Objectively Measured Physical Activity, Sedentary Behavior, and Genetic Predisposition to Obesity in U.S. Hispanics/Latinos: Results From the Hispanic Community Health Study/Study of Latinos (HCHS/SOL)

Jee-Young Moon,[1] Tao Wang,[1] Tamar Sofer,[2] Kari E. North,[3] Carmen R. Isasi,[1] Jianwen Cai,[3] Marc D. Gellman,[4] Ashley E. Moncrieft,[4] Daniela Sotres-Alvarez,[3] Maria Argos,[5] Robert C. Kaplan,[1] and Qibin Qi[1]

Diabetes 2017;66:3001–3012 | https://doi.org/10.2337/db17-0573

Studies using self-reported data suggest a gene–physical activity interaction on obesity, yet the influence of sedentary behavior, distinct from a lack of physical activity, on genetic associations with obesity remains unclear. We analyzed interactions of accelerometer-measured moderate to vigorous physical activity (MVPA) and time spent sedentary with genetic variants on obesity among 9,645 U.S. Hispanics/Latinos. An overall genetic risk score (GRS), a central nervous system (CNS)–related GRS, and a non-CNS-related GRS were calculated based on 97 BMI-associated single nucleotide polymorphisms (SNPs). Genetic association with BMI was stronger in individuals with lower MVPA (first tertile) versus higher MVPA (third tertile) (β = 0.78 kg/m^2 [SE, 0.10 kg/m^2] vs. 0.39 kg/m^2 [0.09 kg/m^2] per SD increment of GRS; $P_{interaction}$ = 0.005), and in those with more time spent sedentary (third tertile) versus less time spent sedentary (first tertile) (β = 0.73 kg/m^2 [SE, 0.10 kg/m^2] vs. 0.44 kg/m^2 [0.09 kg/m^2]; $P_{interaction}$ = 0.006). Similar significant interaction patterns were observed for obesity risk, body fat mass, fat percentage, fat mass index, and waist circumference, but not for fat-free mass. The CNS-related GRS, but not the non-CNS-related GRS, showed significant interactions with MVPA and sedentary behavior, with effects on BMI and other adiposity traits. Our data suggest that both increasing physical activity and reducing sedentary behavior may attenuate genetic associations with obesity, although the independence of these interaction effects needs to be investigated further.

Obesity and related comorbid conditions have become serious threats to public health throughout the world. It is believed that obesity is caused by complex interplay between genetic and environmental factors. Emerging evidence supports a gene–physical activity interaction on obesity (1–3). A previous study reported that physical activity attenuated the effect of a genetic risk score (GRS), calculated based on 12 BMI-associated single nucleotide polymorphisms (SNPs), on BMI and obesity in European populations (1). This gene–physical activity interaction on obesity was confirmed by a follow-up large-scale meta-analysis, although the interaction effect size was relatively smaller (3). In addition, our prior work also suggested that sedentary behavior, indicated by watching television for a prolonged period, may accentuate genetic predisposition to elevated adiposity (estimated by the GRS based on 32 BMI-associated SNPs) in U.S. non-Hispanic white men and women (4). Hispanics and Latinos are the largest and fastest growing minority group in the U.S. (5) and have a greater prevalence of obesity than non-Hispanic whites (6). However, data on gene-environment interactions in relation to obesity are sparse among U.S. Hispanics and Latinos.

[1]Department of Epidemiology and Population Health, Albert Einstein College of Medicine, Bronx, NY
[2]Department of Biostatistics, University of Washington, Seattle, WA
[3]Collaborative Studies Coordinating Center, Department of Biostatistics, University of North Carolina, Chapel Hill, NC
[4]Department of Psychology, University of Miami, Miami, FL
[5]Department of Epidemiology and Biostatistics, University of Illinois, Chicago, IL

Corresponding author: Qibin Qi, qibin.qi@einstein.yu.edu.

Received 15 May 2017 and accepted 27 September 2017.

This article contains Supplementary Data online at http://diabetes.diabetesjournals.org/lookup/suppl/doi:10.2337/db17-0573/-/DC1.

T.S. is currently affiliated with the Division of Sleep and Circadian Disorders, Brigham and Women's Hospital, Boston, MA.

A major challenge in studying gene-environment interaction is the difficulty of accurately measuring environmental exposures. Previous studies assessed physical activity and sedentary behavior using self-reported questionnaires in which inevitable measurement errors reduce statistical power and necessitate studies with large sample sizes (2). In this study, we used data from the Hispanic Community Health Study/Study of Latinos (HCHS/SOL), which has accelerometer-based measurements of physical activity and sedentary time (4), to examine the interactions of physical activity and sedentary behavior with genetic variants in relation to obesity. In addition to BMI, waist circumference and several body composition measures, including body fat mass, body fat percentage, and fat mass index, were also analyzed as indices of obesity.

To date, the largest genome-wide association study of BMI by the Genetic Investigation of Anthropometric Traits (GIANT) consortium has confirmed and identified a total of 97 BMI loci (7). In this study, we calculated an overall GRS based on these 97 BMI-associated SNPs (7) to examine whether physical activity and sedentary behavior may modify genetic associations with BMI, obesity risk, waist circumference, and body composition measures in U.S. Hispanics and Latinos. Further, we created two sets of GRSs from subsets of BMI-related SNPs based on the involvement in the central nervous system (CNS). These two GRSs (CNS-related GRS and non-CNS-related GRS) were in turn examined for their interactions with physical activity and sedentary behavior in relation to obesity.

RESEARCH DESIGN AND METHODS

Study Population

The HCHS/SOL is a prospective cohort study of 16,415 Hispanic/Latino adults aged 18–74 years at baseline (2008–2011) at four U.S. field centers (Bronx, NY; Chicago, IL; Miami, FL; San Diego, CA) (8,9). All participants were comprehensively examined at baseline, obtaining data related to demographics, socioeconomic status, health status, behaviors, and clinical assessment with blood draw. The current study included 9,645 participants with accelerometer measurements (which were obtained for a total of 12,631 participants), genetic data (which were obtained for a total of 12,784 participants), and a BMI $\geq$18.5 but $<$50 kg/m^2. The study was approved by the institutional review boards at the data coordinating center and each field center, and all participants gave written consent for study participation and additional consent for genetic study.

Assessment of Physical Activity and Sedentary Behavior

Detailed information on objective measurement of physical activity and sedentary behavior in the HCHS/SOL has been described elsewhere (10). Briefly, at the HCHS/SOL baseline exam, participants were asked to wear an omnidirectional accelerometer (Actical B-1 version, model 198-0200-03; Respironics Co. Inc., Bend, Oregon) above the iliac crest for 7 days, except when swimming, showering, or sleeping. The accelerometer was programmed to measure omnidirectional accelerations in counts and steps in 1-min intervals. Nonwear time was determined by at least 90 consecutive minutes of zero counts, allowing for 1 or 2 min of nonzero counts in a 30-min window, using the Choi algorithm (11). An adherent day was defined as at least 10 h of wear time, and at least 3 adherent days were required for inclusion in this analysis.

Accelerometer counts were used to classify sedentary behavior ($<$100 counts/min) and moderate to vigorous physical activity (MVPA; $\geq$1,535 counts/min) (12,13). Because of a high correlation between sedentary time and wear time (r^2 = 0.83), we standardized sedentary time to 16 h of wear time per day (the approximate average of both daily wear time and awake time in our study), using the residual from regressing sedentary time on wear time (14,15). After standardization, sedentary time was not correlated with wear time (r^2 = 0.08). Total physical activity level was defined by average counts per minute. For example, spending 40 min walking at a speed of 5 km/h corresponds to an approximately 98,720 total count increase (16), which results in an increment of a mean of 100 counts/min during 16 h of standardized wear time.

