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Physical activity attenuates the association between the *IRS1* genotype and childhood obesity in Chinese children

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Abstract *Background and aims:* The insulin receptor substrate 1 (*IRS1*) rs2943650 was found to be associated with obesity in adults, but the association has not been evaluated in children. The present study aimed to examine whether *IRS1* rs2943650 was associated with obesity in Chinese children and investigate the interaction between rs2943650 and physical activity.
Methods and results: IRS1 rs2943650 was genotyped in 3303 Chinese children aged 6–18 years recruited from four independent studies. Logistic regression and linear regression were performed to examine associations. Meta-analyses were conducted to pool the results of the four independent studies. The C-allele carriers of rs2943650 showed a 29% higher risk of obesity than noncarriers (OR (95% CI) = 1.29 (1.05, 1.58), $P = 0.02$) and a 0.41 kg/m^2 increase in BMI (β (95% CI) = 0.41 (0.05, 0.78) kg/m^2, $P = 0.02$). We also observed significant interactions between rs2943650 and physical activity/sedentary behaviors on obesity ($P_{\text{for interaction}}<0.05$). Compared with the physically active children (physical activity ≥1 h/d and sedentary behaviors <2 h/d), the risk allele (C) of rs2943650 was significantly associated with a 241% increased risk of obesity among inactive children who participated in physical activity <1 h/d and sedentary behaviors ≥2 h/d (OR (95% CI) = 3.41 (1.45, 8.01), $P = 0.005$).
Conclusions: We found that *IRS1* rs2943650 was significantly associated with BMI and risk of childhood obesity. Additionally, we also found significant interaction between *IRS1* rs2943650 polymorphism and physical activity/sedentary behaviors on childhood obesity. Our study would provide novel insights into the function of the *IRS1* gene and the implementation of effective intervention strategies of childhood obesity.

Abbreviations: IRS1, insulin receptor substrate 1; GWAS, genome-wide association study; BMI, body mass index; CPOOA, Comprehensive Prevention project for Overweight and Obese Adolescents; SCICO, School-Based Comprehensive Intervention on Childhood Obesity; SPAICO, School-based Physical Activity Intervention on Childhood Obesity; OR, odds ratio; CI, confidence interval.

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Introduction

The insulin receptor substrate 1 (IRS1) is a substrate of insulin receptor tyrosine kinase and plays an important role in the insulin signaling pathway, mediating between the insulin receptor and phosphatidylinositol 3-kinase (PI3K) [1,2]. Disorder in insulin signal transduction such as insulin resistance is a major risk factor associated with obesity [3]. Therefore, genetic variants influencing the insulin signaling pathway might play a key role in the development of obesity.

Recently, a large-scale meta-analysis of genome-wide association studies (GWAS) identified that a common single nucleotide polymorphism (SNP), rs2943650 near the *IRS1* gene, was associated with adiposity and altered metabolic outcomes in European and Asian descents [4]. Specifically, the C-allele of rs2943650 is associated with increased body fat percentage and a favorable metabolic profile [4]. Lu et al. [5] also confirmed that another SNP near *IRS1* (rs2943652, in high linkage disequilibrium (LD) with rs2943650 ($r^2 = 1.0$)), was associated with body mass index (BMI) and body fat percentage, in a GWAS meta-analysis with up to 100,716 adult individuals of multi-ethnicity. However, the populations of both studies did not include the Chinese. To our knowledge, the association of *IRS1* rs2943650 with obesity is less investigated in the Chinese, with only 2 publications examining its associations with BMI, overweight, obesity, and other obesity-related traits and reporting no significant associations [6,7]. Moreover, all of these studies were conducted in adults, and the association between *IRS1* rs2943650 and childhood obesity has not been investigated.

Although emerging GWAS have identified plenty of genes unequivocally associated with obesity-related traits, the combined results of these variations could only explain a small proportion of obesity variance, suggesting that there is missing heritability [8]. On the quest for the missing heritability, one of the considerations is that gene–environment interactions might contribute to the heritability of obesity [8]. Several studies have found that physical activity and sedentary behaviors could interact with genetic variants and influence the development of obesity [9–12]. Studies have also demonstrated that physical activity may lead to enhanced activation of insulin-stimulated IRS-1-associated PI3K activity [13]. He et al. identified that physical activity might modify the association between polymorphisms near *IRS1* and the risk of type 2 diabetes in women. Jung et al. [15] also found that genetic variants in the *IRS1* gene interacted with physical activity, altering postmenopausal colorectal cancer risk, the development of which is closely associated with obesity. However, no study has analyzed the interaction between genetic variants near the *IRS1* gene and physical activity on the risk of obesity.

