

Correlations Between *SIRT* Genetic Polymorphisms and Postpartum Depressive Symptoms in Chinese Parturients Who Had Undergone Cesarean Section

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Objective: To investigate the association of genetic polymorphisms of *SIRT* with postpartum depressive symptoms and analyze the risk factors for postpartum depressive symptoms in women following cesarean section.

Methods: A total of 368 Chinese woman undergoing cesarean section were enrolled in this study. A cutoff of ≥ 10 for the Edinburgh Postnatal Depression Scale identified postpartum depressive symptoms. Genotypes of *SIRT1*, *SIRT2*, and *SIRT6* were determined using Sequenom MassArray single-nucleotide polymorphism (SNP) analysis. We analyzed the contribution of genetic factors (SNPs, linkage disequilibrium, and haplotype) to postpartum depressive symptoms and performed logistic regression analysis to identify all potential risk factors for postpartum depressive symptoms and define interactions between genetic and environmental factors.

Results: The incidence of postpartum depressive symptoms was 18.7% in this cohort. Univariate analysis suggested that *SIRT2* polymorphism at rs2873703 (TT genotype) and rs4801933 (TT genotype) and *SIRT6* polymorphism at rs350846 (CC genotype) and rs107251 (TT genotype) were significantly correlated with the occurrence of postpartum depressive symptoms ($p < 0.05$). Linkage disequilibrium was identified between *SIRT6* polymorphisms rs350846 and rs107251. Incidence of postpartum depressive symptoms in cesarean-section parturients with *SIRT2* haplotype CCC was decreased (OR 0.407, 95% CI 0.191–0.867; $p = 0.016$). *SIRT2* polymorphisms rs2873703 and rs4801933 were multiply collinear. Logistic regression analysis showed that *SIRT2* polymorphism at rs2873703 (TT genotype) and rs4801933 (TT genotype), domestic violence, stress during pregnancy, and depressive prenatal mood were risk factors for postpartum depressive symptoms ($p < 0.05$).

Conclusion: Pregnant women with *SIRT2* genotypes rs2873703 TT and rs4801933 TT and experiencing domestic violence, stress during pregnancy, and prenatal depression are more likely to suffer from postpartum depressive symptoms.

Keywords: *SIRT*, genetic variants, postpartum depressive symptoms, epigenetics

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Introduction

Postpartum depressive symptoms (PDSs) are serious psychiatric disorders that have a deep impact on maternal life quality. PDSs can be fatal: suicide accounts for approximately 20% of postpartum deaths.^{1–3} PDSs also have adverse effects on family relationships, including marital and maternal–infant interaction problems,

which can result in poor physiological and psychological health of offspring.^{4–6} In recent decades, countries around the world have conducted extensive research on postpartum depression. The etiology and causes of PDSs are considered multifactorial, including hormonal changes, genetic risk factors, inflammation, and psychosocial stress, during pregnancy and the perinatal period.⁷ However, the pathophysiology of the PDSs has still to be elucidated.

Mounting evidence suggests that epigenetic mechanisms, which induce stable and lasting changes in gene expression in response to environmental events and behavioral experiences, may play a role in processes that contribute to the pathophysiology of psychiatric disorders.⁸ It is well known that histone deacetylation is one of the most important mechanisms of epigenetic modification and contributes a lot in regulating gene transcription and translation. Hobara et al described in their study that aberrant transcriptional regulation caused by the altered expression of HDAC was associated with the pathophysiology of mood disorders.⁹ Interestingly, Hollis et al observed a trend toward decreased *HDAC3* mRNA levels following social defeat exposure.¹⁰ Schroeder et al showed in their study that the HDAC inhibitor sodium butyrate exerted antidepressant-like effects in the mouse.¹¹ Meanwhile, in a large and growing body of literature, some HDAC enzymes have been proposed as epigenetic targets involved in the pathophysiology of depression and antidepressant-like action.¹²

