ORIGINAL ARTICLE

Interaction between SIRT-1 polymorphism and life-style on anthropometric and biochemical parameters in obese phenotypes

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ABSTRACT

Background and Objective: Sirtuin 1 (SIRT1) is nicotinamide adenine dinucleotide-dependent histone deacetylase. It plays a crucial role in the regulation of fat and glucose metabolism by influencing proteins involved in nutrient sensing and energy regulation. This study examined the effects of the interaction between the *SIRT1* rs7069102 variant and lifestyle factors on obesity-associated anthropometric and metabolic phenotypes in the local population of Pakistan.

Methods: The study population incorporated 612 participants comprising an equal number of individuals having both normal body mass index and those who were overweight/obese. Anthropometric indices were assessed by employing standard protocols of corresponding body measurements while metabolic variables were determined by conducting relevant biochemical assays. The data related to lifestyle factors was collected by developing a standard questionnaire. Genotyping of rs7069102 was done by performing a TaqMan allelic discrimination assay. The data were analyzed by means of Statistical Package for the Social Sciences software by performing regression analyses adjusted for relevant confounders and corrected for multiple comparisons.

Results: The data analyses revealed that the interaction of *SIRT1* rs7069102 with low physical activity (LPA) and also with irregular sleep-wake cycle (SWC) influenced many anthropometric and metabolic indices such as weight, waist circumference, hip circumference, percent body fat, skinfold thicknesses (triceps, supra-iliac, sub-scapular, abdominal, biceps, and thigh), homeostatic model assessment for insulin resistance, fasting insulin, visceral adiposity index, lipid accumulation product and triglycerides ($p < 0.05$).

Conclusion: In conclusion, the interplay of the *SIRT1* rs7069102 with LPA and also with irregular SWC may have a considerable impact on adiposity-associated anthropometric and metabolic outcomes in the local population of Pakistan.

Keywords: *SIRT1*, rs7069102, gene-behavior interaction, obese, anthropometry, body mass index.

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Introduction

Sirtuin 1 (SIRT1) protein is the most conserved mammalian nicotinamide adenine dinucleotide (NAD+) dependent histone deacetylase.[1] It is encoded by the *SIRT1* gene that is 33.7 kb in size and is positioned on the genome at 10q21.3. SIRT1 is expressed in a variety of tissues including the brain, heart, kidney, endothelial tissue, pancreas, spleen, liver, skeletal muscle, and adipose tissue.[2] It modifies various proteins including those involved in nutrient sensing and control of energy balance.[3] Thus, it plays a crucial role in the regulation of fat and glucose metabolism by promoting lipolysis in white adipose tissue (WAT) while stimulating both differentiation and activation of brown adipose tissue along with browning of WAT. Thereby, it prevents excessive lipid accumulation in skeletal muscle and liver, controlling inflammation, and supporting insulin secretion and sensitivity.[4] Dysregulation of these physiological processes has major repercussions in the manifestation of obesity and related metabolic disorders. A number of metabolic disorders such as liver steatosis, diabetes, and obesity are linked with defects in SIRT1 pathways.[5,6] Observational studies have largely suggested a possible association of sirtuins with obesity and obesity-linked pathological disorders in humans.[7-10] Low NAD(+)/SIRT pathway expression is associated with obesity in subcutaneous adipose tissue of body mass index (BMI)-discordant monozygotic twins, emphasizing a strong link of reduced SIRTs expression with inflammation, insulin resistance, and

impaired mitochondrial homeostasis.[11] Thus, any change in the *SIRT1* gene sequence that affects its expression or activity may lead to metabolic anomalies including obesity. In general, the manifestation of obesity is attributable to the interaction between multiple factors particularly the interaction between the genetic and the environment/behavior/lifestyle factors.[12] The worldwide prevalence of obesity has already reached pandemic proportions with Pakistan representing the world's ninth most obese nation.[13] In addition, the Pakistani population has some unique features that make it ideal for studying various pathophysiological aspects of obesity.[14] In view of the above-mentioned information, the present study aimed to explore the effects of the gene–lifestyle interaction between the *SIRT1* rs7069102 and lifestyle factors (*SIRT1* rs7069102 × lifestyle) on obesity-associated anthropometric and metabolic phenotypes among individuals living in Karachi, the largest city of Pakistan.

Methods

Study framework and ethical approval

The present study is a population-based cross-sectional study based on a case-control design. It involves 612 participants (12 to 63 years old) randomly selected from the general population of Karachi. This research was conducted at the University of Karachi, Pakistan, in the International Center for Chemical and Biological Sciences. The study protocol was approved by the institute's Independent Ethics Committee and the advanced studies and research board. The written informed consent was signed by all the participants or their guardians before their involvement in the study.

The World Health Organization's BMI cut-off values (≥18.5 kg/m^2 for normal BMI, ≥25 kg/m^2 for overweight, and ≥30 kg/m^2 for obesity) were employed as inclusion criteria for the enrollment of study participants over 20 years of age. The Center for Disease Control and Prevention's BMI growth charts (5 to 84 th percentile for normal BMI, 85 to 94 th percentile for overweight, and 95 th percentile or above for obesity) were employed as inclusion criteria for participants ≤20 years of age.

Subjects with a history of medication or any endocrine disease that may cause weight gain were excluded.

After an overnight fast (8-12 hours), a blood sample (5 ml) was drawn from each participant. A blood volume of 2 ml was collected in an Ethylenediamine tetraacetic acid (EDTA)-coated vacutainer tube (purple top, BD, USA), while a 3 ml volume of blood was taken in a separate vacutainer tube (yellow top, BD, USA) containing gel and clot activator for subsequent DNA extraction and serum isolation, respectively.

DNA was isolated from blood samples by spin column method using a commercial blood genomic DNA purification kit (Cat. No. 51306, Qiagen, Germany). The quality of extracted DNA was evaluated on a horizontal gel electrophoresis (Thermo Scientific, MA, USA) and quantity was measured by a NanoDrop spectrophotometer (Thermo Scientific, USA).