Therefore, in the present study, we aimed to examine whether *IRS1* rs2943650 was associated with obesity in Chinese children and investigate the interactions between *IRS1* rs2943650 and physical activity/sedentary lifestyle.

Methods

Subjects

The present case–control study included 3303 genetically unrelated Han Chinese children (1261 normal-weight children, 1014 overweight children, and 1028 obese children) aged 6–18 years recruited from four independent studies in Beijing, China. The study on adolescent lipids, insulin resistance, and candidate genes (ALIR) and the study of Comprehensive Prevention project for Overweight and Obese Adolescents (CPOOA) were similar in terms of study design (case–control study), recruitment of subjects, and data collection, which have been described previously in detail [16,17]. The other two studies are both school-based intervention on childhood and adolescent obesity (School-Based Comprehensive Intervention on Childhood Obesity (SCICO) and School-based Physical Activity Intervention on Childhood Obesity (SPAICO)). The cross-sectional baseline survey data were analyzed in the present study. The SCICO study was performed in 8 elementary schools of the Haidian District of Beijing, involving 1588 normal-weight children, 151 overweight children, and 153 obese children [18]. In the present study, we included all the overweight and obese children, as well as 152 normal-weight children randomly selected from the normal-weight group. The SPAICO study was conducted in 2 primary schools and 2 middle schools in Changping District of Beijing, including 502 normal-weight children and adolescents, 145 overweight children and adolescents, and 170 obese children and adolescents [19]. In all the four studies, we excluded children who were underweight according to the Chinese national screening criteria for malnutrition of school-age children and adolescents [20] and those with any vital organ disease and obesity-related comorbidities such as diseases of the heart, liver, lung, and kidney and diabetes.

Written informed consents were obtained from all participants and their parents. The four studies were approved by the Ethics Committee of Peking University Health Science Center (ALIR, CPOOA, and SPAICO studies) or the Ethics Committee of Chinese Center for Disease Control and Prevention (SCICO study).

Anthropometric measurements

All anthropometric measurements in the four studies, including height, weight, and waist and hip circumferences, were performed by the same methods according to standard protocols [16,17]. BMI was calculated as weight (kg) divided by height (m^2). For children aged 7–18 years, uniform BMI percentile criteria, which were determined in a representative Chinese population [21], were used to screen the obese and overweight participants. Children with an age- and sex-specific BMI $\geq$95th percentile were defined as obese; those with an age- and sex-specific BMI $\geq$85th percentile were defined as overweight. After exclusion of underweight children, those with an age- and

gender-specific BMI less than the 85th percentile were considered as normal-weight children. For children aged 6 years, the Chinese national screening criteria for overweight and obesity among school-age children and adolescents were used [22]. Sex- and age-specific BMI standard deviation score (BMI-SDS) was calculated according to the growth reference data of the World Health Organization for children aged 5–19 years [23]. The body fat percentage was assessed by bioelectrical impedance analysis, except in the ALIR study (CPOOA: Genuis-220, Jawon, Korea; SCICO and SPAICO: DF50, ImpediMed, Australia).

Biochemical and blood pressure measurements

Fasting blood samples were collected for all children. Fasting plasma glucose (FPG), total cholesterol, triglyceride, low-density lipoprotein–cholesterol (LDL-C), and high-density lipoprotein–cholesterol (HDL-C) were determined using a biochemical autoanalyzer (ALIR and CPOOA: Hitachi7060, Tokyo, Japan; SCICO and SPAICO: Olympus AU400, Tokyo, Japan). Fasting insulin (Fins) was determined by radioimmunoassay in ALIR and CPOOA studies and by chemiluminescence immunoassay in the SCICO and SPAICO studies. The homeostasis model assessment of insulin resistance (HOMA-IR) and the homeostasis model assessment of pancreatic beta cell function (HOMA-β) were calculated with the HOMA Calculator version 2.2.3 (available from the Oxford Center for Diabetes, Endocrinology and Metabolism, http://www.dtu.ox.ac.uk/homacalculator/download.php, accessed on November 12th, 2018) [24]. The quantitative insulin sensitivity check index (QUICKI) was calculated according to the formula: QUICKI = 1/[log (Fins, μU/mL) +log (FPG, mg/dL)] [24].