Sirtuins are HDAC3s. They mediate histone deacetylation in an NAD^+ -dependent manner and can deacetylate proteins other than histones, which involves a variety of pathophysiological processes.¹³ Recent studies have shown that *SIRT* plays an important role in the pathophysiology and treatment of depression. Clinical studies have shown that sirtuin is closely related to depression.¹⁴ Animal experiments have suggested that stress and inflammation can affect the main subtypes of the sirtuin family, some of which are related to the pathogenesis of depression.¹⁵ A recent large-scale genome-wide association study showed that genetic variants near the *SIRT1* gene were significantly associated with major depressive disorders, suggesting that *SIRT1* may participate in the pathogenesis of major depressive disorder.¹⁶ Interestingly, a recent study reported that changes in *SIRT1*, *SIRT2*, and *SIRT6* mRNA expression in peripheral blood cells may be a useful biomarker for mood disorders.¹⁷ Numerous studies conducted by Kishi et al have shown that *SIRT1* is associated with major depressive disorder in the Japanese

population.¹⁸ Recently, Liu et al found that *SIRT2* is involved in the modulation of depressive behaviors.¹⁹

Many studies have shown that tryptophan-metabolism disorder, induced by perinatal stress and inflammatory response, is one of the significant mechanisms of PDSs.^{20,21} As one of the end products of tryptophan metabolism, NAD^+ is an important coenzyme of sirtuins. Studies have shown that *SIRT* participates in the pathophysiology and treatment of depression.^{22–24} Therefore, *SIRT* may be involved in the pathogenesis of PDSs, but it is not clear that it gene is involved in PDSs from the perspective of genetics. This study aimed to select parturients undergoing cesarean section to screen *SIRT* for single-nucleotide polymorphisms (SNPs) based on individual genes and genomes, explore the relationship between *SIRT* polymorphism and postpartum depression after cesarean section, provide a genetic basis for individual differences in postpartum depression, and to provide an important reference for predicting genetic susceptibility to postpartum depression. From the perspective of genetics, it provides new ideas for the pathogenesis and treatment of diseases.

Methods

Protocol

This study was approved by the local ethics committee (P2014/s155, February 20, 2014) and was nationally registered in the Chinese Clinical Trials Registry (CHICTR-ROC-17013357). All participants provided written informed consent before entering the study.

Study Participants

By using the sample size–calculation formula for a cohort study, 237 patients needed to be included to attain statistical significance (Figure 1). A total of 368 participants who undergone cesarean sections at the Third Xiangya Hospital of Central South University were enrolled, and all agreed to postoperative intravenous analgesia. Eligibility criteria were pregnant and aged at least 18 years, American Association of Anesthesiologists class II status, ability to communicate with visitors, and agreement to adhere to the study requirements.²⁵ Exclusion criteria were severe clinical complications (pregnancy-induced hypertension syndrome, placental abruption, dangerous placenta previa), history of psychotic disorder, not cooperating with collection of samples and data, and suicidal behavior within the previous month.²