Genotyping of the genetic variant SIRT1 rs7069102

TaqMan® predesigned single nucleotide polymorphism (SNP) genotyping assay (Assay ID C___1340389_10, Cat No. 4351379, Applied Biosystems Thermo Fisher Scientific Inc., USA) and TaqMan® Genotyping Master Mix (Cat No. 4381657, Applied Biosystems Thermo Fisher Scientific Inc., USA) were used to genotype the variant *SIRT1* rs7069102 on an Applied Biosystems QuantStudio 5 real-time polymerase chain reaction (PCR) machine (Thermofisher Scientific, USA). The steps of PCR for allelic discrimination involved an initial stage of polymerase activation at 95°C for 10 minutes. Then, 40 cycles of two steps involving denaturation at 95°C for 15 seconds and annealing and extension at 60°C for 1 minute. With 99% genotypic call rates, successful genotyping was achieved. Following each run, post-amplification analysis was carried out using the Applied Biosystems QuantStudio™ design and analysis software v1.5.1. Two negative controls (No Template Control) and one positive control for each genotype were included in each batch. Of note, 20% of the samples were repeated for genotyping to ensure reproducibility.

Estimations of anthropometric indices

Standard protocols for taking relevant body measurements were employed to calculate the required anthropometric indices. For instance, weight and height were measured by a stadiometer (Seca 214, Germany) and a mechanical column scale (Seca 755), respectively. The measurements of skinfold thicknesses (SFTs) at six distinct body regions (belly, sub-scapula, supra-ilium, thigh, biceps, and triceps) were taken by using a skinfold caliper (Slim Guide, USA). The measurements regarding waist and hip circumferences (HC) were taken via a nonstretchable measuring tape. From these anthropometric measurements, BMI, percent body fat (%BF), waist-to-hip ratio (WHR), and waist-to-height ratio (WHtR) were computed by corresponding formulae using the above-mentioned relevant measurements. A person's BMI was calculated by dividing his or her weight (kg) by the square of his or her height (m^2). Gender-specific formulae were employed to calculate %BF by computing the values of skinfold measurements regarding the abdomen, supra-ilium, thigh, and triceps.

%BF = (0.29669) × (4 skin folds sum) - (0.00043) × (4 skin folds sum)^2 + 0.02963 × (age) + 1.4072 (females)

%BF = (0.29288) × (4 skin folds sum) - (0.0005) × (4 skin folds sum)^2 + 0.15845 × (age) -5.76377 (males).[15] WHtR and WHR were calculated by dividing the waist circumference (WC) by height and HC, respectively.

Estimations of metabolic indices

Fasting blood glucose and insulin levels were estimated by a blood glucose monitoring system (Abbott, UK) and a commercial enzyme-linked immunosorbent assay kit (DIA source INSEASIA Kit, Cat No. KAP1251, Belgium), respectively, on a Multiskan™ FC Microplate Photometer (ThermoFisher Scientific, USA). Calculation of homeostasis model assessment of insulin resistance (HOMA-IR) was done by computing the values of fasting blood glucose and insulin levels in a specific formula, i.e., HOMA-IR = Fasting insulin (µl U/ml) × Fasting glucose (mg/dl)/405.[16] Systolic and diastolic blood pressures were measured twice using a mercury sphygmomanometer (Certeza medical CR-2001). Enzymatic *in vitro* test kits (Merck, Darmstadt, Germany) were utilized to determine the levels of fasting total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and triglycerides (TGs) on a Roche Hitachi chemical analyzer. Very low-density lipoprotein cholesterol (VLDL-C) was calculated as TG/5. The value of total cholesterol levels was divided by the value of HDL-C levels to determine the cholesterol-to-HDL-C ratio (CHR). Similarly, the values of specific anthropometric and metabolic estimations were computed to determine visceral adiposity index (VAI) (mmol/l), lipid accumulation product (LAP) (mmol/l), the product of triglyceride and glucose (TyG) index, and triglyceride-to-HDL-C ratio Gender-specific formulae were employed to determine the VAI and LAP. VAI (males) = [WC÷39.68 + (1.88 × BMI)] × [TG÷1.03] × [1.31÷ HDL-C]. VAI (females) = [WC÷36.58 + (1.89 × BMI] × [TG÷0.81] × [1.52÷ HDL-C]. LAP (males) = (WC-65) × TG. LAP (females) = (WC-58) × TG.[17,18] The TyG index was calculated for both sexes using the formula [Fasting triglycerides (mg/dl) × fasting glucose (mg/dl) ÷ 2].[19]

Collection of lifestyle data

Lifestyle data were collected by devising a standard questionnaire. Eating pattern (specific/random), diet consciousness (yes/no), preference for fat-dense meals (low/moderate/high), sleep-wake cycle (SWC) (regular/irregular), physical activity (low/moderate/high), shiftwork (yes/no), and sleep duration (adequate/inadequate) encompassed the lifestyle parameters considered in this study.

Statistical analysis

Data analyses were accomplished by employing the Statistical Package for the Social Sciences software (Version 21.0). The effects of interaction between the rs7069102 and lifestyle factors on anthropometric and metabolic traits were known by applying linear regression along with the additive genetic model. The possible covariates such as age and gender (also BMI in case of analyzing obesity-related metabolic traits) were adjusted while analyzing the data. The correction for multiple comparisons was made by applying the Benjamini–Hochberg method for controlling the false discovery rate. The $p < 0.05$ was considered statistically significant.

Results

Conformity to Hardy–Weinberg equilibrium

For both cases and controls the genotypic distribution of the *SIRT1* rs7069102 was observed in compliance with Hardy–Weinberg equilibrium ($p > 0.05$).

SIRT1 rs7069102 × irregular SWC increased anthropometric indices

A significant impact of the interaction between the *SIRT1*rs7069102 and irregular SWC was observed on obesity-related anthropometric variables. For instance, this interaction significantly increased many anthropometric indices including WC, %BF, weight, triceps, supra-iliac SFT, sub-scapular SFT, and abdominal SFT ($p < 0.05$) as shown in Table 1. All these interactions sustained significance even after adjusting for covariates and correction for multiple comparisons (Table 1).