Blood pressure was measured with an auscultation mercury sphygmomanometer using an appropriately sized cuff for children according to the recommendation of the National High Blood Pressure Education Program Working Group in Children and Adolescents [25]. Mean systolic and diastolic blood pressures (SBP and DBP) were used by averaging three measurements.

Physical activity and sedentary behaviors

A validated questionnaire was used to investigate the physical activity and sedentary behaviors of children in the CPOOA and SPAICO studies [9,19,26,27]. The level of physical activity was evaluated by the time spent on physical activity per day during the last week. It was then divided into two groups: <1 h/d and ≥ 1 h/d, based on the WHO recommendations that children should accumulate at least 60 min of moderate-to-vigorous physical activity daily [28]. Sedentary behaviors were determined by the time spent on watching television and playing computer and video games per day during the last week. It was then categorized into two groups: <2 h/d and ≥ 2 h/d, according to the suggestion of American Academy of Pediatrics that children's total media time should be limited to no more than 2 h per day [29].

Genotyping

Genomic DNAs of all children were extracted from blood leukocytes by the phenol-chloroform extraction (ALIR, CPOOA, and SCICO studies) and salt extraction (SPAICO study) methods. Genotyping of rs2943650 near *IRS1* was conducted with a MassARRAY System (Agena Bioscience Inc., San Diego, CA, USA). The detail genotyping process has been described in our previous studies [30,31]. The call rate for rs2943650 was above 99.5%. We performed genotyping on 5% randomly selected duplicated samples, and the concordance rates were 100%. The genotype data of the normal-weight children were tested for deviation from Hardy–Weinberg equilibrium (HWE) with χ^2 test.

Statistical analysis

The differences in general characteristics among normal-weight, overweight, and obese children were tested with one-way analysis of variance (*ANOVA*) (continuous variables) or the χ^2 test (categorical variables).

We tested additive, dominant, and recessive genetic models and found that the dominant model could best explain the effect of rs2943650 on childhood obesity. Logistic regression was performed to examine the effect of rs2943650 near *IRS1* on obesity, and linear regression was performed to examine its effect on BMI, assuming the dominant model and adjusting for sex, age, and age square. Stratified analyses were conducted to evaluate the association of rs2943650 near *IRS1* with risk of obesity among children with different levels of physical activity and sedentary behaviors in the CPOOA and SPAICO studies.

Meta-analyses were conducted to pool the results of different studies with the inverse variance method. Heterogeneity among studies was assessed by the Cochran's Q and the inconsistency index (I^2). In case of no significant heterogeneity between the studies in the meta-analyses ($I^2 < 70\%$, $P > 0.05$), we used fixed-effects models; otherwise, a random effects model was used [32,33].

In the four independent studies, data of socioeconomic factors were available in CPOOA, SCICO, and SPAICO studies and those of dietary and lifestyle factors were available in CPOOA and SPAICO studies. Therefore, we also performed sensitivity analyses with additional adjustment for socioeconomic, dietary, and lifestyle factors in available studies. We also conducted sex-specific and age-specific analyses to test whether sex and age modified the association between *IRS1* rs2943650 and obesity.

$P < 0.05$ (two-tailed) was considered as significant. All statistical analyses were performed using SPSS 24.0 (IBM Corp., Armonk, NY, USA). Meta-analyses were conducted with Revman 5.3 (available from the Cochrane Community https://community.cochrane.org/help/tools-and-software/revman-5).

Results

Basic characteristics

The general characteristics of the 3303 Han Chinese children are shown in Table 1. Significant differences in sex, age, height, weight, and BMI among the normal-weight group, overweight group, and obese group were observed (all $P < 0.001$). Differences in physical activity and sedentary behaviors among the three groups were not statistically significant ($P > 0.05$). The detailed general characteristics of the four study samples are presented in the Supplementary Table 1.

Genetic association of rs2943650 near IRS1 with obesity

Table 2 shows the genotyping information of rs2943650 near *IRS1* in Chinese children. The minor allele frequency (C) of rs2943650 near *IRS1* is 0.078 in the normal-weight group (genotype distribution: TT/TC/CC = 1064/181/7) in our study, which was similar to that reported in the HapMap Han Chinese (the frequency of C allele is 0.100). There was no deviation from HWE for rs2943650 in the normal-weight group ($P = 0.816$).