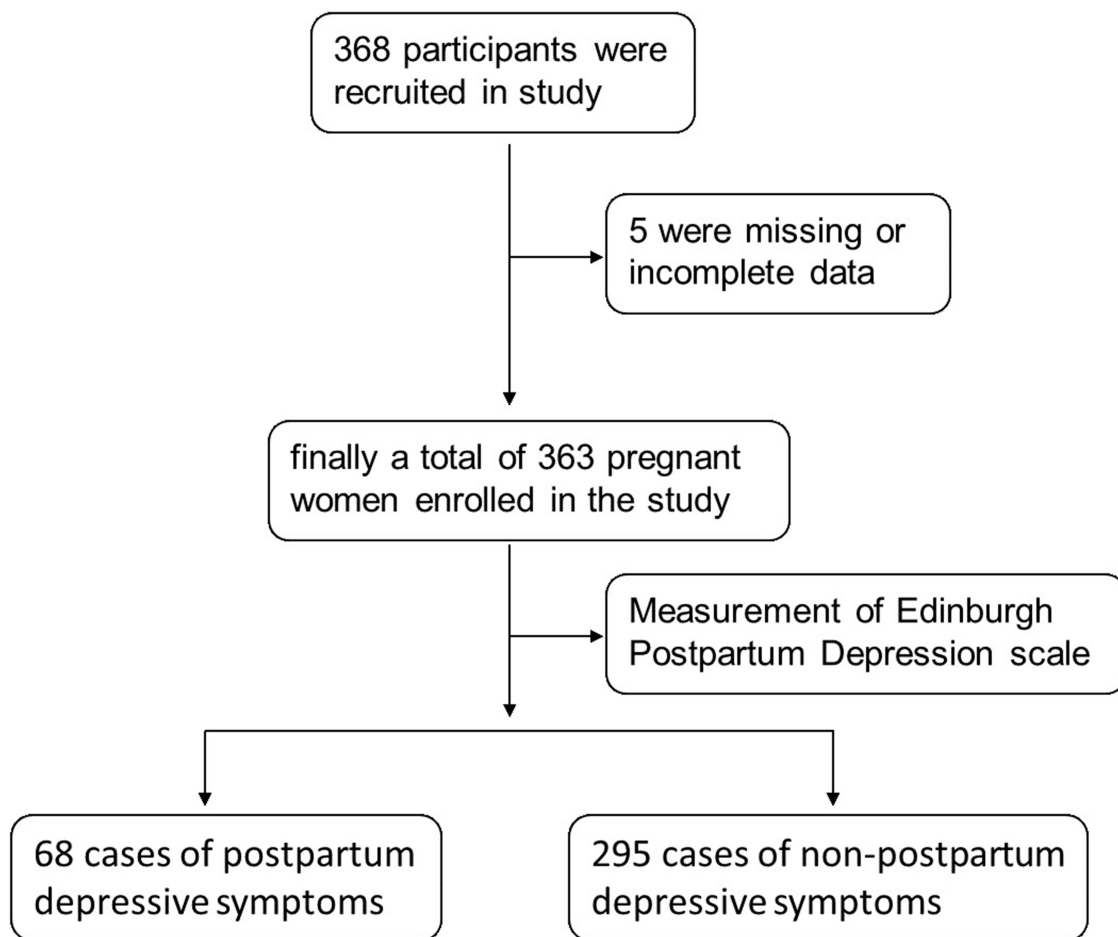


Figure 1 Flowchart of participants.

Collection of General Data, Clinical Data, and Samples of Parturients

A preoperative questionnaire was used to collect basic information on all parturients, including age, height, weight, gestational age, whether unipara or not, education, employment and partner employment, monthly family income, artificial or natural pregnancy, and planned or unintended pregnancy. We used the Pregnancy Pressure Scale, and parturients were assessed on severe/moderate/mild stress during pregnancy,²⁵ good/moderate/poor marital relationship, mood during pregnancy, and domestic violence during pregnancy, defined as one or more acts or threats of physical, sexual, or psychological/emotional violence reported by any family member (Figure 2).²⁶ Additionally, prenatal depressive symptoms were assessed with the Edinburgh Postnatal Depression Scale (EPDS) by trained investigators.^{27–29} Finally, 2 mL venous blood was taken from each woman and marked with name and serial number in anticoagulant vessels containing EDTA, then stored in a freezer at -20°C .

Maternal Surgery, Postpartum Follow-Up, and Determination of Outcome Indicators

All women were admitted to the operating room after preoperative preparation. Monitoring was conducted using of electrocardiography, noninvasive blood pressure, and heart rate. Oxygen was administered by clear nasal catheter until delivery at a rate of 2L/minute. Subarachnoid block was performed with a disposable spinal–epidural anesthesia puncture bag (Tuoren Medical Devices, Henan, China). After skin disinfection and local anesthesia with lidocaine, a 25 G needle was inserted at the L3–L4 or L2–L3 interspace. When cerebrospinal fluid flowed, 1% ropivacaine 1.5 mL + 10% fentanyl 25 μg + 10% glucose solution 0.5 mL was administered into the subarachnoid space, aiming for a level of analgesia $<T_4$. Attention was paid to observe and prevent supine hypotension syndrome.