Assessment of BMI, Waist Circumference, Body Composition, and Covariates

Standing height and waist circumference at the top of the iliac crest were measured to the nearest centimeter; body weight was measured to the nearest 0.1 kg. BMI was calculated as weight in kilograms divided by height in meters squared. Fat mass and fat-free mass were estimated from bioimpedance using a Total Body Composition Analyzer (model TBF-300A; Tanita Corporation, Arlington Heights, IL). Fat percentage was calculated as 100 $\times$Fat mass $\div$ (Fat mass + Fat free mass); the fat mass index (kilograms per meters squared) was calculated as fat mass in kilograms divided by height in meters squared. The Tanita device yields a high correlation with fat percentage measured by DXA (r = 0.96; $P < 0.001$) and a low corresponding SE of the estimate (2.74%) (validation data were provided by Tanita Corporation; http://www.tanita.com/es/supporting-research/). Our recent work in this U.S. Hispanics study showed a high correlation between the estimated fat percentages from Tanita and those assessed with the ^{18}O dilution method (r = 0.84 in women; r = 0.81 in men) (17). The Alternative Healthy Eating Index (AHEI) 2010 (18) was calculated based on two 24-h dietary recalls using the National Cancer Institute's methodology (19). The AHEI 2010 uses values from 0 to 110, with higher scores representing healthy eating habits and lower scores representing unhealthy eating habits. Self-reported perspectives on overall health were collected in a questionnaire through a five-point scale: 0, poor; 1, fair; 2, good; 3, very good; 4, excellent.

Genotyping and Calculating GRS

We selected 97 BMI-associated SNPs that reached genome-wide significance levels ($P < 5 \times 10^{-8}$) in the GIANT BMI genome-wide association study (7). SNP data were derived from the HCHS/SOL Custom 15041502 B3 SNP array (Illumina Omni 2.5M array plus ~150,000 custom SNPs); this

was followed by imputation based on the 1000 Genomes Project phase 3 reference panel, which includes Hispanic/Latino populations (i.e., Mexicans, Colombians, and Puerto Ricans). An iterative procedure to simultaneously estimate principal components reflecting population structure and kinship coefficients measuring familial relatedness has been described elsewhere (20). Genetic analysis groups (Hispanic/Latino background groups: Cuban, Dominican, Puerto Rican, Mexican, Central American, and South American) were constructed based on a combination of self-identified Hispanic/Latino background and genetic similarity (20).

In the current analysis, 66 SNPs were genotyped and 31 SNPs were imputed with a high imputation quality (IMPUTE2 info >0.9). An overall GRS was calculated by summing the number of BMI-increasing alleles among these 97 SNPs (7). According to possible biological categories of these BMI loci (7), we classified the SNPs into two subgroups to create two GRSs: CNS-related GRS and non-CNS-related GRS. Information on these 97 SNPs is shown in Supplementary Table 1.

Statistical Analyses

Descriptive characteristics of the study population across tertiles of total physical activity, MVPA, and sedentary time were computed as means and SEs for continuous variables, tested by a survey linear regression, and as percentages and SEs for categorical variables, tested by a survey logistic regression; both account for the complex study design. We examined the main effects of total physical activity, MVPA, sedentary behavior, and overall GRS on BMI and other obesity measures using linear mixed models, and we examined obesity risk using mixed effects logistic models (20). We also tested whether the overall GRS is associated with total physical activity, MVPA, or sedentary behavior using linear mixed models, which may cause reverse causation (21). To test the interactions of the overall GRS with total physical activity, MVPA, or sedentary behavior and their effects on BMI and other obesity measures, we included the respective interaction term (e.g., GRS $\times$ MVPA) in the models (20). We also examined the effects of the GRS on BMI and other obesity measures according to tertiles of total physical activity, MVPA, or sedentary behavior using linear mixed effects models, and the effects of the GRS on obesity (BMI $\geq$30 vs. $<$30 kg/m^2) using mixed effects logistic models. Further, we simultaneously tested the GRS $\times$ MVPA interaction and GRS $\times$ sedentary behavior interaction by including interaction terms in the same model. All mixed effects models were adjusted for sampling weight, age, field center, sex, education, annual family income, employment, smoking, alcohol use, total energy intake, AHEI, and five principal components for population structure as fixed effects, and genetic relatedness, household, and sampling block as random effects. In addition, we estimated predicted BMI levels according to the joint groups of tertiles of the overall GRS with tertiles of total physical activity, MVPA, or sedentary behavior in similar multivariable-adjusted linear mixed models and compared those with predictions based on counterfactual BMI levels without interaction effects. Interactions between the two GRS subgroups (CNS-related GRS and non-CNS-related GRS) and MVPA or sedentary behavior were examined using linear mixed models. All statistical tests were two-sided, and analyses were performed using R (version 3.3.2; R Foundation) (22).

In addition, we implemented approaches from Tyrrell et al. (23) to conduct negative control simulations. One approach was random reassignment of participants into groups of low or high total physical activity, MVPA, or sedentary behavior, restricting these to have BMI distributions similar to those of the original groupings. Each participant was randomly assigned to the low or high group; probability was predicted from a logistic regression of the low or high group on BMI using the original data. Another approach was to use dummy variables, which were created to be associated with BMI in a similar way to the real environmental variables (total physical activity, MVPA, or sedentary behavior) but were only minimally associated with the real variable itself. The dummy variable was created as the sum of the predicted environmental value and the permuted residual from the model of environmental variable with the predictors of age, sex, BMI, and overall GRS. Then, interactions of the overall GRS with these created category variables (low or high group) and dummy continuous variables and the effect on BMI were examined in linear mixed models, adjusting for sampling weight, age, sex, five principal components, and field center. These simulation analyses were repeated 10,000 times.

RESULTS

Characteristics of Individuals in This Study

Table 1 summarizes the characteristics of individuals in this study according to tertiles of total physical activity, MVPA, and sedentary time. Total physical activity was positively correlated with MVPA ($r = 0.89$; $P < 0.001$) and inversely correlated with sedentary time ($r = -0.72$; $P < 0.001$). MVPA and sedentary time showed a moderately inverse correlation ($r = -0.47$; $P < 0.001$). Individuals with more total physical activity, more MVPA, or less sedentary time were more likely to be younger, male, employed, and a current smoker and alcohol drinker; to have higher education levels, annual family income, and energy intake; and to have a lower BMI. Individuals with less sedentary time tended to eat more healthful foods, but no significant correlation was found between the AHEI and MVPA.

Main Effects of Physical Activity, Sedentary Behavior, and GRS on Obesity

Total physical activity, MVPA, and sedentary behavior were significantly associated with BMI and obesity. BMI was 0.54 kg/m^2 (SE, 0.05 kg/m^2) lower ($P = 3.1 \times 10^{-29}$) with each 100 counts/min increment in total physical activity (corresponding to approximately 40min walking at speed of 5 km/h), 0.27 kg/m^2 (SE, 0.02 kg/m^2) lower ($P = 1.2 \times 10^{-34}$) with each 10-min increment in MVPA, and 0.31 kg/m^2 (SE, 0.03 kg/m^2) higher ($P = 2.3 \times 10^{-19}$) with each 1-h increment of sedentary time. Similarly, these increments in the accelerometer-derived measures were

Table 1—Characteristics of Hispanics/Latinos with accelerometer-measured physical activity and sedentary behavior in the HCHS/SOL