Genetic associations of rs2943650 near *IRS1* with risk of obesity and BMI were analyzed using logistic and linear regression under dominant genetic model, respectively, adjusted for sex, age, and age square. The effects of rs2943650 on obesity and BMI in the four studies were pooled with meta-analysis using fixed-effects model due to little heterogeneity ($I^2 = 0\%$, Fig. 1). The pooled odds ratio (OR) of rs2943650 for obesity was 1.29 (95% confidence interval (CI) = (1.05, 1.58), $P = 0.02$, Fig. 1a), indicating that children with the TC + CC genotypes had a 29% higher risk for obesity than those with the TT genotype. In addition, we also found that children with the TC + CC genotypes had higher BMI (β (95% CI) = 0.41 (0.05, 0.78) kg/m^2, $P = 0.02$, Fig. 1b) and BMI-SDS (β (95% CI) = 0.11 (0.01, 0.22), $P = 0.03$, Fig. 1c) than those with the TT genotype.

Sensitivity analyses showed that genetic association of rs2943650 near *IRS1* with obesity, BMI and BMI-SDS remained significant after additional adjustment for socioeconomic, dietary, and lifestyle factors (Supplementary Table 2).

As sex and age have significantly different distributions by obesity, we also conducted gender-specific and age-specific analyses. The results showed that rs2943650 was significantly associated with BMI-SDS among children aged 6–12 years old. No significant associations of rs2943650 with obesity, BMI, and BMI-SDS were observed in other subgroups. However, the results in different sex and age subgroups showed directionally consistent associations (see Supplementary Table 3).

In addition, we further analyzed the relationships between rs2943650 near *IRS1* and obesity-related phenotypes (Table 3). Children with the TC + CC genotypes had higher waist circumference (β (95% CI) = 1.08 (0.12, 2.05) cm, $P = 0.028$), WHR (β (95% CI) = 0.01 (0.0003, 0.01), $P = 0.040$), and WHtR (β (95% CI) = 0.01 (0.001, 0.01), $P = 0.024$) than those without these genotypes. However, these associations were abolished after additionally adjusting for BMI (all $P > 0.05$). No significant associations were observed between rs2943650 and other obesity-related phenotypes ($P > 0.05$).

Interaction analyses between rs2943650 and physical activity/sedentary behaviors on obesity

As illustrated in Table 4, in the pooled results from the CPOOA and SPAICO studies, the risk allele (C) of rs2943650 was significantly associated with an increased risk of

Table 1 General characteristics of the 3303 Han Chinese children.

	Normal-weight group	Overweight group	Obese group	*P* value
Number	1261	1014	1028	–
Male (%)	604 (48.0)	633 (62.4)	691 (67.2)	**< 0.001**
Age, years	11.28 ± 2.95	12.20 ± 2.81	11.86 ± 2.84	**< 0.001**
Height, cm	149.73 ± 16.54	156.51 ± 15.56	157.78 ± 15.62	**< 0.001**
Weight, kg	41.40 ± 13.35	57.68 ± 16.10	69.58 ± 21.36	**< 0.001**
BMI, kg/m^2	17.87 ± 2.43	22.90 ± 2.64	27.12 ± 4.10	**< 0.001**
PA[a]				
≥1 h/d	343 (49.6)	184 (54.8)	192 (54.4)	0.176
<1 h/d	349 (50.4)	152 (45.2)	161 (45.6)	
SB[a]				
<2 h/d	513 (73.0)	233 (67.5)	249 (68.0)	0.102
≥2 h/d	190 (27.0)	112 (32.5)	117 (32.0)	
PA/SB[a]				
PA ≥ 1 h/d and SB < 2 h/d	229 (35.0)	128 (38.9)	122 (35.8)	0.057
PA ≥ 1 h/d and SB ≥ 2 h/d	95 (14.5)	49 (14.8)	63 (14.5)	
PA < 1 h/d and SB < 2 h/d	241 (36.9)	92 (28.0)	107 (31.4)	
PA < 1 h/d and SB ≥ 2 h/d	89 (13.6)	60 (18.2)	49 (14.4)	

Data were provided as mean ± standard deviation (continuous variables), or n (%) (categorical variables). Significant differences in general characteristics among three groups are highlighted in bold. BMI, body mass index; PA, physical activity; SB, sedentary behaviors.