After the anesthetic effect had met surgical conditions, the surgeon began the operation and performed cesarean

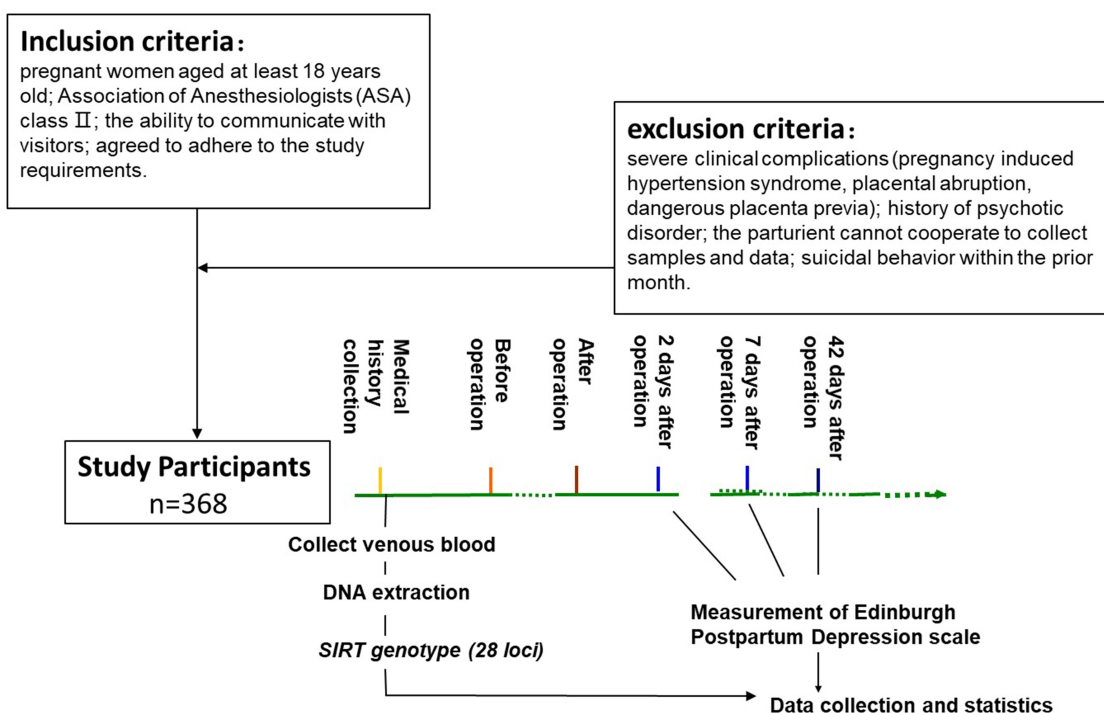


Figure 2 Study flowchart.

section of the lower segment of the uterus. Changes of electrocardiography and output were closely observed during the operation. After the fetus had been removed, it was weighed to determine whether or not to transfer it to the neonatal intensive care unit according to maternal condition and birth quality. After the placenta had been removed by surgery and sutured layer by layer, it was decided whether to transfer the mother to postanesthesia care unit or back to the ward, according to the anesthesia resuscitation.

The parturients were evaluated with the EPDS at 2, 7, and 42 days after delivery. Scores ≥ 10 at 42 days after delivery were regarded as postpartum depression, and scores ≥ 10 on the day before delivery were rated as prenatal depression.^{28,30} Self-harm ideation (the last EPDS item) was assessed before childbirth on postpartum days 7 and 42, with parturients who gave a response of “yes, quite often”, “sometimes”, or “seldom”, being categorized as “yes”, with only a response of “never” being classified as “no”. If parturients could not be contacted on days 7 and 42 after delivery, the investigator could call them again within 2 days. If there were still no response, these cases were classified as lost.

Selection of SNP Loci

SNP loci were selected by querying the relevant literature to understand the SNP loci active in related *SIRT* research,

especially those active in the field of psychosomatic medicine; querying relevant SNP sites in the dbSNP database so as to select SNP sites and coding sequences; (3) and querying the Ensembl website to download relevant files and import Haploview software so as to view and select SNP sites of the Beijing and southern populations. Loci selection also needed to meet a minimum allele frequency of >0.05 . Genotypes of 28 *SIRT* loci were selected and gene polymorphisms of these analyzed with Sequenom MassArray (gene chip; Table 1).