	Total physical activity (average counts/min)				MVPA (min/day)				Sedentary time (h/day)			
	T1	T2	T3	*P* value	T1	T2	T3	*P* value	T1	T2	T3	*P* value
Median (range)	77 (4–108)	139 (108–177)	242 (177–1,526)		3.3 (0–8.2)	14.5 (8.2–23.4)	38.4 (23.4–377)		10.3 (0.8–11.4)	12.1 (11.4–12.7)	13.5 (12.7–16)	
Individuals, *n*	3,211	3,231	3,203		3,238	3,224	3,183		3,222	3,186	3,237	
Total physical activity, counts/min	75 ± 1	141 ± 1	286 ± 4	—	90 ± 1	145 ± 1	271 ± 4	<0.001	271 ± 5	158 ± 2	94 ± 1	<0.001
MVPA, min/day	6.0 ± 0.2	16.9 ± 0.3	45.2 ± 1.0	<0.001	3.7 ± 0.1	15.2 ± 0.1	48.8 ± 0.9	—	37.3 ± 1.2	21.1 ± 0.6	13.5 ± 0.5	<0.001
Sedentary time, hours/day	13.4 ± 0.02	12.01 ± 0.02	10.5 ± 0.04	<0.001	12.7 ± 0.04	12 ± 0.04	11.1 ± 0.05	<0.001	10 ± 0.04	12.1 ± 0.01	13.6 ± 0.02	—
Age, years	48.1 ± 0.5	40.4 ± 0.4	37.5 ± 0.4	<0.001	48.3 ± 0.5	40.2 ± 0.4	37.4 ± 0.4	<0.001	39.2 ± 0.4	41.1 ± 0.4	44.7 ± 0.5	<0.001
Field center, %				<0.001				<0.001				<0.001
Bronx	30 (2)	27 (2)	27 (2)		17 (2)	24 (2)	41 (2)		20 (2)	25 (2)	39 (2)	
Chicago	13 (1)	14 (1)	17 (1)		12 (1)	17.2 (1)	15 (1)		20 (1)	14 (1)	11 (1)	
Miami	40 (3)	33 (3)	26 (2)		49 (3)	31 (3)	21 (2)		30 (2)	35 (3)	33 (3)	
San Diego	17 (2)	25 (2)	30 (2)		22 (2)	28 (2)	24 (2)		31 (2)	26 (2)	17 (2)	
BMI, kg/m^2	30.4 ± 0.2	29.2 ± 0.2	28.4 ± 0.1	<0.001	30.3 ± 0.2	29.5 ± 0.2	28.2 ± 0.1	<0.001	28.8 ± 0.1	29.2 ± 0.2	29.7 ± 0.2	<0.001
Fat mass, kg	29.6 ± 0.4	26.8 ± 0.3	23.9 ± 0.3	<0.001	29.5 ± 0.3	27.3 ± 0.5	23.5 ± 0.3	<0.001	31.3 ± 0.3	26.8 ± 0.3	27.9 ± 0.4	<0.001
Fat percentage, %	36.1 ± 0.3	33.2 ± 0.3	29.8 ± 0.2	<0.001	36.3 ± 0.3	33.1 ± 0.3	29.6 ± 0.2	<0.001	31.3 ± 0.3	33.1 ± 0.3	34.0 ± 0.3	<0.001
Fat mass index, kg/m^2	11.3 ± 0.1	10.1 ± 0.1	8.8 ± 0.1	<0.001	11.3 ± 0.1	10.2 ± 0.2	8.7 ± 0.1	<0.001	9.4 ± 0.1	10.1 ± 0.1	10.5 ± 0.1	<0.001
Fat-free mass, kg	50.2 ± 0.3	51.3 ± 0.3	54.2 ± 0.3	<0.001	49.8 ± 0.3	52.1 ± 0.3	53.8 ± 0.3	<0.001	53.0 ± 0.3	51.6 ± 0.3	51.5 ± 0.3	<0.001
Fat-free mass index, kg/m^2	19.0 ± 0.1	19.1 ± 0.1	19.6 ± 0.1	<0.001	18.9 ± 0.1	19.3 ± 0.1	19.5 ± 0.1	<0.001	19.5 ± 0.1	19.5 ± 0.1	19.5 ± 0.1	<0.001
Waist circumference, cm	100 ± 0.4	97 ± 0.4	95 ± 0.3	<0.001	100 ± 0.4	98 ± 0.5	95 ± 0.4	<0.001	96 ± 0.3	97 ± 0.4	98 ± 0.4	<0.001
Women, %	63.5 (1.3)	54.9 (1.4)	36.0 (1.2)	<0.001	65.6 (1.3)	51.1 (1.4)	37.4 (1.2)	<0.001	43.3 (1.3)	53.6 (1.3)	54.9 (1.3)	<0.001
Genetically identified Hispanic/Latino group, %				<0.001				<0.001				<0.001
Central American	7 (1)	8 (1)	9 (1)		8 (1)	8 (1)	9 (1)		10 (1)	7 (1)	8 (2)	
Cuban	33 (3)	24 (2)	18 (2)		39 (3)	22 (2)	15 (1)		21 (2)	27 (2)	26.9 (2)	
Dominican	13 (2)	11 (1)	8 (1)		8 (2)	9 (1)	13 (1)		6 (1)	8 (1)	17 (3)	
Mexican	24 (2)	37 (2)	43 (2)		28 (2)	40 (2)	37 (2)		46 (2)	36 (2)	23 (2)	
Puerto Rican	18 (1)	14 (1)	16 (1)		12 (1)	15 (1)	20 (1)		13 (1)	16 (1)	19 (1)	
South American	6 (1)	6 (1)	6 (1)		5 (1)	6 (1)	7 (1)		5 (1)	7 (1)	6 (1)	
Education, %				<0.001				<0.001				<0.001
<High school	36 (2)	30 (1)	29 (1)		34 (1)	30 (1)	31 (1)		32 (1)	29 (1)	34 (1)	
High school	26 (2)	28 (1)	31 (1)		26 (2)	27 (1)	31 (1)		31 (1)	28 (1)	26 (2)	
College degree	39 (2)	42 (1)	40 (1)		40 (2)	43 (2)	39 (2)		38 (2)	43 (1)	40 (2)	
Annual family income ($), %				<0.001				<0.001				<0.001
<20,000	53 (2)	44 (2)	41 (2)		51 (2)	43 (2)	44 (2)		41 (2)	45 (2)	51 (2)	
20,000–50,000	36 (2)	42 (1)	44 (2)		38 (2)	43 (1)	42 (2)		47 (2)	39 (1)	37 (2)	
>50,000	11 (1)	14 (1)	15 (2)		11 (1)	15 (1)	14 (1)		12 (1)	16 (1)	13 (1)	

Continued on p. 3005

Table 1—Continued

	Total physical activity (average counts/min)				MVPA (min/day)				Sedentary time (h/day)			
	T1	T2	T3	*P* value	T1	T2	T3	*P* value	T1	T2	T3	*P* value
Employment, %				<0.001				<0.001				<0.001
Retired and not currently employed	17 (1)	6 (1)	4 (0.4)		15 (1)	7 (1)	5 (1)		3 (0.4)	7 (1)	16 (1)	
Not retired and not currently employed	50 (2)	41 (1)	32 (1)		47 (2)	38 (1)	36 (1)		27 (1)	45 (1)	49 (2)	
Employed part-time (≤35 h/week)	12 (1)	17 (1)	21 (1)		13 (1)	18 (1)	20 (1)		22 (1)	17 (1)	13 (1)	
Employed full-time (>35 h/week)	21 (1)	36 (1)	44 (1)		26 (1)	37 (1)	39 (1)		49 (1)	31 (1)	23 (1)	
Current smoker, %	19 (1)	20 (1)	23 (1)	<0.001	19 (1)	21 (1)	22 (1)	<0.001	23 (1)	22 (1)	18 (1)	<0.001
Alcohol consumption, servings/day	0.22 ± 0.01	0.29 ± 0.01	0.34 ± 0.01	<0.001	0.24 ± 0.02	0.29 ± 0.01	0.32 ± 0.01	<0.001	0.33 ± 0.01	0.28 ± 0.01	0.25 ± 0.02	<0.001
Alcohol use, %				<0.001				<0.001				<0.001
No current use	56 (2)	49 (1)	41 (1)		57 (2)	46 (2)	43 (1)		44 (1)	48 (1)	52 (2)	
Low use	39 (2)	46 (1)	52 (1)		38 (1)	48 (2)	51 (1)		49 (2)	46 (1)	43 (2)	
High use*	4 (1)	6 (1)	7 (1)		5 (1)	5 (1)	6 (1)		7 (1)	6 (1)	5 (1)	
Total energy intake, kcal/day	1,757 ± 21	1,904 ± 21	2,095 ± 22	<0.001	1,816 ± 20	1,934 ± 23	2,022 ± 24	<0.001	2,076 ± 22	1,913 ± 21	1,800 ± 23	<0.001
2010 AHEI (range, 0–110)	47.3 ± 0.2	47.3 ± 0.2	47.6 ± 0.2	0.289	47.4 ± 0.2	47.5 ± 0.3	47.3 ± 0.2	0.894	47.9 ± 0.2	47.2 ± 0.2	47.2 ± 0.2	0.007