[a] Data were available from the CPOOA and SPAICO studies; sedentary behaviors included watching television and playing computer and video games.

Table 2 Genotyping information of rs2943650 near *IRS1* in Chinese children.

		All	Sample		
			Normal-weight group	Overweight group	Obese group
rs2943650 (C/T)	EAF (C)	0.082	0.078	0.075	0.093
	Genotype (TT/TC/CC)	2768/493/22	1064/181/7	865/137/7	839/175/8
	HWE *P* value	0.992	0.816	0.539	0.733

EAF, effect allele frequency; HWE, Hardy–Weinberg equilibrium.

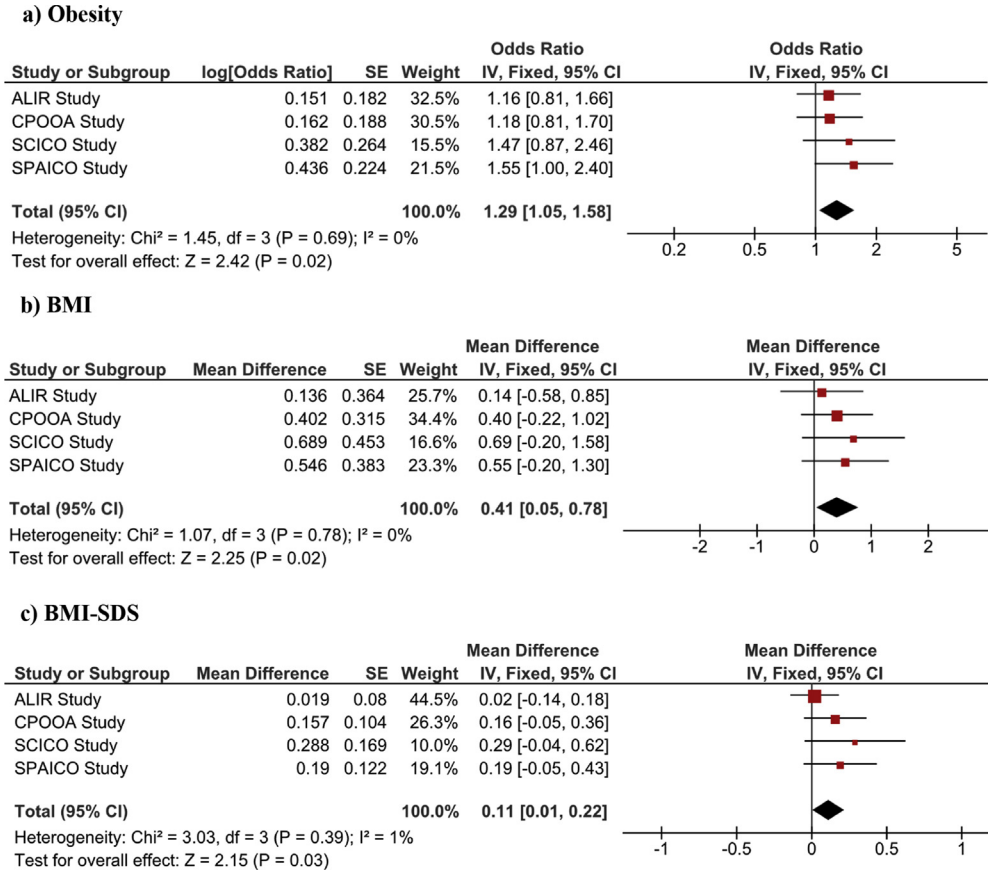

Figure 1 Genetic association of rs2943650 near *IRS1* gene with obesity (a), BMI (b), and BMI-SDS (c) in the meta-analysis. Meta-analyses were conducted by the inverse variance (IV) method using fixed-effects models due to little heterogeneity (I^2 = 0–1%). BMI, body mass index; BMI-SDS, BMI standard deviation score.

obesity among children who participated in physical activity <1 h/d (pooled OR (95% CI) = 1.65 (1.03, 2.65), P = 0.040, heterogeneity: I^2 = 0%). We observed a significant interaction between rs2943650 and physical activity on obesity ($P_{\text{for interaction}}$ = 0.020). In addition, we combined the physical activity and sedentary behaviors and found that the TC + CC genotypes of rs2943650 was significantly associated with a 241% higher risk of obesity than the TT genotype among inactive children (physical activity < 1 h/d and sedentary behaviors ≥ 2 h/d) (pooled OR (95% CI) = 3.41 (1.45, 8.01), P = 0.005, heterogeneity: I^2 = 0%), while no significant association was observed among children who engaged in physical activity ≥ 1 h/d and/or sedentary behaviors < 2 h/d. The interaction was also significant ($P_{\text{for interaction}}$ = 0.005). No such interactions were found for BMI and BMI-SDS.