Statistical Analysis

SPSS 23.0 was used to analyze all data. Measurement data are described as means \pm SD, and counting and grade data as rate or constituent ratio. The relationship between the basic data of selected parturients and PDSs was assessed by χ^2 and *t*-tests. The Hardy–Weinberg equilibrium test was used for all SNP loci, and χ^2 to analyze the relationship between the incidence of PDSs and SNPs. In addition, linkage-disequilibrium analysis and haploid analysis of SNPs were carried out on the SHEsis platform. Collinear analysis was used to find collinear factors and eliminate the list of multivariate analysis, and then logistic regression analysis was used to analyze the relationship between PDSs and various factors (forced-entry method). Factors

Table I Correlations between *SIRT* polymorphisms and postpartum depressive symptoms

SNP	Genotype	PDSs (%)	No PDSs (%)	Additive, <i>p</i>	Dominant, <i>p</i>	Recessive, <i>p</i>	Gene
rs113045253	CC	53 (18.7%)	230 (81.3%)	Reference	1 ^a	0.790	<i>SIRT1</i>
	CA	10 (18.5%)	44 (81.5%)	0.971			
	AA	0	4 (100%)	0.338			
rs12765828	GG	35 (18.7%)	152 (81.3%)	Reference	0.846	0.931	
	GT	27 (19.4%)	112 (80.6%)	0.872			
	TT	6 (17.6%)	28 (82.4%)	0.883			
rs12778366	TT	50 (18.2%)	224 (81.8%)	Reference	0.599 ^a	0.678	
	TC	18 (21.7%)	65 (78.3%)	0.485			
	CC	0	6 (100%)	0.248			
rs3740051	AA	35 (18%)	159 (82%)	Reference	0.276 ^a	0.785	
	AG	30 (21%)	113 (79%)	0.499			
	GG	2 (8.3%)	22 (91.7%)	0.232			
rs3758391	TT	48 (18.5%)	212 (81.5%)	Reference	1 ^a	0.833	
	TC	19 (20.2%)	75 (79.8%)	0.710			
	CC	1 (11.1%)	8 (88.9%)	0.574			
rs7896005	AA	48 (18.5%)	212 (81.5%)	Reference	1 ^a	0.833	
	AG	19 (20.2%)	75 (79.8%)	0.710			
	GG	1 (11.1%)	8 (88.9%)	0.574			
rs10997870	GG	47 (18.1%)	212 (81.9%)	Reference	1 ^a	0.748	
	GT	19 (20.4%)	74 (79.6%)	0.628			
	TT	1 (11.1%)	8 (88.9%)	0.588			
rs4746720	TT	20 (16.9%)	98 (83.1%)	Reference	0.818	0.572	
	TC	33 (20.2%)	130 (79.8%)	0.486			
	CC	14 (17.7%)	65 (82.3%)	0.888			
rs932658	AA	47 (18.1%)	212 (81.9%)	Reference	1 ^a	0.622	
	AC	20 (21.3%)	74 (78.7%)	0.507			
	CC	1 (11.1%)	8 (88.9%)	0.588			
rs2873703	CC	0	9 (100%)	Reference	0.009*	0.145	<i>SIRT2</i>
	CT	9 (10.7%)	75 (89.3%)	0.301			
	TT	59 (21.9%)	211 (78.1%)	0.114			
rs10421741	CC	34 (23.1%)	113 (76.9%)	Reference	0.392	0.077	
	CT	28 (16.2%)	145 (83.8%)	0.117			
	TT	6 (14%)	37 (86%)	0.194			

(Continued)

Table I (Continued).