Data are mean ± SE for continuous variables and percentage (SE) for categorical variables, accounting for the complex study design of the HCHS/SOL. T, tertile. *High use equates to ≥7 drinks/week for women and ≥14 drinks/week for men.

associated with obesity (BMI ≥30 vs. <30 kg/m^2), with odds ratios of 0.84 (95% CI, 0.81–0.87; $P = 3.4 \times 10^{-17}$) for total physical activity, 0.91 (95% CI, 0.90–0.93; $P = 1.0 \times 10^{-19}$) for MVPA, and 1.10 (95% CI, 1.07–1.13; $P = 1.4 \times 10^{-11}$) for sedentary time. The overall GRS was significantly associated with BMI (β = 0.65 kg/m^2 [SE, 0.05 kg/m^2] per SD [an approximately six-allele increase]; $P = 1.1 \times 10^{-39}$) and obesity (odds ratio, 1.23 [95% CI, 1.18–1.29]; $P = 3.3 \times 10^{-23}$). The overall GRS showed relatively stronger associations with waist circumference and body fat measures than with fat-free mass (Supplementary Table 2). In addition, no significant associations were found for the overall GRS with total physical activity, MVPA, or sedentary behavior ($P > 0.70$ for all).

Interactions of GRS With Physical Activity and Sedentary Behavior on Obesity

As shown in Table 2, we observed a significant interaction between the overall GRS and total physical activity affecting BMI ($\beta_{interaction} = -0.12$ kg/m^2 [SE, 0.04 kg/m^2] per 100 counts/min × 1 SD of GRS; $P = 0.005$). Genetic effect sizes, expressed here as β coefficients (SEs), on BMI for each 1-SD increment of GRS were 0.82 kg/m^2 (0.10 kg/m^2), 0.72 kg/m^2 (0.10 kg/m^2), and 0.43 kg/m^2 (0.09 kg/m^2) across tertiles of total physical activity. A similar pattern of interaction was observed between GRS and MVPA, affecting BMI ($\beta_{interaction} = -0.06$ kg/m^2 [0.02 kg/m^2] per 10-min increment of MVPA × 1-SD increment of GRS; $P = 0.005$). Conversely, a significant positive interaction occurred between the GRS and sedentary time, with an effect on BMI ($\beta_{interaction} = 0.09$ kg/m^2 [0.03 kg/m^2] per 1-h increment of sedentary time × 1-SD increment of GRS; $P = 0.006$). Genetic effects (β coefficients [SEs]) on BMI across tertiles of sedentary time were 0.44 kg/m^2 (0.09 kg/m^2), 0.81 kg/m^2 (0.10 kg/m^2), and 0.73 kg/m^2 (0.10 kg/m^2) for a 1-SD increment of GRS.

Similar patterns of significant interactions were observed for waist circumference, fat mass, fat mass index, and fat percentage, contrary to no significant interactions for fat-free mass (Table 2). We then simultaneously examined interactions of GRS with MVPA and sedentary behavior and their effects on BMI in one model and found that both interactions became nonsignificant (P for GRS × MVPA interaction = 0.11; P for GRS × sedentary behavior interaction = 0.10), although patterns of attenuated and accentuated genetic effects on BMI across tertiles of MVPA and sedentary behavior, respectively, remained similar. Our power calculation indicated that this study had 20% power to detect both interactions simultaneously (Supplementary Table 3). Similarly, after adjusting for each other, effects of both the GRS × MVPA interaction and the GRS × sedentary behavior interaction on waist circumference, fat mass, fat mass index, and fat percentage were attenuated, with P values ranging from nominally significant to nonsignificant levels (P for GRS × MVPA interaction, 0.03–0.33; P for GRS × sedentary behavior, 0.02–0.14).

Figure 1 shows results of gene–physical activity interactions from another perspective: the effects of physical activity and sedentary behavior on BMI and other adiposity traits according to GRS tertiles. Participants in the upper two tertiles of the GRS tended to have accentuated effects of total physical activity, MVPA, and sedentary behavior on BMI and other adiposity measures compared with those in the lowest tertile of the GRS.

Consistent with analyses of the continuous BMI outcome and other adiposity measures, the significant interactions of the GRS with total physical activity ($P_{interaction} = 0.005$), MVPA ($P_{interaction} = 0.016$), and sedentary behavior ($P_{interaction} = 0.037$) were observed for obesity risk (Fig. 2). The genetic effects on obesity risk were attenuated in participants with more total physical activity, more MVPA, and less sedentary time.

Joint Effect of GRS and Physical Activity on BMI

To further illustrate the effect of observed gene-environment interactions on BMI, we estimated BMI levels across tertiles of physical activity or sedentary behavior based on tertiles of the GRS (Fig. 3), with the presence of interaction (solid lines) and assuming no interaction (dashed lines). For individuals genetically predisposed to obesity (GRS tertile 2 and 3), the predicted BMI levels across tertiles of total physical activity or MVPA levels were lower in the presence of interaction (Fig. 3*A* and *B*, solid lines) than in those assuming no interaction (Fig. 3*A* and *B*, dashed lines). Conversely, for individuals genetically predisposed to obesity, the predicted BMI levels across tertiles of sedentary time were higher in the presence of interaction (Fig. 3*C*, solid lines) than with no interaction (Fig. 3*C*, dashed lines).

Interactions of GRS Subgroups With MVPA and Sedentary Behavior on BMI and Other Adiposity Measures

To explore potential mechanisms underlying interactions between behaviors and genetic predisposition and their effect on obesity, we created two GRS subgroups based on potential biological categories of the 97 BMI loci (7,24). Figure 4 shows that MVPA and sedentary behavior showed significant interactions with the CNS-related GRS (MVPA: $P_{interaction} = 0.003$; sedentary behavior: $P_{interaction} = 0.003$), but not with the non-CNS-related GRS (MVPA: $P_{interaction} = 0.35$; sedentary behavior: $P_{interaction} = 0.85$) in relation to BMI. Consistently, the CNS-related GRS, but not the non-CNS-related GRS, showed significant interactions with MVPA or sedentary behavior, with effects on waist circumference, fat mass, fat mass index, and fat percentage ($P_{interaction} < 0.05$ for all).

Robustness of Interaction Effects

To examine the robustness of interaction effects and the potential influences of bias and confounding, we conducted various sensitivity analyses and subgroup analyses, and we also adapted several approaches from previous studies (21,23).

Our sensitivity analyses (N = 7,379) excluding individuals with prevalent diabetes (N = 1,957) and excluding those

Table 2—Interactions of physical activity, MVPA, and sedentary behavior with the overall GRS and effects on BMI, body composition measures, and waist circumference