Sensitivity analyses showed that interactions between rs2943650 and physical activity/sedentary behaviors on obesity remained significant after additional adjustment for socioeconomic, dietary, and lifestyle factors ($P_{\text{for interaction}}$<0.05, Supplementary Table 4).

Discussion

In the present study, we identified that *IRS1* rs2943650 was significantly associated with BMI and risk of obesity among 3303 Chinese children. In addition, we found the association between rs2943650 and childhood obesity was modified by physical activity and sedentary behaviors.

For polymorphisms near *IRS1*, most previous studies focused on its association with type 2 diabetes and other

Table 3 Association of rs2943650 near *IRS1* gene with obesity-related phenotypes in Chinese children.

	Model 1[a]		Model 2[b]	
	β (95% CI)	*P* value	β (95% CI)	*P* value
Waist circumference, cm	1.082 (0.117, 2.046)	**0.028**	0.163 (−0.217, 0.543)	0.400
Hip circumference, cm [c]	0.496 (−0.329, 1.322)	0.238	−0.100 (−0.468, 0.267)	0.592
WHR [c]	0.006 (0.0003, 0.012)	**0.040**	0.003 (−0.001, 0.007)	0.174
WHtR	0.007 (0.001, 0.012)	**0.024**	0.001 (−0.001, 0.004)	0.315
Body fat percentage, % [d]	0.562 (−0.257, 1.382)	0.178	−0.137 (−0.672, 0.399)	0.617
FPG, mmol/l	0.021 (−0.039, 0.082)	0.491	0.026 (−0.034, 0.087)	0.391
Fasting insulin[f], μU/mL [e]	0.011 (−0.022, 0.044)	0.507	−0.004 (−0.034, 0.026)	0.798
HOMA-β[e,f]	0.0004 (−0.022, 0.023)	0.974	−0.010 (−0.030, 0.010)	0.342
HOMA-IR[e,f]	0.013 (−0.020, 0.046)	0.457	−0.002 (−0.032, 0.028)	0.887
QUICKI [e]	−0.001 (−0.006, 0.003)	0.624	0.001 (−0.004, 0.005)	0.761
Total cholesterol, mmol/l[f]	0.002 (−0.005, 0.008)	0.614	0.001 (−0.006, 0.008)	0.808
Triglyceride, mmol/l[f]	−0.007 (−0.024, 0.011)	0.459	−0.013 (−0.029, 0.002)	0.098
LDL-C, mmol/l[f]	−0.001 (−0.012, 0.011)	0.932	−0.004 (−0.015, 0.007)	0.500
HDL-C, mmol/l[f]	−0.007 (−0.017, 0.004)	0.213	−0.004 (−0.014, 0.007)	0.496
SBP, mmHg	−0.417 (−1.603, 0.769)	0.491	−0.998 (−2.044, 0.048)	0.061
DBP, mmHg	0.062 (−1.304, 1.428)	0.929	−0.307 (−1.627, 1.012)	0.648

DBP, diastolic blood pressure; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein−cholesterol; HOMA-β, homeostasis model assessment of pancreatic beta cell function; HOMA-IR, homeostasis model assessment of insulin resistance; LDL-C, low-density lipoprotein−cholesterol; QUICKI, quantitative insulin sensitivity check index; SBP, systolic blood pressure; WHR, waist-to-hip ratio; WHtR, waist-to-height ratio.

$P < 0.05$ (highlighted in bold) was considered as significant.

[a] Model 1 was adjusted for sex, age, and age square under the dominant model.

[b] Model 2 was adjusted for sex, age, age square, and BMI under the dominant model.

[c] Data were available from the ALIR, CPOOA, and SPAICO studies (N = 2845).

[d] Data were available from the CPOOA, SCICO, and SPAICO studies (N = 2364).