SNP	Genotype	PDSs (%)	No PDSs (%)	Additive, <i>p</i>	Dominant, <i>p</i>	Recessive, <i>p</i>	Gene
rs2015	TT	14 (16.7%)	70 (83.3%)	Reference	0.208	0.561	
	TG	33 (17.6%)	154 (82.4%)	0.844			
	GG	21 (23.3%)	69 (76.7%)	0.273			
rs3136638	AA	60 (20.3%)	236 (79.7%)	Reference	1 ^a	0.115	
	AT	8 (12.7%)	55 (87.3%)	0.164			
	TT	0	4 (100%)	0.314			
rs4801933	CC	1 (14.3%)	6 (85.7%)	Reference	0.025*	1 ^a	
	CT	8 (10.3%)	70 (89.7%)	0.740			
	TT	59 (21.5%)	216 (78.5%)	0.647			
rs10410544	TT	0	2 (100%)	Reference	0.396 ^a	1 ^a	
	TC	2 (10.5%)	17 (89.5%)	0.630			
	CC	66 (19.3%)	276 (80.7%)	0.490			
rs11083483	AA	1 (20%)	4 (80%)	Reference	0.801	1 ^a	
	AG	18 (19.6%)	74 (80.4%)	0.981			
	GG	49 (18.4%)	217 (81.6%)	0.928			
rs2053071	CC	14 (26.9%)	38 (71.3%)	Reference	0.405	0.104	
	CG	27 (14.8%)	155 (85.2%)	0.043*			
	GG	27 (21.1%)	101 (78.9%)	0.398			
rs2082435	CC	31 (19.1%)	131 (80.9%)	Reference	0.451	0.860	
	CG	29 (17.4%)	138 (82.6%)	0.678			
	GG	8 (23.5%)	26 (76.5%)	0.560			
rs2241704	AA	46 (18.5%)	202 (81.5%)	Reference	0.439 ^a	0.895	
	AT	19 (18.3%)	85 (81.7%)	0.951			
	TT	3 (27.3%)	8 (72.7%)	0.470			
rs892034	TT	0	6 (100%)	Reference	0.200	0.599 ^a	
	TC	14 (15.4%)	77 (84.6%)	0.299			
	CC	54 (20.4%)	211 (79.6%)	0.217			
rs350846	CC	10 (34.5%)	19 (65.5%)	Reference	0.881	0.021*	SIRT6
	CG	21 (14.9%)	120 (85.1%)	0.013*			
	GG	36 (18.8%)	155 (81.2%)	0.054			
rs352492	CC	43 (22.5%)	148 (77.5%)	Reference	0.293	0.055	
	CT	19 (12.8%)	130 (87.2%)	0.021*			
	TT	6 (27.3%)	16 (72.3%)	0.615			

(Continued)

Table I (Continued).

SNP	Genotype	PDSs (%)	No PDSs (%)	Additive, <i>p</i>	Dominant, <i>p</i>	Recessive, <i>p</i>	Gene
rs76366923	TT	37 (17.7%)	172 (82.3%)	Reference	0.055	0.558	
	TA	24 (17.9%)	110 (82.1%)	0.961			
	AA	7 (35%)	13 (65%)	0.061			
rs107251	TT	10 (33.3%)	20 (66.7%)	Reference	0.993	0.032*	
	TC	22 (15.6%)	119 (84.4%)	0.024*			
	CC	36 (18.8%)	156 (81.3%)	0.067			
rs3760905	GG	10 (14.7%)	58 (85.3%)	Reference	0.123	0.334	
	GT	31 (17.4%)	147 (82.6%)	0.610			
	TT	27 (23.5%)	88 (76.5%)	0.153			
rs4807546	TT	31 (20.1%)	123 (79.9%)	Reference	0.182	0.558	
	TC	24 (15.2%)	134 (84.8%)	0.252			
	CC	13 (25.5%)	38 (74.5%)	0.419			
rs8104543	CC	54 (18.8%)	234 (81.3%)	Reference	0.588	0.987	
	CA	14 (20%)	56 (80%)	0.811			
	AA	0	5 (100%)	0.284			
rs724235	GG	41 (19.2%)	173 (80.8%)	Reference	0.546 ^a	0.782	
	GA	23 (19.2%)	97 (80.2%)	0.999			
	AA	2 (10.5%)	17 (89.5%)	0.353			

Notes: * $p < 0.05$ vs control. ^aUses Fisher's exact test; ^bMonte Carlo method.

Abbreviations: PDSs, postpartum depressive symptoms; SNP, single-nucleotide polymorphism.

with variance-inflation factor >10 and independent variables with tolerance <0.2 may have multiple collinearity. Interactions between genes and environment were analyzed with GMDR software. There was a statistical difference between the two sides if $p < 0.05$.

Results

General Data and Analysis of Postpartum Depressive Symptoms

In this study, 368 participants were recruited, of which five were missing or had incomplete data, and finally a total of 363 pregnant women were enrolled in the study. Among the 363 pregnant women, there were 68 cases of PDSs, with an incidence of 18.7%. Among the 68 patients with PDSs, 39 had relatively low EPDS scores (<13) and 29 had relatively high EPDS scores (≥ 13).