SIRT1 rs7069102 × low physical activity (LPA) augmented anthropometric indices

The interaction between the rs7069102 and LPA was seen to significantly influence anthropometric parameters. This interaction significantly augmented the anthropometric parameters such as weight, biceps SFT, triceps SFT, abdominal SFT, supra-iliac SFT, thigh SFT, sub-scapular SFT, %BF, HC, and WC ($p < 0.05$). All these interactions remained significant after adjusting for confounders and correction for multiple comparisons (Table 1).

SIRT1 rs7069102 × irregular SWC enhanced metabolic indices

The interaction of the *SIRT1* rs7069102 with irregular SWC was observed to affect two obesity-associated metabolic variables namely fasting insulin and HOMA-IR (Table 2). This interaction significantly enhanced the fasting insulin and HOMA-IR ($p < 0.05$). The interactions persisted after adjustment of confounding factors and correction for multiple comparisons.

SIRT1 rs7069102 × LPA escalated metabolic indices

SIRT1 rs7069102 interacted with LPA to influence obesity-associated metabolic indices such as VAI, LAP, and TG. All these metabolic indices were significantly escalated by the SIRT1 rs7069102 × LPA interaction ($p < 0.05$) as presented in Table 2.

Table 1. *Interactive effects of the SIRT1 rs7069102 and behavioral factors on obesity-related anthropometric phenotypes.*

Behavioral factors	β	95% CI	p-value	p-value corrected	β	95% CI	p-value	p-value corrected
		Unadjusted				Age- and gender-adjusted		
BMI								
REP	0.123	-0.343-0.589	0.603	0.5194	0.076	-0.382-0.533	0.746	0.677
DUC	-0.138	-0.573-0.296	0.532	0.4965	-0.222	-0.650-0.206	0.309	0.381
M-H TFDF	0.127	-0.325-0.580	0.581	0.5191	0.080	-0.365-0.524	0.725	0.677
IS	0.663	-0.155-1.481	0.112	0.151	0.430	-0.385-1.245	0.300	0.381
Irregular SWC	0.970	0.143-1.797	0.022	0.0916	0.926	0.107-1.744	0.027	0.113
Shift work	0.299	-0.357-0.955	0.371	0.3623	0.085	-0.570-0.739	0.799	0.699
LPA	1.246	0.349-2.143	0.007	0.042	1.092	0.200-1.985	0.017	0.102
WC								
REP	0.879	-0.305-2.063	0.145	0.190	0.752	-0.410-1.914	0.204	0.285
DUC	0.735	-0.370-1.840	0.192	0.217	0.473	-0.615-1.561	0.394	0.435
M-H TFDF	1.180	0.032-2.328	0.044	0.1232	1.075	-0.051-2.201	0.061	0.220
IS	2.455	0.378-4.532	0.021	0.0916	1.666	-0.401-3.734	0.114	0.299
Irregular SWC	3.519	1.423-5.615	0.001	0.008	3.169	1.096-5.242	0.003	**0.021**
Shift work	2.135	0.473-3.797	0.012	0.063	1.453	-0.206-3.111	0.086	0.277
LPA	4.832	2.568-7.096	0.000	<0.001	4.180	1.925-6.434	0.000	**<0.001**
HC								
REP	0.639	-0.274-1.551	0.170	0.21	0.574	-0.331-1.478	0.213	0.288
DUC	0.224	-0.628-1.076	0.606	0.5194	0.133	-0.714-0.981	0.758	0.677
M-H TFDF	0.781	-0.105-1.666	0.084	0.1306	0.708	-0.170-1.586	0.114	0.299
IS	1.374	-0.230-2.978	0.093	0.1346	1.144	-0.466-2.754	0.163	0.238
Irregular SWC	1.814	0.191-3.437	0.029	0.0936	1.863	0.244-3.482	0.024	0.112
Shift work	1.197	-0.087-2.480	0.068	0.1785	0.991	-0.301-2.284	0.132	0.213
LPA	3.275	1.525-5.026	0.000	<0.001	3.221	1.466-4.977	0.000	**<0.001**
WHR								
REP	0.001	-0.004-0.006	0.709	0.5955	0.000	-0.005-0.006	0.871	0.746
DUC	0.001	-0.003-0.006	0.557	0.5085	0.000	-0.005-0.005	0.916	0.769
M-H TFDF	0.003	-0.002-0.008	0.258	0.2851	0.002	-0.003-0.007	0.331	0.386
IS	0.005	-0.004-0.014	0.267	0.287	0.001	-0.008-0.011	0.752	0.677
Irregular SWC	0.010	0.001-0.020	0.028	0.093	0.009	0.000-0.018	0.063	0.220
Shift work	0.005	-0.002-0.013	0.175	0.21	0.002	-0.006-0.009	0.620	0.605
LPA	0.012	0.002-0.022	0.024	0.0916	0.008	-0.002-0.018	0.103	0.299
WHtR								
REP	0.016	-0.006-0.037	0.164	0.208	0.013	-0.008-0.035	0.226	0.296
DUC	0.009	-0.011-0.030	0.362	0.362	0.006	-0.013-0.026	0.527	0.539
M-H TFDF	0.018	-0.003-0.039	0.090	0.134	0.015	-0.005-0.036	0.140	0.217
IS	0.034	-0.004-0.073	0.077	0.124	0.027	-0.011-0.064	0.165	0.238
Irregular SWC	0.041	0.002-0.079	0.040	0.12	0.043	0.006-0.081	0.024	0.112
Shift work	0.021	-0.010-0.051	0.185	0.215	0.013	-0.017-0.043	0.389	0.435
LPA	0.080	0.038-0.121	0.000	<0.001	0.078	0.038-0.119	0.000	**<0.001**
%BF								
REP	0.289	-0.341-0.920	0.368	0.362	0.230	-0.385-0.845	0.463	0.498
DUC	0.079	-0.509-0.668	0.791	0.651	0.014	-0.562-0.590	0.963	0.793
M-H TFDF	0.254	-0.358-0.867	0.415	0.396	0.179	-0.418-0.776	0.556	0.556