[e] Data were available from all children in the ALIR, SCICO, and SPAICO studies and a subgroup in the CPOOA study (N = 2479).

[f] Values of fasting insulin, HOMA-β, HOMA-IR, total cholesterol, triglyceride LDL-C, and HDL-C were log10-transformed.

Table 4 Association of rs2943650 near *IRS1* gene with risk of obesity stratified by physical activity and sedentary behaviors.

	Number of the subgroup (Percentage of obese children)		OR (95% CI)	*P* value	Heterogeneity (I^2)	OR (95% CI)	$P_{\text{for interaction}}$
	TC + CC	TT (ref)					
PA							
≥1 h/d	100 (21.0)	614 (27.5)	0.69 (0.41, 1.16)	0.170	0%	**2.29 (1.14, 4.58)**	**0.020**
<1 h/d	110 (33.6)	546 (22.5)	**1.65 (1.03, 2.65)**	**0.040**	0%		
SB[a]							
<2 h/d	144 (26.4)	842 (24.8)	1.19 (0.35, 4.05)	0.790	88%	1.71 (0.44, 6.62)	0.850
≥2 h/d	73 (37.0)	345 (25.8)	1.71 (0.97, 3.00)	0.060	0%		
PA/SB							
PA ≥ 1 h/d and SB < 2 h/d	64 (17.19)	412 (26.7)	0.57 (0.28, 1.14)	0.11	0%	**1.66 (1.20, 2.30)**	**0.002**
PA ≥ 1 h/d and SB ≥ 2 h/d	34 (29.41)	172 (30.23)	0.97 (0.42, 2.23)	0.94	0%		
PA < 1 h/d and SB < 2 h/d	68 (27.94)	365 (23.56)	1.38 (0.41, 4.64)	0.6	73%		
PA < 1 h/d and SB ≥ 2 h/d	38 (44.7)	161 (19.9)	**3.41 (1.45, 8.01)**	**0.005**	0%		

Effects of rs2943650 on risk of obesity stratified by physical activity and sedentary behaviors were analyzed by using logistic regression under the dominant model, adjusted for sex, age, and age square in the CPOOA study and SPAICO study. The results of the two studies were pooled with meta-analysis using fixed-effects models (I^2<70%) or random effects models (I^2>70%). Significant associations are highlighted in bold. CI, confidence interval; OR, odds ratios; PA, physical activity; SB, sedentary behaviors.

[a] Sedentary behaviors include watching television and playing computer and video games.

metabolic syndrome-related traits [34–36]. It is not until recently genetic polymorphisms near *IRS1* were identified to be associated with adiposity. In 2011, a large-scale meta-analysis of GWAS conducted by Kilpelainen and colleagues identified that rs2943650 was associated with body fat percentage [4]. In 2016, Lu et al. [4] confirmed that rs2943652 (in high LD with rs2943650 (r^2 = 1.0)) was associated with BMI and body fat percentage. Qi et al. [37] also found that rs2943650 was significantly associated with body fat percentage in U.S. Hispanics/Latinos. However, most of the previous studies were restricted to European and adult populations, and limited information regarding the association of *IRS1* rs2943650 with obesity and other obesity-related traits is available in children. Therefore, our study for the first time reported that the *IRS1* rs2943650 was associated with BMI and obesity among Chinese children. Studies have demonstrated that the effects of genetic variants in children are different from

those in adults, as children tend to have higher BMI or obesity heritability than adults [30]. Our study thus provides more evidence for the effects of *IRS1* rs2943650 on obesity in a Han Chinese population and at a younger age.

The findings of our study and previous studies that *IRS1* variants are associated with various metabolic traits are in line with the biological function of IRS1, which plays an important part in the insulin signaling pathway [1,2]. Inhibition of IRS1 inactivates PI3K, disrupts nutrient homeostasis, and prolongs activation of mitogen-activated protein kinases (MAPKs), hence promoting mitogenesis and overgrowth, resulting in obesity [3].