	Continuous*		Tertiles†		
	β for interaction (SE)	*P* value	1	2	3
BMI, kg/m^2					
Total physical activity					
Model 1	−0.12 (0.04)	0.005	0.82 (0.10)	0.72 (0.10)	0.43 (0.09)
MVPA					
Model 1	−0.06 (0.02)	0.005	0.78 (0.10)	0.75 (0.10)	0.39 (0.09)
Model 2	−0.04 (0.02)	0.11	0.74 (0.11)	0.75 (0.10)	0.41 (0.10)
Sedentary time					
Model 1	0.09 (0.03)	0.006	0.44 (0.09)	0.81 (0.10)	0.73 (0.10)
Model 2	0.06 (0.04)	0.10	0.46 (0.10)	0.77 (0.10)	0.69 (0.11)
Fat mass, kg					
Total physical activity					
Model 1	−0.26 (0.09)	0.003	1.58 (0.20)	1.37 (0.20)	0.73 (0.18)
MVPA					
Model 1	−0.13 (0.04)	0.001	1.48 (0.20)	1.48 (0.20)	0.65 (0.17)
Model 2	−0.09 (0.05)	0.06	1.36 (0.22)	1.48 (0.20)	0.76 (0.20)
Sedentary time					
Model 1	0.20 (0.06)	0.002	0.70 (0.18)	1.60 (0.20)	1.41 (0.20)
Model 2	0.13 (0.07)	0.08	0.73 (0.20)	1.52 (0.19)	1.34 (0.23)
Fat mass index, kg/m^2					
Total physical activity					
Model 1	−0.10 (0.03)	0.002	0.60 (0.07)	0.52 (0.07)	0.27 (0.06)
MVPA					
Model 1	−0.05 (0.02)	0.001	0.56 (0.07)	0.56 (0.07)	0.24 (0.06)
Model 2	−0.04 (0.02)	0.03	0.53 (0.08)	0.56 (0.07)	0.27 (0.07)
Sedentary time					
Model 1	0.07 (0.02)	0.004	0.27 (0.07)	0.61 (0.07)	0.51 (0.07)
Model 2	0.04 (0.03)	0.14	0.29 (0.07)	0.58 (0.07)	0.48 (0.08)
Fat percentage, %					
Total physical activity					
Model 1	−0.13 (0.06)	0.023	0.94 (0.12)	0.85 (0.13)	0.49 (0.12)
MVPA					
Model 1	−0.07 (0.03)	0.012	0.84 (0.12)	0.99 (0.13)	0.41 (0.13)
Model 2	−0.04 (0.03)	0.20	0.77 (0.14)	0.99 (0.13)	0.50 (0.14)
Sedentary time					
Model 1	0.11 (0.04)	0.007	0.43 (0.12)	0.99 (0.13)	0.86 (0.13)
Model 2	0.09 (0.05)	0.08	0.45 (0.14)	0.94 (0.13)	0.86 (0.15)
Fat-free mass, kg					
Total physical activity					
Model 1	−0.05 (0.05)	0.291	0.67 (0.11)	0.50 (0.11)	0.49 (0.10)
MVPA					
Model 1	−0.02 (0.02)	0.433	0.66 (0.11)	0.51 (0.11)	0.45 (0.11)
Model 2	0.00 (0.03)	0.971	0.58 (0.12)	0.51 (0.11)	0.44 (0.12)
Sedentary time					
Model 1	0.06 (0.04)	0.117	0.50 (0.10)	0.53 (0.11)	0.67 (0.11)
Model 2	0.06 (0.04)	0.161	0.49 (0.11)	0.50 (0.11)	0.64 (0.13)
Waist circumference, cm					
Total physical activity					
Model 1	−0.28 (0.10)	0.006	1.70 (0.23)	1.59 (0.23)	0.85 (0.21)
MVPA					
Model 1	−1.15 (0.47)	0.014	1.60 (0.22)	1.67 (0.23)	0.80 (0.21)
Model 2	−0.05 (0.05)	0.33	1.57 (0.25)	1.67 (0.23)	0.93 (0.24)
Sedentary time					
Model 1	0.40 (0.13)	0.001	0.76 (0.21)	1.82 (0.22)	1.54 (0.23)
Model 2	0.21 (0.09)	0.02	0.79 (0.24)	1.75 (0.22)	1.53 (0.26)

Model 1 and model 2 are adjusted for the log of sampling weight, field center, age, sex, five principal components for population structure, education, income, employment, smoking, alcohol use, energy intake, and AHEI as fixed effects, and genetic relatedness, household, and block groups as random effects. Model 2 was simultaneously tested for MVPA × GRS and sedentary behavior × GRS interactions. *Data are interaction effect sizes per 1-SD (six-unit) increment of GRS × 100 counts/min increment of total physical activity, per 1-SD increment of GRS × 10-min increment of MVPA, and per 1-SD increment of GRS × 1-h increment of sedentary time. †Data are effect sizes per 1-SD increment of GRS according to tertiles of total physical activity, MVPA, and sedentary time.

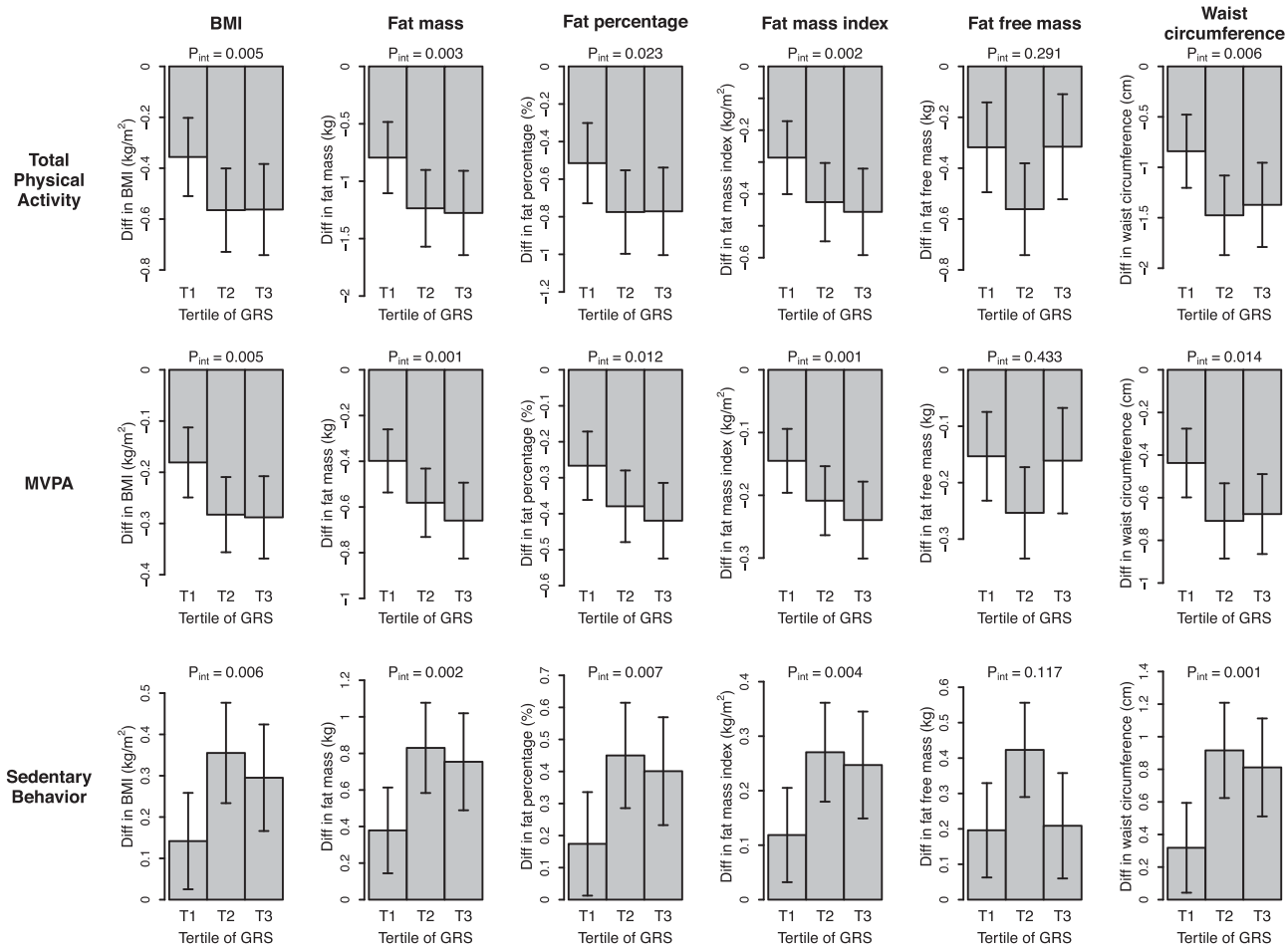

Figure 1—Associations of total physical activity, MVPA, and sedentary behavior with BMI and other adiposity traits according to tertiles (T) of overall GRS. Data are effect sizes per 100 counts/min increments of total physical activity, per 10-min increment of MVPA, and per 1-h increment of sedentary time for BMI, fat mass, fat percentage, fat mass index, fat-free mass, and waist circumference, adjusting for sampling weight, field center, age, sex, the five principal components for population structure, education, income, employment, smoking, alcohol use, energy intake, and AHEI as fixed effects, and genetic relatedness, household, and block groups as random effects. Diff, difference; P_{int}, $P_{interaction}$.

with prevalent cardiovascular disease (N = 526) showed similar results (Supplementary Table 4). Subgroup analyses stratified by sex, field center, age group, and Hispanic/Latino background group presented comparable interaction effect sizes across subgroups, with no significant heterogeneity (P for heterogeneity >0.10 for all) (Supplementary Fig. 1).