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Behavioral factors	β	95% CI		p-value	p-value corrected	β	95% CI		p-value	p-value corrected
		Unadjusted					Age- and gender-adjusted			
IS	0.899	-0.209-2.006		0.112	0.151	0.558	-0.542-1.658		0.320	0.384
Irregular SWC	1.590	0.473-2.708		0.005	0.035	1.726	0.630-2.822		0.002	**0.016**
Shift work	0.463	-0.425-1.351		0.306	0.321	0.312	-0.567-1.191		0.486	0.510
LPA	1.983	0.772-3.195		0.001	0.008	2.013	0.818-3.207		0.001	**0.01**
					WEIGHT					
REP	0.719	-0.638	2.076	0.298	0.370	0.699	-0.601	2.000	0.291	0.32
DUC	0.329	-0.937	1.596	0.610	0.569	0.009	-1.209	1.227	0.988	0.85
M-H TFDF	0.523	-0.796	1.841	0.437	0.437	0.556	-0.707	1.820	0.388	0.381
IS	2.952	0.574	5.329	0.015	0.052	1.921	-0.383	4.225	0.102	0.168
Irregular SWC	4.306	1.908	6.703	0.000	0.000	3.411	1.092	5.731	0.004	**0.024**
Shift work	2.153	0.247	4.058	0.027	0.054	1.246	-0.605	3.098	0.187	0.275
LPA	5.074	2.475	7.673	0.000	<0.001	3.741	1.210	6.272	0.004	**0.024**
HEIGHT										
REP	0.303	-0.413	1.020	0.406	0.421	0.309	-0.292	0.911	0.313	0.337
DUC	0.286	-0.382	0.954	0.400	0.421	0.130	-0.433	0.693	0.651	0.588
M-H TFDF	0.040	-0.656	0.736	0.910	0.796	0.140	-0.445	0.725	0.639	0.58
IS	0.944	-0.315	2.202	0.141	0.202	0.330	-0.738	1.398	0.544	0.516
Irregular SWC	1.677	0.406	2.948	0.010	0.037	0.706	-0.374	1.785	0.200	0.282
Shift work	0.950	-0.057	1.957	0.064	0.099	0.469	-0.388	1.326	0.283	0.323
LPA	0.369	-1.018	1.757	0.601	0.569	-0.647	-1.825	0.531	0.281	0.323
BICEPS SFT										
REP	0.289	-0.272	0.851	0.312	0.372	0.286	-0.236	0.809	0.282	0.323
DUC	-0.001	-0.525	0.523	0.998	0.859	0.085	-0.404	0.575	0.732	0.640
M-H TFDF	0.374	-0.171	0.919	0.178	0.243	0.322	-0.186	0.829	0.213	0.284
IS	0.087	-0.901	1.075	0.863	0.767	0.430	-0.497	1.357	0.363	0.367
Irregular SWC	0.437	-0.564	1.438	0.392	0.421	0.973	0.037	1.908	0.042	0.084
Shift work	0.145	-0.647	0.936	0.720	0.660	0.422	-0.323	1.166	0.266	0.323
LPA	1.125	0.041	2.209	0.042	0.075	1.7030	0.688	2.718	0.001	**0.01**
TRICEPS SFT										
REP	0.449	-0.307	1.204	0.244	0.325	0.444	-0.300	1.189	0.242	0.315
DUC	0.186	-0.520	0.892	0.605	0.569	0.226	-0.471	0.923	0.525	0.506
M-H TFDF	0.377	-0.357	1.111	0.313	0.372	0.338	-0.386	1.061	0.359	0.367
IS	0.569	-0.761	1.899	0.401	0.421	0.751	-0.570	2.072	0.265	0.32
Irregular SWC	1.495	0.151	2.839	0.029	0.056	1.853	0.524	3.182	0.006	**0.030**
Shift work	0.540	-0.525	1.605	0.320	0.373	0.682	-0.379	1.742	0.207	0.2827
LPA	2.266	0.812	3.720	0.002	0.011	2.626	1.181	4.070	0.000	**<0.001**
ABDOMINAL SFT										
REP	1.098	0.000	2.196	0.050	0.087	1.071	-0.002	2.143	0.050	0.0933
DUC	1.254	0.231	2.276	0.016	0.034	1.041	0.037	2.044	0.042	0.084
M-H TFDF	1.222	0.157	2.287	0.025	0.051	1.175	0.134	2.216	0.027	0.1008
IS	2.724	0.799	4.650	0.006	0.030	2.112	0.211	4.014	0.030	0.105
Irregular SWC	3.173	1.225	5.121	0.001	0.009	3.008	1.092	4.923	0.002	**0.01**
Shift work	2.462	0.922	4.001	0.002	0.011	1.890	0.365	3.416	0.015	0.0646
LPA	4.037	1.929	6.146	0.000	<0.001	3.399	1.310	5.488	0.001	**0.01**

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Behavioral factors	β	95% CI		p-value	p-value corrected	β	95% CI		p-value	p-value corrected
		Unadjusted					Age- and gender-adjusted			
SUPRA-ILIAC SFT										
REP	0.952	-0.032	1.937	0.058	0.095	0.933	-0.007	1.874	0.052	0.093
DUC	0.891	-0.027	1.809	0.057	0.095	0.639	-0.242	1.521	0.155	0.241
M-H TFDF	0.905	-0.051	1.861	0.063	0.099	0.917	0.004	1.831	0.049	0.093
IS	2.390	0.664	4.116	0.007	0.032	1.584	-0.085	3.254	0.063	0.106
Irregular SWC	3.003	1.259	4.747	0.001	0.009	2.377	0.694	4.060	0.006	**0.03**
Shift work	2.171	0.791	3.551	0.002	0.011	1.463	0.124	2.802	0.032	0.068
LPA	3.867	1.980	5.754	0.000	<0.001	2.852	1.019	4.686	0.002	**0.01**
THIGH SFT										
REP	0.555	-0.660	1.771	0.370	0.414	0.551	-0.647	1.749	0.367	0.367
DUC	0.162	-0.972	1.296	0.779	0.703	0.242	-0.879	1.364	0.671	0.596
M-H TFDF	0.341	-0.840	1.521	0.571	0.560	0.284	-0.880	1.448	0.632	0.586
IS	1.026	-1.111	3.163	0.346	0.395	1.369	-0.755	3.494	0.206	0.282
Irregular SWC	1.868	-0.295	4.031	0.090	0.136	2.435	0.293	4.578	0.026	0.100
Shift work	0.694	-1.018	2.406	0.426	0.433	0.965	-0.741	2.672	0.267	0.323
LPA	3.679	1.343	6.015	0.002	0.011	4.304	1.982	6.627	0.000	**<0.001**
SUB-SCAPULAR SFT										
REP	0.530	-0.238	1.299	0.176	0.243	0.521	-0.237	1.279	0.178	0.26
DUC	0.405	-0.312	1.123	0.267	0.347	0.370	-0.340	1.079	0.306	0.336
M-H TFDF	0.624	-0.122	1.370	0.101	0.148	0.581	-0.155	1.316	0.122	0.195
IS	0.719	-0.633	2.071	0.297	0.370	0.660	-0.686	2.005	0.336	0.355
Irregular SWC	1.849	0.486	3.213	0.008	0.034	2.074	0.723	3.426	0.003	**0.02**
Shift work	1.124	0.042	2.205	0.042	0.075	1.050	-0.029	2.129	0.056	**0**.098
LPA	1.956	0.475	3.438	0.010	0.037	2.007	0.529	3.484	0.008	**0.03**