Another interesting finding of the GWAS by Kilpelainen et al. [4] was that the adiposity-decreasing allele was associated with an impaired metabolic profile. Qi et al. [37] later confirmed the finding in U.S. Hispanics/Latinos. However, these findings were not replicated in our study. We did not observe significant associations between *IRS1* rs2943650 and metabolic traits in children in the present study. The reasons might be as follows. First, children with obesity-related comorbidities such as diabetes were excluded from the present study. The effect sizes of *IRS1* rs2943650 on these metabolic traits were likely to be small in our study population, which, therefore, might be difficult to be detected with our limited sample. Second, both studies of Kilpelainen et al. [4] and Qi et al. [37] were conducted in adults. It is well acknowledged that children's development and metabolic processes are somewhat different from those of adults. Thus, genetic variants in the *IRS1* gene probably did not sufficiently lead to impaired metabolic profiles in children, which may partly account for the inconsistent findings between our study and previous studies. Another possible reason might be due to ethnic difference for effect of *IRS1* rs2943650 on obesity and other metabolic-related phenotypes between Chinese and European population. Our study demonstrated the value of conducting genetic epidemiology studies in populations with different ethnicity.

Previous studies have already reported that polymorphisms near *IRS1* and physical activity interacted on type 2 diabetes and postmenopausal colorectal cancer risk [14,15]. In the present study, we further examined the associations of *IRS1* rs2943650 with the risk of childhood obesity stratified by physical activity and sedentary behaviors. Additionally, we found that *IRS1* rs2943650 was significantly associated with childhood obesity among inactive children (physical activity $<$ 1 h/d and sedentary behaviors $\geq$ 2 h/d), while it was not associated with obesity among active children, suggesting that physical activity can attenuate the effects of *IRS1* rs2943650 on childhood obesity. Studies have shown that physical activity might interact with genetic variants and attenuate their effects on risk of obesity among children [9,38,39]. It is explained that physical activity may downregulate gene expression in fatty acid synthesis and reduce lipogenesis, therefore weakening the effects of obesity-related genes [9,38]. Our findings were also in line with evidence from experimental studies [13]. Kirwan and colleagues [13] found that regular exercise led to enhanced insulin-stimulated IRS-1-associated PI3-kinase activation in human skeletal muscle, resulting in greater insulin-mediated glucose uptake. Therefore, more blood glucose was synthesized into glycogen in skeletal muscles, while less glucose was transformed into fat. This might explain the reason why physical activity can attenuate the influence of rs2943650 near *IRS1* on the development of obesity. However, the precise mechanisms underlying the finding that physical activity attenuated the association between the *IRS1* polymorphism and childhood obesity remain unclear, and more studies are needed to confirm this.

The public health significance of our findings is that the effect of *IRS1* rs2943650 on childhood obesity may be, at least partly, offset by more physical activity and less sedentary behavior in Chinese children. Therefore, the present study strengthens the basis for recommending children engage in more physical activity (at least 60 min per day) and less sedentary behaviors (up to 120 min every day) as a preventive measure to reduce the risk of obesity.

Strengths and limitations

To the best of our knowledge, this is the first study to assess the association of *IRS1* rs2943650 with childhood obesity, and assess gene−physical activity interactions on the risk of obesity in Chinese children. Our findings may provide more evidence for the development and implementation of effective intervention strategies of obesity based on genetic background.

However, several limitations of this study should be mentioned. First, the data of physical activity and sedentary behaviors in our study were acquired through self-reported questionnaire, which might be less precise than the objective instruments such as accelerometer. However, the questionnaire has been validated and shown to perform well in determining different physical activity levels in our previous studies [9,26]. Second, although we adjusted for several major socioeconomic, dietary, and lifestyle factors, the other potential confounding factors including emotional/mental stresses from schoolwork/friends, family support, etc., still existed. Third, the present study design did not permit us to make conclusions about causal relationship among the rs2943650, physical activity, sedentary behaviors, and childhood obesity. The insufficient latent period between physical activity/sedentary behaviors and obesity could not be enough to justify a potential temporal association.

In summary, we found *IRS1* rs2943650 was significantly associated with BMI and risk of obesity among 3303 Chinese children aged 6−18 years old. Additionally, we also found significant interaction between *IRS1* rs2943650 polymorphism and physical activity/sedentary behaviors on childhood obesity. The risk of obesity was higher for the rs2943650 C-allele carriers among inactive children (physical activity$<$1 h/d and sedentary behaviors $\geq$ 2 h/d) than among active children (physical activity $\geq$ 1 h/d or sedentary behaviors $<$ 2 h/d). Our study would provide

novel insights into the function of the *IRS1* gene and might be useful for personalized treatment of obesity in the future.

Conflicts of interest

The authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.numecd.2019.05.058.

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