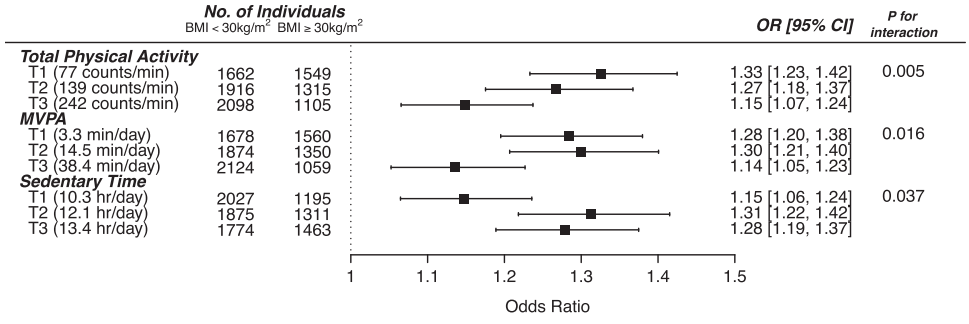

Figure 2—Interactions of total physical activity, MVPA, and sedentary behavior with the overall GRS for obesity risk. Data are odds ratios (95% CIs) for obesity risk (BMI ≥30 vs. <30 kg/m^2) per 1-SD increment of the overall GRS according to tertiles (T) of total physical activity, MVPA, and sedentary behavior, adjusting for sampling weight, field center, age, sex, five principal components for population structure, education, income, employment, smoking, alcohol use, energy intake, and AHEI as fixed effects, and genetic relatedness, household, and block groups as random effects.

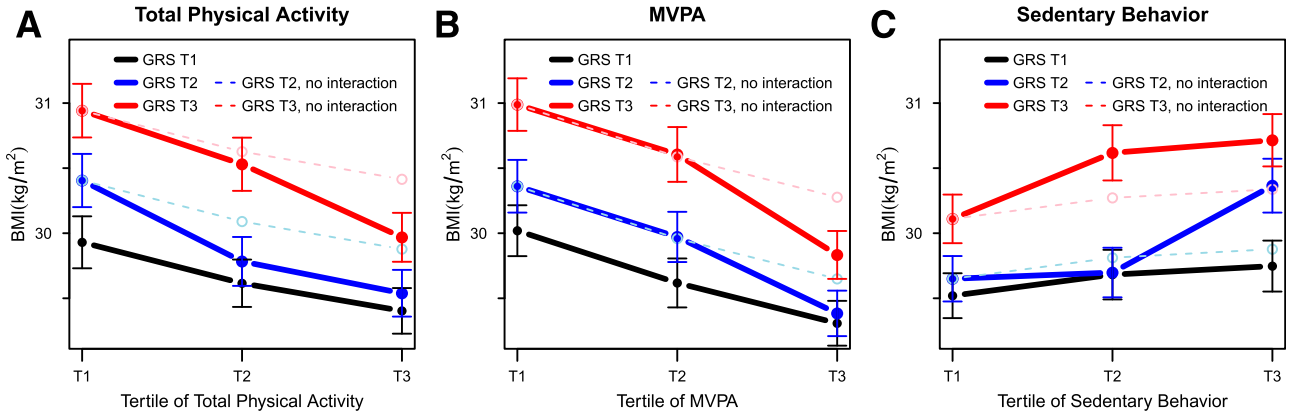

Figure 3—BMI among individuals grouped by tertiles (T) of the overall GRS and tertiles of total physical activity (*A*), MVPA (*B*), and sedentary time (*C*). Solid lines indicate the estimated BMI levels across tertiles of total physical activity, MVPA, or sedentary behavior by individuals with low (GRS T1), medium (GRS T2) and high (GRS T3) genetic risk for obesity. Dashed lines indicate the projected BMI levels among individuals with medium (GRS T2) and high (GRS T3) genetic risk for obesity, assuming no gene–environment interactions. The dashed lines are parallel to the black solid line of the estimated BMI levels among individuals with low genetic risk (GRS T1) for obesity. Values are means (95% CIs), adjusted for sampling weight, field center, age, sex, five principal components for population structure, education, income, employment, smoking, alcohol use, energy intake, and AHEI as fixed effects, and genetic relatedness, household, and block groups as random effects.

We then examined whether interactions of GRS with physical activity and sedentary behavior are related to overall health. The overall health score was inversely associated with BMI ($P < 0.001$), but no significant interaction was found between the health score and the GRS in affecting BMI ($P_{interaction}$ = 0.91). After adjusting for the GRS × health score interaction, the interactions of GRS with total physical activity, MVPA, and sedentary behavior with effects on BMI remained significant (Supplementary Table 5).

In our negative control analyses, the median *P* value for interaction between the GRS and the randomized environment groups affecting BMI, based on 10,000 simulations, was not significant ($P_{interaction} \geq 0.37$), and only 0.05–1.2% had smaller *P* values for simulated interactions than for the observed interactions (Supplementary Table 6). Based on 10,000 simulations, the median *P* value for interactions between the GRS and the dummy continuous variables on BMI was not significant ($P_{interaction} \geq 0.50$), and only 0.46–2.4% had smaller *P* values for simulated interactions than for the observed interactions (Supplementary Table 7).

DISCUSSION

In this population-based study of U.S. Hispanics/Latinos using accelerometer data, we found significant interactions

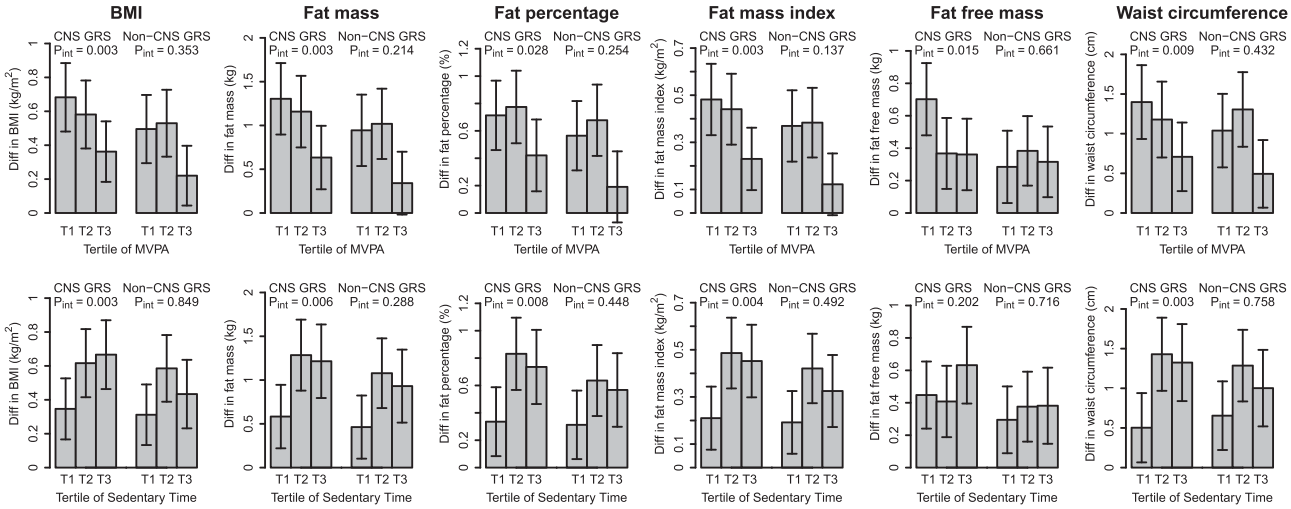

Figure 4—Interactions of MVPA and sedentary behavior with the CNS-related GRS and the non-CNS-related GRS on BMI, body composition measures, and waist circumference. Data are effect sizes (95% CIs) per 1-SD increment of the CNS-related GRS and the non-CNS-related GRS on BMI, fat mass, fat percentage, fat mass index, fat-free mass, and waist circumference, adjusting for sampling weight, field center, age, sex, five principal components for population structure, education, income, employment, smoking, alcohol use, energy intake, and AHEI as fixed effects, and genetic relatedness, household, and block groups as random effects. Diff, difference; P_{int}, $P_{interaction}$; T, tertile.

of physical activity and sedentary behavior with a BMI-related GRS, with effects on BMI and obesity risk. Further analyses using body composition data suggested that the observed interactions might be specific to fat mass rather than fat-free mass. Our data suggest that individuals with less physical activity and more sedentary behavior may be more susceptible to genetic effects on adiposity. Viewed from another perspective, individuals with a greater genetic predisposition to obesity seemed to be more susceptible to the beneficial effects of physical activity and the deleterious effects of sedentary behavior on adiposity. Our findings further emphasize the importance of both increasing physical activity and decreasing sedentary behavior to prevent obesity, particularly in those genetically predisposed to obesity.

