

Overall, there were significant declines in MVPA and increases in sedentary behavior ($P \leq 0.05$). MVPA as measured by

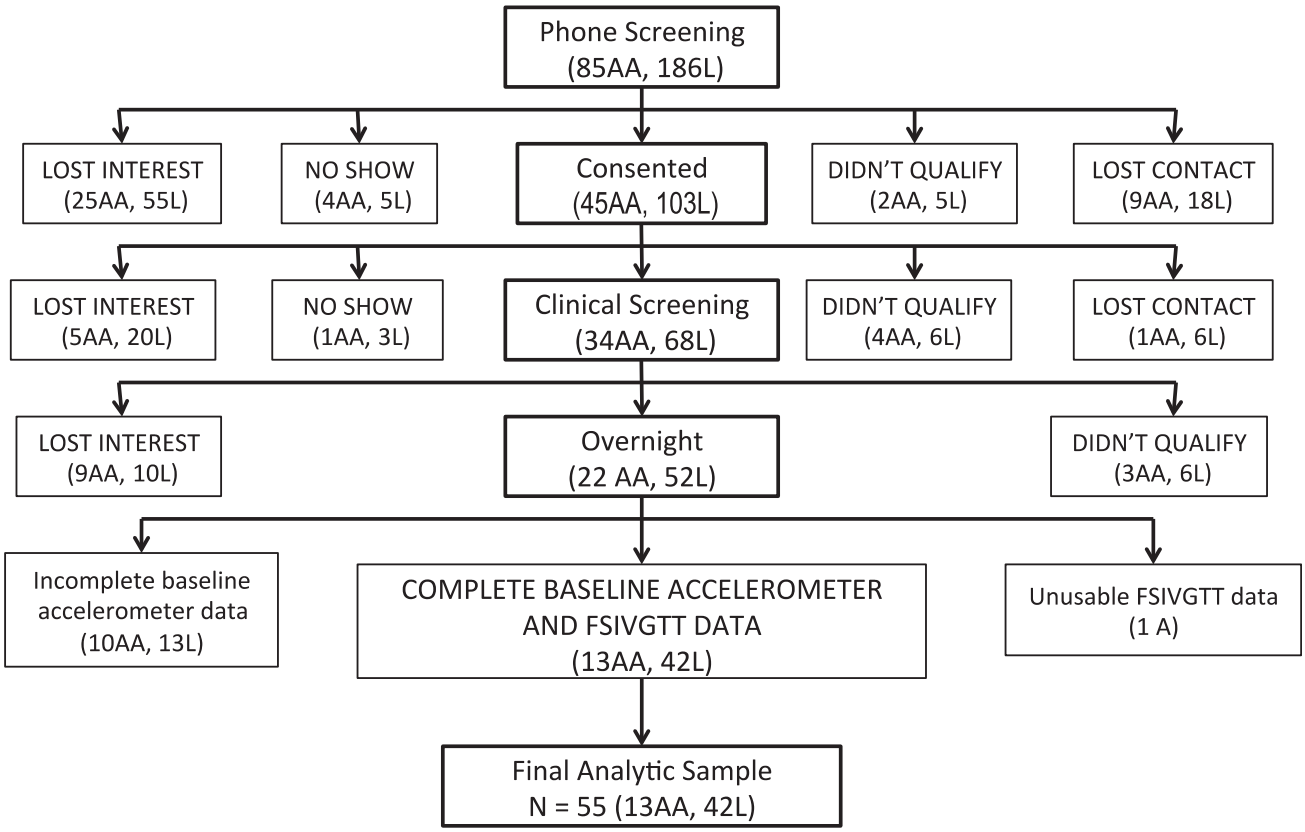

Figure 1—*Consort diagram: 1-year observational study. AA, African American; L, Latina.*

Table 1—*Baseline characteristics of the study sample* (N = 55)