Interactive effects of the *SIRT1* rs7069102 and behavioral traits on anthropometric traits were determined by linear regression. The *β* and 95% CI were estimated to seek the extent of the interaction effect. The correction for multiple comparisons was performed by the Benjamini-Hochberg method of false discovery rate (FDR) control. Statistically significant *p*-value after correction for multiple comparisons is shown in **bold**. Abbreviations: *β*, the effect size for the interaction term; CI, confidence interval; REP, random eating pattern; DUC, diet unconsciousness; M-HTFDF, the moderate-to-high tendency toward fat-dense food; IS, inadequate sleep; SWC, sleep-wake cycle; LPA, low physical activity; BMI, body mass index; WC, waist circumference; HC, hip Circumference; WHR, waist-to hip-ratio; WHtR, waist-to-height ratio; %BF, body fat percentage.

Table 2. *Interactive effects of the SIRT1 rs7069102 and behavioral factors on obesity-related metabolic phenotypes.*

Behavioral factors	β	95% CI		p-value	p-value corrected	β	95% CI		p-value	p-value corrected
		Unadjusted					Age- gender and BMI adjusted			
SBP (mmHg)										
REP	0.256	-0.651-1.163		0.579	0.646	0.240	-0.618-1.098		0.583	0.687
DUC	0.540	-0.305-1.385		0.210	0.316	0.295	-0.507-1.098		0.470	0.619
M-H TFDF	0.216	-0.664-1.097		0.630	0.69	0.237	-0.596-1.070		0.577	0.687
IS	2.074	0.487-3.660		0.011	0.08	1.281	-0.238-2.800		0.098	0.239
Irregular SWC	2.013	0.404-3.622		0.014	0.09	1.337	-0.199-2.873		0.088	0.225
Shift work	1.519	0.247-2.791		0.019	0.066	0.818	-0.403-2.039		0.189	0.353
LPA	1.857	0.107-3.607		0.038	0.105	0.799	-0.880-2.478		0.350	0.532
DBP (mmHg)										
REP	0.261	-0.386-0.908		0.428	0.535	0.253	-0.379-0.885		0.432	0.585
DUC	0.340	-0.263-0.943		0.269	0.376	0.217	-0.374-0.808		0.472	0.619

(Continued)

Behavioral factors	β	95% CI	p-value	p-value corrected	β	95% CI	p-value	p-value corrected
		Unadjusted				Age- gender and BMI adjusted		
M-H TFDF	0.401	-0.226-1.029	0.210	0.3165	0.407	-0.206-1.020	0.192	0.353
IS	1.282	0.148-2.416	0.027	0.081	0.889	-0.231-2.009	0.119	0.271
Irregular SWC	1.313	0.164-2.463	0.025	0.079	1.01	-0.119-2.144	0.080	0.215
Shift work	0.914	0.005-1.824	0.049	0.122	0.568	-0.332-1.468	0.216	0.383
LPA	0.462	-0.791-1.715	0.469	0.691	-0.060	-1.298-1.178	0.924	0.866
VAI (mmol l^{-1})								
REP	0.123	-0.009-0.255	0.068	0.148	0.120	-0.009-0.250	0.069	0.215
DUC	0.115	-0.008-0.238	0.067	0.148	0.105	-0.017-0.226	0.091	0.227
M-H TFDF	0.154	0.026-0.282	0.019	0.066	0.145	0.019-0.270	0.024	0.21
IS	0.264	0.031-0.496	0.026	0.080	0.243	0.013-0.472	0.038	0.15
Irregular SWC	0.194	-0.042-.0430	0.107	0.1904	0.231	-0.002-0.463	0.052	0.182
Shift work	0.245	0.059-0.431	0.010	0.0807	0.221	0.037-0.406	0.019	0.181
LPA	0.395	0.140-0.649	0.001	0.002	0.393	0.140-0.645	0.002	**0.016**
LAP mmol l^{-1})								
REP	1.247	-1.437-3.932	0.362	0.479	1.179	-1.443-3.800	0.378	0.536
DUC	1.251	-1.252-3.754	0.327	0.451	0.792	-1.661-3.245	0.526	0.657
M-H TFDF	1.660	-0.945-4.265	0.211	0.316	1.500	-1.045-4.045	0.248	0.413
IS	4.462	-0.248-9.173	0.063	0.146	3.218	-1.429-7.865	0.174	0.334
Irregular SWC	5.954	1.189-10.71	0.014	0.091	5.973	1.290-10.65	0.013	0.151
Shift work	4.589	0.824-8.355	0.017	0.066	3.393	-0.334-7.120	0.074	0.215
LPA	11.953	6.840-17.065	0.000	<0.001	10.910	5.847-15.97	0.000	**<0.001**
TyG								
REP	-0.005	-0.044-0.034	0.813	0.8208	-0.005	-0.044-0.033	0.780	0.799
DUC	0.002	-0.034-0.039	0.903	0.8619	-0.005	-0.041-0.031	0.780	0.799
M-H TFDF	-0.004	-0.042-0.034	0.850	0.838	-0.004	-0.042-0.033	0.815	0.799
IS	0.023	-0.045-0.092	0.506	0.595	0.001	-0.067-0.069	0.983	0.908
Irregular SWC	0.032	-0.037-0.102	0.362	0.479	0.021	-0.048-0.089	0.554	0.684
Shift work	0.032	-0.023-0.086	0.259	0.372	0.011	-0.044-0.066	0.692	0.781
LPA	0.108	0.033-0.183	0.001	0.002	0.083	0.009-0.158	0.029	0.229
FBG (mgdL^{-1})								
REP	0.030	-1.264-1.323	0.964	0.8878	0.011	-1.256-1.279	0.986	0.908
DUC	-0.450	-1.655-0.756	0.464	0.5691	-0.472	-1.657-0.713	0.435	0.585
M-H TFDF	-0.106	-1.362-1.150	0.869	0.8448	-0.196	-1.427-1.035	0.755	0.799
IS	-0.213	-2.488-2.062	0.854	0.8380	-0.172	-2.421-2.077	0.881	0.848
Irregular SWC	0.521	-1.785-2.827	0.657	0.6968	1.053	-1.220-3.326	0.363	0.536
Shift work	-0.570	-2.392-1.251	0.539	0.6151	-0.604	-2.409-1.202	0.512	0.647
LPA	2.291	-0.207-4.788	0.072	0.1512	2.603	0.130-5.076	0.039	0.15
HOMA-IR								
REP	0.108	-0.156-.0372	0.421	0.5325	0.107	-0.156-0.371	0.425	0.585
DUC	0.083	-0.163-0.328	0.510	0.595	0.085	-0.162-0.332	0.498	0.645
M-H TFDF	0.073	-0.183-0.329	0.578	0.6467	0.067	-0.189-0.323	0.606	0.699
IS	0.319	-0.144-0.782	0.177	0.2815	0.337	-0.130-0.804	0.157	0.317
Irregular SWC	0.674	0.207-1.141	0.005	0.0177	0.721	0.251-1.190	0.003	**0.021**
Shift work	0.183	-0.188-0.554	0.333	0.454	0.195	-0.180-0.571	0.307	0.481
LPA	0.517	0.008-1.026	0.046	0.1178	0.557	0.043-1.072	0.034	0.229