In addition to consistent results of gene–physical activity interactions with effects on BMI and obesity reported in previous studies (1–4), we found a significant interaction between objectively measured sedentary time and the GRS, with effects on BMI and obesity risk; this has been rarely reported. A previous study found that prolonged sedentary behavior, indicated by self-reported time spent watching television, may accentuate genetic associations with BMI in non-Hispanic white men and women (4), whereas another study did not find strong evidence for interactions between screen time and the majority of established obesity loci in a multiethnic cohort of adolescents (25). Compared with self-reported television watching and screen time used in previous studies (4,25), the sedentary time measured through an accelerometry protocol in our study is less subjective and captures more sedentary behaviors beyond watching television and screen time. However, whether the GRS × sedentary behavior interaction effect on obesity is independent of the GRS × MVPA interaction, or vice versa, was not addressed in our study. Simultaneous tests of both interactions showed attenuated interaction effects on BMI and other adiposity traits, ranging from nominal significance to nonsignificance, and no clear evidence indicated that the observed results were driven by either interaction. These data suggest that both the GRS × MVPA and the GRS × sedentary behavior interactions might have effects on obesity, but our study did not have sufficient power to detect both interactions simultaneously in the same model. Nevertheless, future studies with large sample sizes are needed to elucidate the mutual independence of GRS × MVPA and GRS × sedentary behavior interactions in relation to obesity.

It is plausible that the CNS-related GRS, rather than the non-CNS-related GRS, showed significant interactions with both MVPA and sedentary behavior in relation to adiposity, as the CNS plays a key role in regulating energy balance and circadian rhythm (26,27). For example, exercise induces leptin signaling, which regulates energy balance in the hypothalamus or ventral tegmental area, which can result in the reduction of food intake and weight loss (28). Previous studies also showed significant interactions between CNS-related genetic variants and dietary factors, with effects on BMI (26,27). Effects of physical activity on circadian rhythm and central metabolism have been shown; these are closely related to obesity (28), although underlying mechanisms remain unknown (29). Sedentary behavior is associated with low serotonergic responsivity of the CNS (30), which is involved in carbohydrate cravings and the development of obesity (31,32). However, our GRS subgroups were calculated according to putative biological categories of these BMI loci (7), whereas biological functions of these genetic loci in obesity remain unclear.

Findings from this and many other observational studies provide consistent evidence for gene-environment interactions and their effects on obesity (1–4,21,23,26,27), but results from weight loss clinical trials are controversial. A recent meta-analysis suggested that individuals carrying the homozygous FTO obesity-predisposing allele may lose more weight through diet and lifestyle interventions than noncarriers (33), whereas another meta-analysis reported that the FTO variation was not associated weight loss after interventions (34). Data from observational studies are more likely to be confounded or biased than data from clinical trials, but these genetic variants were identified to be associated with BMI rather than weight loss, which may explain this discordance. Indeed, a previous study found that most obesity-predisposing variants were not associated with weight loss or regain in clinical trials (35). Genetic factors and their potential interactions with diet and lifestyle, and their effects on weight loss after interventions, remain to be identified in future studies.

One unique feature of this study is the sample of participants from diverse Hispanic/Latino backgrounds. Our consistent results across Hispanic/Latino background groups, including groups with origins in both North and South America as well as the Caribbean, provide evidence for the generalization of a gene–physical activity interaction effect on obesity in Europeans to the diverse U.S. Hispanic/Latino population. Major strengths of this study include objectively measured data on physical activity and sedentary behavior, comprehensive coverage of established BMI-associated genetic factors, and multiple adiposity measures. In addition, data from our sensitivity analyses, subgroup analyses, and negative control simulations support the robustness of the observed interaction effects.

Several limitations of our study need to be acknowledged. Time spent standing still may have been measured by the accelerometer as time spent sitting, and some types of physical activity, such as swimming, cycling, and upper-body work, cannot be measured by an accelerometer. Accelerometer data during 3 to 7 adherent days may not reflect physical activity and sedentary behavior over a long period. Although bioelectrical impedance has been widely used as an efficient method to estimate body composition in large epidemiological studies (36), fat mass estimated by Tanita bioelectrical impedance might be biased by obesity status compared with more accurate methods using DXA, MRI, or ^{18}O dilution (17,37,38). Other limitations of this study include cross-sectional data and an inadequate sample

size to detect both interactions of MVPA and sedentary behavior simultaneously with the GRS and their effects on BMI and obesity risk.

In conclusion, our study provides evidence for the roles of gene–physical activity and gene–sedentary behavior interactions in the development of obesity, although the independence of these interaction effects remains unclear. Consideration of genetic predisposition to obesity might help develop more efficient strategies and personalize activity programs in the prevention of obesity, but applications of these findings in public health need to be investigated further.

Acknowledgments. The authors thank the staff and participants of HCHS/SOL for their important contributions. A complete list of HCHS/SOL staff and investigators can be found in Ann Epidemiol 2010;20:642–649 or at http://sites.cscc.unc.edu/hchs/.

Funding. The baseline examination of the HCHS/SOL was carried out as a collaborative study supported by the National Heart, Lung, and Blood Institute (NHLBI) to the University of North Carolina (contract N01-HC65233), the University of Miami (contract N01-HC65234), the Albert Einstein College of Medicine (contract N01-HC65235), Northwestern University (contract N01-HC65236), and San Diego State University (contract N01-HC65237). The following institutes/centers/offices contributed to the first funding period of the HCHS/SOL through a transfer of funds to the NHLBI: National Institute on Minority Health and Health Disparities, the National Institute of Deafness and Other Communications Disorders, the National Institute of Dental and Craniofacial Research, the National Institute of Diabetes and Digestive and Kidney Diseases, the National Institute of Neurological Disorders and Stroke, and the National Institutes of Health Office of Dietary Supplements. The Genetic Analysis Center at the University of Washington was supported by the NHLBI (contract HHSN268201300005C AM03) and the National Institute of Dental and Craniofacial Research (contract MOD03). Genotyping efforts were supported by the NHLBI (HSN 26220/20054C), the National Center for Advancing Translational Sciences (Clinical and Translational Science Award grant UL1TR000123), and the National Institute of Diabetes and Digestive and Kidney Diseases Diabetes Research Center (grant DK063491). Q.Q. is supported by a Scientist Development Award (K01HL129892) from the NHLBI.

Duality of Interest. No conflicts of interest relevant to this article were reported.

Author Contributions. J.-Y.M. and Q.Q. designed the study and wrote the manuscript. J.Y.-M. performed statistical analysis. T.W., K.E.N., C.R.I., J.C., M.D.G., A.E.M., M.A., and R.C.K. contributed to the discussion and edited and reviewed the manuscript. T.S. and D.S.-A. researched and reviewed data and edited and reviewed the manuscript. Q.Q. 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.

Prior Presentation. Parts of this study were presented in abstract and poster form at the American Heart Association's (AHA's) EPI/LIFESTYLE Scientific Sessions, Portland, OR, 7–10 March 2017; CHARGE Investigator meeting, New York, NY, 23–24 March 2017; and Best of AHA Specialty Conferences Invitation for Abstracts Scientific Session, Anaheim, CA, 11–15 November 2017.