Variable	
Ethnicity, *n* (%)	
Hispanic (white)	42 (76.36)
African American	13 (23.64)
Pubertal Tanner Stage	
Stage 1, *n* (%)	27 (49.09)
Stage 2, *n* (%)	28 (50.91)
Mean age, years (SD)	9.40 (0.91)
Mean SI [($\times 10^{-4}$/min^{-1}/(μIU/mL)], (SD)	3.30 (1.93)
Mean AIRg, μU/mL $\times$ min (SD)	1,255.66 (991.93)
Mean BMI percentile (SD)	80.83 (22.94)
Weight status, *n* (%)*	
Underweight/normal weight	22 (40.00)
Overweight	13 (23.64)
Obese	20 (36.36)
Mean fat mass, kg (SD)	12.56 (8.15)
Mean lean mass, kg (SD)	31.01 (6.83)
Mean MVPA, min/day (SD)	
Accelerometry	55.03 (68.71)
3-Day PAR	118.82 (72.60)
Mean sedentary behavior, min/day (SD)	
Accelerometry	418.28 (70.37)
3-Day PAR	188.45 (100.53)

*Underweight/normal weight defined as BMI <85th percentile; overweight defined as BMI between 85th and 94th percentile; obese defined as BMI ≥95th percentile (40).

accelerometry declined by 11.6 min/day over a year, and MVPA as measured by self-report declined 29 min/day over a year. Time spent in sedentary behavior as measured by accelerometry increased by >49 min over the year, and as measured by 3-day PAR it increased by >25 min over the year.

Influence of baseline SI and AIRg on MVPA

Table 2 presents the results of the linear mixed models that were used to examine the influence of baseline SI and AIRg on the change in MVPA over a year by activity level and measurement type. Baseline age ($P < 0.003$), fat mass ($P = 0.001$), and ethnicity ($P < 0.001$) predicted declines in mean minutes per day of MVPA as measured by accelerometry over the five visits. Similar to earlier studies, girls who were older, more adipose, and/or Hispanic had lower physical activity at baseline (3). However, age, fat mass, and ethnicity were not significant in the model of MVPA measured by 3-day PAR. There was a significant effect for baseline SI on MVPA when measured by accelerometry ($P = 0.007$). For every one unit of lower baseline SI, mean MVPA decreased by 3.6 min per visit across 5 visits. There was no effect of baseline SI on MVPA as measured by the 3-day PAR ($P = 0.173$). There was a significant effect for baseline AIRg on MVPA when measured by 3-day PAR ($P = 0.015$). For each one unit of higher AIRg, mean MVPA decreased by 1.2 h over the entire year. There was no effect of baseline AIRg on MVPA when measured by accelerometer ($P = 0.44$).

Influence of baseline SI and AIRg on sedentary behavior

Table 3 shows the results of the linear mixed models that were used to examine the influence of baseline SI and AIRg on the change in sedentary behavior over a year by measurement type. At baseline, girls at Tanner stage 2 spent 60 min/day more in sedentary behavior than those in Tanner stage 1. Baseline pubertal Tanner stage significantly predicted the increase in sedentary behavior over time using accelerometry ($P = 0.001$), as did ethnicity ($P = 0.008$) (Table 2). Using 3-day PAR, being at a higher Tanner stage ($P = 0.05$) and having a lower baseline lean mass ($P = 0.02$) predicted an increase in mean minutes per day spent in sedentary behavior. Baseline SI predicted the decline in MVPA as measured by both accelerometry ($P = 0.04$) and 3-day PAR ($P = 0.006$). Using accelerometry, each one-unit decrease in SI predicted an 8.5-min increase in sedentary behavior across all visits. Using 3-day PAR, each one-unit decrease in SI predicted a 17.8-min increase in sedentary behavior across all visits. AIRg did not predict changes in sedentary behavior.

CONCLUSIONS—To our knowledge, this is the first study to show that insulin resistance predicts the decline in physical activity and increase in sedentary behavior experienced by peripubertal minority females over a year. Each unit lower in baseline SI was associated with an extra 3.6-min mean decrease in physical activity per day as measured by accelerometry over a year, while each one unit lower in baseline SI was associated with an extra mean 8.5-min increase in sedentary behavior per day over a year, regardless of adiposity, age, pubertal stage, or ethnicity. Each unit lower in SI at baseline predicted an extra 17.8-min increase in sedentary behavior as measured by self-report. While interventions to increase physical activity in youth have shown some promise, none have been able to increase activity to recommended levels. This may be because the association between pubertal declines in SI and activity levels has been ignored in intervention approaches.