(Continued)

Behavioral factors	β	95% CI	p-value	p-value corrected	β	95% CI	p-value	p-value corrected
		Unadjusted				Age- gender and BMI adjusted		
TC (mg dl^{-1})								
REP	-0.596	-3.151-1.959	0.647	0.6932	-0.638	-3.171-1.895	0.621	0.7087
DUC	-0.389	-2.772-1.994	0.749	0.7864	-0.684	-3.053-1.686	0.571	0.6878
M-H TFDF	-0.592	-3.073-1.889	0.639	0.6917	-0.689	-3.150-1.771	0.582	0.6878
IS	-1.478	-5.971-3.015	0.519	0.5988	-2.336	-6.827-2.155	0.307	0.4811
Irregular SWC	3.387	-1.160-7.935	0.144	0.2433	3.371	-1.167-7.908	0.145	0.304
Shift work	0.125	-3.475-3.724	0.946	0.8868	-0.688	-4.297-2.920	0.708	0.7908
LPA	4.169	-0.768-9.105	0.098	0.1805	3.426	-1.527-8.379	0.175	0.3340
TG (mg dl^{-1})								
REP	0.331	-4.087-4.749	0.883	0.85059	0.250	-4.030-4.530	0.909	0.8598
DUC	1.491	-2.628-5.610	0.477	0.56914	0.487	-3.517-4.491	0.811	0.7997
M-H TFDF	0.404	-3.886-4.694	0.853	0.8380	0.412	-3.745-4.569	0.846	0.822
IS	5.754	-2.004-13.511	0.146	0.2433	2.562	-5.029-10.153	0.508	0.6477
Irregular SWC	6.217	-1.644-14.078	0.121	0.3165	3.915	-3.759-11.589	0.317	0.4894
Shift work	5.496	-0.711-11.704	0.083	0.16759	2.654	-3.440-8.748	0.393	0.550
LPA	16.305	7.850-24.760	0.000	<0.001	12.480	4.158-20.801	0.003	**0.021**
HDL-C (mg dl^{-1})								
REP	-0.645	-1.241-0.049	0.034	0.0964	-0.643	-1.234-0.053	0.033	0.2296
DUC	-0.552	-1.108-0.005	0.052	0.12697	-0.499	-1.051-0.054	0.077	0.2153
M-H TFDF	-0.829	-1.406-0.252	0.005	0.0477	-0.846	-1.417-0.274	0.004	0.06
IS	-1.458	-2.504--0.413	0.006	0.0525	-1.2820	-2.328-0.235	0.016	0.168
Irregular SWC	-0.879	-1.943-0.186	0.105	0.1900	-0.660	-1.722-0.402	0.223	0.383
Shift work	-1.055	-1.894--0.217	0.014	0.091875	-0.907	-1.749--0.066	0.035	0.229
LPA	-0.422	-1.579-0.736	0.475	0.56914	-0.138	-1.299-1.022	0.815	0.799
LDL-C (mg dl^{-1})								
REP	-0.094	-2.432-2.244	0.937	0.8863	-0.134	-2.438-2.170	0.909	0.8598
DUC	0.056	-2.124-2.237	0.960	0.88789	-0.341	-2.497-1.814	0.756	0.7997
M-H TFDF	-0.553	-2.824-1.717	0.632	0.69125	-0.594	-2.832-1.643	0.602	0.6992
IS	0.601	-3.511-4.713	0.774	0.79412	-0.630	-4.718-3.458	0.762	0.7997
Irregular SWC	4.372	0.217-8.526	0.039	0.105	3.7680	-0.356-7.892	0.073	0.215
Shift work LPA	1.520 4.056	-1.772-4.811 -0.459-8.572	0.365 0.078	0.4790 0.160588235	0.406 2.664	-2.876-3.689 -1.843-7.170	0.808 0.246	0.799 0.413
VLDL-C (mg dl^{-1})								
REP	0.128	-0.746-1.001	0.774	0.79412	0.112	-0.733-0.957	0.795	0.799
DUC	0.339	-0.475-1.153	0.414	0.53012	0.139	-0.651-0.929	0.729	0.799
M-H TFDF	0.121	-0.727-0.969	0.779	0.79414	0.126	-0.694-0.947	0.763	0.799
IS	0.902	-0.633-2.436	0.249	0.36312	0.257	-1.241-1.756	0.736	0.7997
Irregular SWC	1.333	-0.220-2.886	0.092	0.1756	0.855	-0.659-2.369	0.268	**0**.4329
Shift work	1.134	-0.093-2.361	0.070	0.15	0.567	-0.635-1.770	0.355	0.5325
LPA	2.979	1.305-4.653	0.001	0.02625	2.1980	0.553-3.842	0.009	**0**.1181
Fasting insulin (µl U ml^{-1})								
REP	0.508	-0.391-1.407	0.267	0.3766	0.510	-0.390-1.409	0.266	0.4329
DUC	0.497	-0.341-1.335	0.245	0.36232	0.526	-0.316-1.367	0.220	0.3838
M-H TFDF	0.397	-0.476-1.270	0.372	0.48222	0.395	-0.479-1.269	0.375	0.5363
IS	1.334	-0.245-2.912	0.098	0.18052	1.443	-0.150-3.037	0.076	0.2153
Irregular SWC	2.479	0.888-4.070	0.002	0.015	2.584	0.982-4.187	0.002	**0.03**