References

1. Li S, Zhao JH, Luan J, et al. Physical activity attenuates the genetic predisposition to obesity in 20,000 men and women from EPIC-Norfolk prospective population study. PLoS Med 2010;7:e1000332

2. Kilpeläinen TO, Qi L, Brage S, et al. Physical activity attenuates the influence of *FTO* variants on obesity risk: a meta-analysis of 218,166 adults and 19,268 children. PLoS Med 2011;8:e1001116

3. Ahmad S, Rukh G, Varga TV, et al.; InterAct Consortium; DIRECT Consortium. Gene × physical activity interactions in obesity: combined analysis of 111,421 individuals of European ancestry. PLoS Genet 2013;9:e1003607

4. Qi Q, Li Y, Chomistek AK, et al. Television watching, leisure time physical activity, and the genetic predisposition in relation to body mass index in women and men. Circulation 2012;126:1821–1827

5. Kit BK, Fakhouri THI, Park S, Nielsen SJ, Ogden CL. Trends in sugar-sweetened beverage consumption among youth and adults in the United States: 1999–2010. Am J Clin Nutr 2013;98:180–188

6. Flegal KM, Carroll MD, Kit BK, Ogden CL. Prevalence of obesity and trends in the distribution of body mass index among US adults, 1999–2010. JAMA 2012;307:491–497

7. Locke AE, Kahali B, Berndt SI, et al.; LifeLines Cohort Study; ADIPOGen Consortium; AGEN-BMI Working Group; CARDIOGRAMplusC4D Consortium; CKDGen Consortium; GLGC; ICBP; MAGIC Investigators; MuTHER Consortium; MIGen Consortium; PAGE Consortium; ReproGen Consortium; GENIE Consortium; International Endogene Consortium. Genetic studies of body mass index yield new insights for obesity biology. Nature 2015;518:197–206

8. Lavange LM, Kalsbeek WD, Sorlie PD, et al. Sample design and cohort selection in the Hispanic Community Health Study/Study of Latinos. Ann Epidemiol 2010;20:642–649

9. Sorlie PD, Avilés-Santa LM, Wassertheil-Smoller S, et al. Design and implementation of the Hispanic Community Health Study/Study of Latinos. Ann Epidemiol 2010;20:629–641

10. Evenson KR, Sotres-Alvarez D, Deng YU, et al. Accelerometer adherence and performance in a cohort study of US Hispanic adults. Med Sci Sports Exerc 2015;47:725–734

11. Choi L, Liu Z, Matthews CE, Buchowski MS. Validation of accelerometer wear and nonwear time classification algorithm. Med Sci Sports Exerc 2011;43:357–364

12. Colley RC, Garriguet D, Janssen I, Craig CL, Clarke J, Tremblay MS. Physical activity of Canadian adults: accelerometer results from the 2007 to 2009 Canadian Health Measures Survey. Health Rep 2011;22:7–14

13. Wong SL, Colley R, Connor Gorber S, Tremblay M. Actical accelerometer sedentary activity thresholds for adults. J Phys Act Health 2011;8:587–591

14. Healy GN, Matthews CE, Dunstan DW, Winkler EAH, Owen N. Sedentary time and cardio-metabolic biomarkers in US adults: NHANES 2003–06. Eur Heart J 2011;32:590–597

15. Willett W, Stampfer MJ. Total energy intake: implications for epidemiologic analyses. Am J Epidemiol 1986;124:17–27

16. Colley RC, Tremblay MS. Moderate and vigorous physical activity intensity cut-points for the Actical accelerometer. J Sports Sci 2011;29:783–789

17. Wong WW, Strizich G, Heo M, et al. Relationship between body fat and BMI in a US Hispanic population-based cohort study: results from HCHS/SOL. Obesity (Silver Spring) 2016;24:1561–1571

18. Chiuve SE, Fung TT, Rimm EB, et al. Alternative dietary indices both strongly predict risk of chronic disease. J Nutr 2012;142:1009–1018

19. Siega-Riz AM, Sotres-Alvarez D, Ayala GX, et al. Food-group and nutrient-density intakes by Hispanic and Latino backgrounds in the Hispanic Community Health Study/Study of Latinos. Am J Clin Nutr 2014;99:1487–1498

20. Conomos MP, Laurie CA, Stilp AM, et al. Genetic diversity and association studies in US Hispanic/Latino populations: applications in the Hispanic Community Health Study/Study of Latinos. Am J Hum Genet 2016;98:165–184

21. Young AI, Wauthier F, Donnelly P. Multiple novel gene-by-environment interactions modify the effect of FTO variants on body mass index. Nat Commun 2016;7:12724

22. R Core Team. *R: A Language and Environment for Statistical Computing*. 3.3.2 ed. Vienna, Austria, R Foundation for Statistical Computing, 2016

23. Tyrrell J, Wood AR, Ames RM, et al. Gene-obesogenic environment interactions in the UK Biobank study. Int J Epidemiol 2017;46:559–575

24. Pers TH, Karjalainen JM, Chan Y, et al.; Genetic Investigation of Anthropometric Traits (GIANT) Consortium. Biological interpretation of genome-wide association studies using predicted gene functions. Nat Commun 2015;6:5890

25. Graff M, North KE, Richardson AS, et al. Screen time behaviours may interact with obesity genes, independent of physical activity, to influence adolescent BMI in an ethnically diverse cohort. Pediatr Obes 2013;8:e74–e79

26. Qi Q, Chu AY, Kang JH, et al. Fried food consumption, genetic risk, and body mass index: gene-diet interaction analysis in three US cohort studies. BMJ 2014; 348:g1610
27. Qi Q, Chu AY, Kang JH, et al. Sugar-sweetened beverages and genetic risk of obesity. N Engl J Med 2012;367:1387–1396
28. Morgan JA, Corrigan F, Baune BT. Effects of physical exercise on central nervous system functions: a review of brain region specific adaptations. J Mol Psychiatry 2015;3:3
29. Huang W, Ramsey KM, Marcheva B, Bass J. Circadian rhythms, sleep, and metabolism. J Clin Invest 2011;121:2133–2141
30. Muldoon MF, Mackey RH, Williams KV, Korytkowski MT, Flory JD, Manuck SB. Low central nervous system serotonergic responsivity is associated with the metabolic syndrome and physical inactivity. J Clin Endocrinol Metab 2004;89:266–271
31. Wurtman RJ, Wurtman JJ. Brain serotonin, carbohydrate-craving, obesity and depression. Obes Res 1995;3(Suppl. 4):477S–480S
32. Crane JD, Palanivel R, Mottillo EP, et al. Inhibiting peripheral serotonin synthesis reduces obesity and metabolic dysfunction by promoting brown adipose tissue thermogenesis. Nat Med 2015;21:166–172
33. Xiang L, Wu H, Pan A, et al. FTO genotype and weight loss in diet and lifestyle interventions: a systematic review and meta-analysis. Am J Clin Nutr 2016;103: 1162–1170
34. Livingstone KM, Celis-Morales C, Papandonatos GD, et al. FTO genotype and weight loss: systematic review and meta-analysis of 9563 individual participant data from eight randomised controlled trials. BMJ 2016;354:i4707
35. Papandonatos GD, Pan Q, Pajewski NM, et al.; GIANT Consortium; Diabetes Prevention Program and the Look AHEAD Research Groups. Genetic predisposition to weight loss and regain with lifestyle intervention: analyses from the Diabetes Prevention Program and the Look AHEAD randomized controlled trials. Diabetes 2015; 64:4312–4321
36. Böhm A, Heitmann BL. The use of bioelectrical impedance analysis for body composition in epidemiological studies. Eur J Clin Nutr 2013;67(Suppl. 1):S79–S85
37. Ellegård L, Bertz F, Winkvist A, Bosaeus I, Brekke HK. Body composition in overweight and obese women postpartum: bioimpedance methods validated by dual energy X-ray absorptiometry and doubly labeled water. Eur J Clin Nutr 2016;70: 1181–1188
38. Lloret Linares C, Ciangura C, Bouillot JL, et al. Validity of leg-to-leg bioelectrical impedance analysis to estimate body fat in obesity. Obes Surg 2011;21:917–923