Changes in insulin resistance might affect physical activity through alterations in circulating levels of multiple neuropeptides, including leptin, corticotropin-releasing hormone, neuropeptide Y, agouti-related protein, and ghrelin (28). These neuropeptides can cross the blood-brain barrier and could potentially affect physical activity through direct effects on the central and/or autonomic nervous system. For instance, leptin, secreted by adipocytes, binds to receptor sites in the central nervous system and influences satiety signals, regulation of physical activity, and energy expenditure (29). Girls have higher leptin levels than boys, and leptin levels rise throughout puberty in girls, independent of BMI (30). Importantly, orexin, a neurotransmitter that regulates arousal, wakefulness, and appetite, has recently been implicated in regulation of glucose metabolism, leptin sensitivity, and spontaneous physical activity (31). In light of our findings, these possible mechanisms deserve further study.

Higher baseline AIRg predicted the decline in physical activity as measured by self-report. This may be because insulin binds to receptors in multiple brain

Table 2—*Longitudinal mixed model predicting change in MVPA by measurement type over five visits* (N = 55)

	MVPA							
	Accelerometer				3-Day PAR			
Variable	β	SE*	*t*	*P*‡	β	SE*	*t*	*P*‡
Intercept	66.61	24.36	2.75	—	77.65	84.05	0.92	—
Age (years)	−6.60	2.32	−2.85	0.003	0.34	7.59	0.05	0.482
Tanner (vs. 2)	6.73	4.52	1.49	0.069	−11.93	15.31	−0.78	0.218
Ethnicity (vs. African American)	−20.86	4.79	−4.36	<0.001	−8.55	15.04	−0.57	0.285
Fat mass (kg)	−1.09	0.33	−3.28	0.001	0.57	1.35	0.42	0.336
Lean mass (kg)	1.38	0.25	5.54	<0.001	0.49	1.21	0.41	0.343
SI [($\times 10^{-4}$/min^{-1}/(μIU/mL)]	3.61	1.45	2.49	0.007	4.54	4.80	0.95	0.173
AIRg (μU/mL × min)	−0.001	0.00	−0.16	0.435	−0.02	0.01	−2.19	0.015

*All models have a random intercept with visit as a repeated effect; regression coefficients are not standardized. ‡*P* values are divided by 2 to show accurate statistical significance by the one-sided hypothesis. *df* = 52

centers involved in energy metabolism, promoting satiation and decreased food intake. Insulin may directly affect function of serotonergic neurons (32), and therefore elevated AIRg may be related to reduced serotonergic responsivity and physical inactivity (33). AIRg reflects β-cell functionality. Declines in SI may be initially compensated for by an increase in AIRg, which eventually can contribute to β-cell exhaustion. Furthermore, AIRg can serve as an indicator of risk for future type 2 diabetes, independent of insulin action, even when glucose tolerance and fasting plasma glucose levels are otherwise normal (34). Taken together, our data suggest that poorer insulin indices in early puberty predict the decline of physical activity and increase in sedentary behavior over time regardless of how physical activity is measured.

Lower baseline SI predicted increased time spent in sedentary behavior regardless of measurement type. Time spent in sedentary behavior as measured by accelerometry increased by ≥49 min (12%) over the year, and as measured by self-report it increased by ≥25 min (13%) over the year. Higher Tanner stage at baseline was related to greater increase in sedentary behavior over time regardless of measurement modality. Fat mass was not related to time spent in sedentary behavior, nor was age. Prolonged sedentary behavior has been identified as health compromising, with specific biological harmful consequences (35). In a sample of 105 Hispanic and African American youth (mean age 13 years), time spent in sedentary behavior was related to higher odds of having metabolic syndrome, independent of MVPA (27). The deleterious effects of prolonged sedentary behaviors on metabolic health are well documented. However, little is known about the psychosocial, environmental, or biological determinants of sedentary behavior. Our findings suggest that possible biological determinants for increases in sedentary behavior during puberty deserve further study.

Table 3—*Longitudinal mixed model predicting change in sedentary behavior by measurement type over five visits* (N = 55)

	Sedentary behavior							
	Accelerometer				3-Day PAR			
Variable	β	SE*	*t*	*P*‡	β	SE*	*t*	*P*‡
Intercept	506.05	80.56	6.28	—	426.47	118.70	3.59	—
Age (years)	1.30	7.27	0.18	0.429	−1.59	10.63	−0.15	0.441
Tanner (vs. 2)	−59.37	14.36	−4.14	<0.001	−34.08	20.78	−1.64	0.052
Ethnicity (vs. African American)	36.48	14.89	2.45	0.008	17.46	20.66	0.85	0.200
Fat mass (kg)	0.41	1.24	0.33	0.372	0.72	1.88	0.38	0.351
Lean mass (kg)	−0.43	1.11	−0.39	0.349	−3.28	1.65	−1.99	0.024
SI [($\times 10^{-4}$/min^{-1}/(μIU/mL)]	−8.49	4.80	−1.77	0.039	−17.77	6.99	−2.54	0.006
AIRg (μU/mL × min)	−0.01	0.01	−1.18	0.119	−0.02	0.01	−1.34	0.090