(Continued)

Behavioral factors	β	95% CI	p-value	p-value corrected	β	95% CI	p-value	p-value corrected
		Unadjusted				Age- gender and BMI adjusted		
Shift work	0.921	-0.344-2.186	0.153	0.247153	1.018	-0.262-2.299	0.119	0.271
LPA	1.638	-0.098-3.375	0.064	0.14608	1.790	0.032-3.547	0.046	0.166
CHR								
REP	0.083	-0.028-0.194	0.142	0.24333	0.081	-0.027-0.189	0.141	0.302
DUC	0.069	-0.034-0.173	0.189	0.29619	0.046	-0.056-0.147	0.377	0.536
M-H TFDF	0.095	-0.013-0.202	0.085	0.168396	0.094	-0.011-0.199	0.078	0.215
IS	0.233	0.038-0.427	0.019	0.0665	0.159	-0.033-0.351	0.104	0.248
Irregular SWC	0.220	0.022-0.418	0.029	0.084583	0.170	-0.024-0.364	0.086	0.225
Shift work	0.163	0.007-0.319	0.041	0.107625	0.096	-0.058-0.250	0.221	0.383
LPA	0.247	0.032-0.461	0.024	0.07875	0.154	-0.057-0.366	0.153	0.315
TG-to-HDL ratio								
REP	0.145	-0.052-0.342	0.149	0.2444	0.141	-0.046-0.329	0.139	0.302
DUC	0.176	-0.008-0.360	0.060	0.1431	0.124	-0.051-0.300	0.164	0.324
M-H TFDF	0.165	-0.026-0.357	0.091	0.17563	0.169	-0.013-0.351	0.068	0.215
IS	0.491	0.146-0.837	0.005	0.04772	0.324	-0.008-0.656	0.056	0.189
Irregular SWC	0.405	0.054-0.755	0.024	0.078	0.264	-0.072-0.600	0.123	0.274
Shift work	0.426	0.150-0.703	0.03	0.045	0.280	0.01-0.546	00.4	0.15
LPA	0.747	0.369-1.125	0.00	<0.001	0.532	0.167-0.897	0.04	0.06

Interaction effects of the *SIRT1* rs7069102 and behavioral factors on metabolic traits were determined by linear regression. The *β* and 95% CI were estimated to seek the extent of the interaction effect. The correction for multiple comparisons was performed by the Benjamini-Hochberg method of false discovery rate (FDR) control. Statistically significant *p*-value after correction for multiple comparisons is shown in **bold**. Abbreviations: *β*, the effect size for the interaction term; CI, confidence interval; REP, random eating pattern; DUC, diet unconsciousness; M-HTFDF, the moderate-to-high tendency toward fat-dense food; IS, inadequate sleep; SWC, sleep-wake cycle; LPA, low physical activity; SBP, systolic blood pressure; TyG, product of triglycerides and glucose; TG/HDL-C, triglyceride-to-HDL-C ratio; TC, total cholesterol; LAP, lipid accumulation product; VAI, visceral adiposity index; DBP, diastolic blood pressure; LDL-C, low-density lipoprotein cholesterol; VLDL-C, very-low-density lipoprotein cholesterol; FBG, fasting blood glucose; HDL-C, high-density lipoprotein cholesterol; CHR, cholesterol-to- HDL-C ratio; TG, triglyceride; HOMA-IR, Homeostatic model assessment-insulin resistance; CI, confidence interval; SD, standard deviation; BMI, body mass index.

In contrast, no interactive effect of rs7069102 and lifestyle factors such as diet unconsciousness, random eating pattern, moderate-to-high tendency toward fat-dense food (M-H TFDF), IS, and shift work was seen on any obesity-associated anthropometric and metabolic variable ($p > 0.05$, Tables 1 and 2).

Discussion

As obesity and being overweight result from the gene-lifestyle interaction (gene × lifestyle) and Pakistanis are in particular at-risk population, the effects of interactions between the *SIRT1* (a master metabolic regulator) variant and lifestyle factors on obesity-associated anthropometric and metabolic indices were examined in a sample of 612 subjects living in Karachi city of Pakistan employing a case-control protocol. The predisposition to obesity is primarily determined by hereditary factors but its final outcome is a result of the interaction between genetic and lifestyle risk factors.[20] According to the gene × lifestyle interaction studies, genetic predisposition to obesity might be considerably influenced by exposure to certain environmental or lifestyle factors.[12] Today, poor eating habits, irregular SWCs, and a sedentary lifestyle are viewed as the main obesogenic factors probably due to the drastic transition in people's lifestyle habits.[21] In the present study, the interaction between the rs7069102 and irregular SWC was seen to influence obesity-related anthropometric and metabolic indices such as %BF, weight, triceps, supra-iliac SFT, sub-scapular SFT abdominal SFT, WC, fasting insulin, and HOMA-IR. The SWC consists of 16 hours of daytime wakefulness and 8 hours of nighttime sleep. It is critical for maintaining physiological homeostasis. Reduced sleep, shift work, and light exposure during sleep hours may disrupt normal SWC, resulting in metabolic disturbances associated with many pathological conditions such as obesity.[22] SIRT1 modulates a variety of cellular processes and maintains physiological homeostasis. It is considered as a master metabolic regulator and has been suggested as a novel adipocyte regulator because it targets numerous signaling pathways including Forkhead box protein O1 and Peroxisome proliferator-activated receptor γ

to maintain energy metabolism in the body.[23] It also regulates circadian clock genes' expression through deacetylation and any impairment in the regulation of this mechanism may impair the normal physiological circadian rhythm and energy homeostasis consequently leading to the manifestation of metabolic anomalies including obesity.[24] A study by Watson et al.[25] suggested that irregular sleep provides an environment permissive to the expression of genes that promote obesity whereas regular sleep may suppress such genetic impacts. Another study demonstrated that individuals experiencing sleep disturbances are more prone to overeating and thus gain body weight.[26] It has also been known that SIRT1 may have a considerable impact on sleep through its connection with wake-sleep neurotransmitters and somnogens.[27] Therefore, in this way the interaction between the *SIRT1* gene variant rs7069102 and irregular SWC may lead to pronounced disturbances in many obesity-associated anthropometric and metabolic variables.

The current study also revealed that the genetic variant *SIRT1* rs7069102 interacted with LPA (rs7069102 × LPA) to significantly augment the adiposity-associated anthropometric and metabolic indices such as weight, thigh, biceps SFT, triceps SFT, abdominal SFT, supra-iliac SFT, sub-scapular SFT, %BF, HC, WC, VAI, LAP, and TG. Physical activity contributes significantly to the total energy expenditure, which helps to maintain body weight.[28] LPA in the presence of genetic susceptibility further aggravates the probability of having overweight/obese phenotype suggesting more hereditary burden in physically inactive individuals compared to active.[12] Expression of fatty acid synthase may get up-regulated due to low physical activity (PA) that consequently increases lipogenesis and further elevates the genetic risk of obesogenic loci.[29] Epigenetic modifications in DNA are sensitive to environmental/behavioral/lifestyle factors (e.g., PA and diet), thus, PA may influence epigenetic modification and mRNA expression pattern of metabolic genes in both muscle and adipose tissue.[30,31] *In vivo* investigations also indicated that exercise increases the expression of the brown adipocyte markers in both visceral and subcutaneous WAT.[32] Therefore, changes in lifestyle like high PA may modulate (weaken) the effect of obesity-associated genes. It has been reported that an acute load of exercise activates SIRT1 which in turn activates biogenesis and mitochondrial oxidative capacity. Moreover, a number of exercise (training) sessions stimulate SIRT1 and also SIRT3, which together with the biogenesis and mitochondrial oxidative function, jointly activate adenosine triphosphate production and the mitochondrial antioxidant function.[33] It has also been revealed recently that regular exercise leads to systemic adaptation that restores the level of SIRT1 in various organs (kidney, liver, and brain) in patients having neurodegenerative disorders, thus, normalizing cellular metabolic processes to diminish the severity of these disorders.[34] Based on the above-mentioned findings, it may be suggested that the interaction between the *SIRT1* rs7069102 and LPA may result in aberrant obesity-associated anthropometric and metabolic variables.

Conclusion

It can be concluded that the genetic variant rs7069102 may interact with aberrant lifestyle factors (irregular SWC and LPA) to influence the manifestation of adiposity in the Pakistani population. Identifying these interactions could be crucial in planning appropriate personalized lifestyle advice for the prevention and management of obesity and also to potentially improve the risk assessment for obesity and its related health consequences. In addition, continued evaluation of gene-environment or gene-behavior/lifestyle interactions may further define mechanistic pathways linked to obesity.

Limitations of the study

As far as the limitations of the current study are concerned, first the sample size used in this investigation was moderate. Second, we have explored only one SNP of the SIRT1 gene. Finally, the information about the lifestyle data of the study participants was based on self-reporting as it was collected via a questionnaire.

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List of Abbreviations

BMI	Body mass index
CHR	Cholesterol-to-HDL-C ratio
HC	Hip circumference
HDL-C	High-density lipoprotein cholesterol
HOMA-IR	Homeostatic model assessment-insulin resistance
LAP	Lipid accumulation product
LDL-C	Low-density lipoprotein cholesterol
LPA	Low physical activity
M-HTFDF	Moderate-to-high tendency toward fat-dense food
NAD	Nicotinamide adenine dinucleotide
rs	Reference sequence
SFT	Skinfold thicknesses
SIRT1	Sirtuin 1
SNP	Single nucleotide polymorphism
SPSS	Statistical Package for the social sciences
SWC	Sleep-wake cycle
TFDF	Tendency toward fat dense food
TG	Triglyceride
TG/HDL-C	Triglyceride-to-HDL-C
TyG index	Product of triglyceride and glucose index
VAI	Visceral adiposity index
VLDL-C	Very-low-density lipoprotein cholesterol
WAT	White adipose tissue

WC	Waist circumference
WHR	Waist-to-hip ratio
WHtR	Waist to height ratio
%BF	Percentage body fat

Conflict of interest
None to declare.

Grant support and financial disclosure
None to disclose.

Ethical approval
The ethical approval of the study was obtained from the Independent Ethics Committee (IEC) of ICCBS vide approval number ICCBS-001-BC-/Protocol/1.0.

Authors' contributions
SR: Concept and design of the study, acquisition, and analysis of the data, and critical revision of the manuscript.
HN: Acquisition and analysis of the data, and drafted the manuscript.
ALL AUTHORS: Approval of the final version of the manuscript to be published.

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