*All models have a random intercept with visit as a repeated effect. ‡*P* values are divided by 2 to show accurate statistical significance by the one-sided hypothesis.

It is important to note that estimates of self-reported MVPA and sedentary behavior were higher than the accelerometer estimates. Overestimation of activity by self-report measures compared with device-based measures of activity has been noted repeatedly in the literature (36). A potential explanation for these differences is that the modalities are measuring different aspects of activity. The self-report measure is capturing specific activities or perceptions of specific activities, whereas the accelerometer is capturing body movement. Therefore, both device-based and self-report measures of activity provide useful data for the study of physical activity (27). Few studies have included multiple activity measures and reported on their respective relationships with biological outcomes. This is the first study to show that, although estimates of minutes of MVPA per day vary broadly depending upon measurement modality, there is agreement across accelerometry and 3-day PAR self-report measures on the relative decline in physical activity over time. MVPA as measured by accelerometry declined by 11.6 min/day, representing a 25% decline over 1 year. MVPA as measured by self-report declined 29 min/day over the year, which also represents a 25% decline. According to baseline accelerometry measures, at the start of the study participants already were averaging about 14 min below the recommended 60 min/day of MVPA (37). The mean age at study entry was 9.4 years. At the rate of an 11-min decline per year in physical activity, and assuming a similar continuing decline, these girls risk becoming completely sedentary by 13 years of age.

Although these results are novel, it is important to acknowledge several limitations. This study focused on the biological mechanisms that might drive the pubertal decline in physical activity. However, several psychosocial factors not reported in this article have been related to physical activity in peripubertal females. These may influence the development of physical activity behavior during puberty or interact with biological mechanisms to influence

physical activity. Another weakness is the small sample size, which allowed for repeated-measures models but precluded modeling a growth curve of interactions. The small sample of African American girls further precluded making ethnic comparisons. Power calculations for this study called for recruiting 100 peripubertal females (50 Hispanic and 50 African American). However, the difficulty of recruiting young minority participants for an intensive metabolic study, coupled with constraints of study budget and timeline, affected our final recruitment, as documented by Shahabi et al. (15). Although this study was underpowered, we were able to detect several important associations. A larger sample might have affected any null findings. Finally, this is an observational study, and while a temporal relationship was demonstrated between baseline measures of insulin resistance and subsequent change in physical activity behavior, this relationship may not be causal. Therefore, our findings must be interpreted with caution.

The results of this study suggest that interventions to improve insulin resistance in childhood should be tested to examine the possibility that they could prevent or ameliorate the decline in physical activity. Lowering sugar intake, particularly consumption of sugar-sweetened beverages, is independently related to improvements in SI independent of physical activity or adiposity (38). Thus, interventions to decrease sugar intake could improve SI, paving the way for increases in physical activity without depending on obtaining decreases in adiposity first. However, on the basis of our models, reduced body fat would also lead to increased physical activity, or at least a less steep decline in physical activity during puberty. Because sugar consumption is also tightly related to adiposity (39), decreasing added sugar and consumption of sugar-sweetened beverages could kill two birds with one stone. These findings are particularly important in the face of the epidemic of inactivity, obesity, and poor metabolic health facing minority females today.

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D.S.-M. conceptualized and designed the study and drafted the article. B.R.B., Y.-W.H., and A.D.M. acquired data and wrote the article. B.R.B. conducted the data analyses and analyzed the accelerometry data. Y.-W.H. managed the study database and analyzed the 3-day PAR data. A.D.M. assisted with recruitment. C.-P.C. conceptualized the study and analyzed the data. S.N.-R. managed and collected data and wrote the article. M.J.W. served as clinical principle investigator, oversaw all hospital visits, and wrote the article. M.I.G. critically revised the article, oversaw some analyses, and provided important intellectual content. D.S.-M. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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