Results showed that there was no significant difference in age (29.87 ± 4.528 vs 30.28 ± 4.513 years, $t = 0.682$, $df = 360$,

Cohen's $p = 0.092$; $p = 0.495$), height (1.59 ± 0.047 vs 1.59 ± 0.046 m, $t = -0.173$, Cohen's $p = -0.023$, $df = 361$; $p = 0.826$), prepregnancy weight (53.85 ± 7.908 vs 53.76 ± 8.579 kg, $t = -0.073$, $df = 355$, Cohen's $p = -0.010$, $p = 0.942$), prenatal weight (70.62 ± 8.327 vs 70.34 ± 9.727 kg, $t = -0.220$, $df = 361$, Cohen's $p = -0.030$, $p = 0.826$), and preoperative BMI (27.83 ± 2.970 vs 27.76 ± 3.704 , $t = -0.146$, $df = 361$, Cohen's $p = -0.020$; $p = 0.884$) between PDSs and no PDSs ($p > 0.05$). Therefore, the two groups were regarded as comparable in terms of age and body shape.

When using χ^2 to compare general and clinical data of parturients, we found differences in pregnancy stress, domestic violence, and depressive prenatal mood between PDSs and no PDSs ($p < 0.05$). Compared with ordinary cesarean section, incidence of PDSs in pregnant women suffering domestic violence was significantly higher (OR 7.02, 95% CI 1.92–25.60; $p = 0.004$). Incidence of PDSs of parturients undergoing cesarean section was significantly higher than pregnant women with high stress and low

stress and between moderate stress and low stress (OR 3.714, 95% CI 1.660–8.312 and OR 2.615, 95% CI 1.428–4.789, respectively). The likelihood of PDSs in pregnant women with prenatal depression was significantly higher than women without prenatal depression (OR 5.35, 95% CI 3.02–9.48; $p=0$; Table 2).

Univariate Analysis of *SIRT* Polymorphisms and Postpartum Depressive Symptoms

All selected SNPs conformed to the Hardy–Weinberg equilibrium and were genetically representative and able to be used for gene analysis. Incidence of PDSs after cesarean section in each genotype of *SIRT* polymorphisms rs350846, rs352492, rs107251, rs2873703, rs4801933, and rs2503071 was different. Further analysis and comparison showed that homozygous TT with rs2873703 mutation at SNP sites of *SIRT2* had higher incidence of PDSs (OR 2.610, 95% CI 1.238–5.501; $p=0.009$) than wild-type homozygous CC and heterozygous CT. Compared with wild-type homozygote CC and heterozygote CT, homozygous TT with rs4801933 mutation at SNP sites of *SIRT2* had higher incidence of PDSs (OR 2.307, 95% CI 1.091–4.876; $p=0.025$). *SIRT6* gene SNP locus rs350846 wild homozygous CC has a higher incidence of PDSs than mutant homozygous GG and heterozygous CG (OR 2.539, 95% CI 1.122–5.749; $p=0.021$). *SIRT6* SNP locus rs107251 wild homozygous TT had higher incidence of PDSs than mutant homozygous CC and heterozygous TC (OR 2.371, 95% CI 1.054–5.330; $p=0.032$; Table 1).

Linkage-Disequilibrium Test and Haplotype Analysis of *SIRT* Loci

SHEsis software was used to detect linkage disequilibrium of rs2873703, rs4801933, and rs2503071 in *SIRT2*. $R^2>0.8$ indicated that there was disequilibrium between the two loci. There was little linkage disequilibrium between rs2873703 and rs4801933 (Figure 3). Haplotypes of *SIRT2* rs2873703, rs4801933, and rs2503071 loci gene three haplotypes (CCC, TTC, TTG) with frequency >0.03 were analyzed. Haplotype analysis showed that incidence of PDSs after cesarean section was decreased in parturients with haplotype CCC ($p<0.05$, Table 3).

SHEsis software was used to detect linkage disequilibrium of *SIRT6* rs350846, rs352492, and rs107251 loci. $R^2>0.80$ indicated that there was disequilibrium between the two loci. The results showed that there was linkage

imbalance between rs350846 and rs107251 (Figure 4). Haplotypes of *SIRT6* rs350846, rs352492, and rs107251 loci and three haplotypes (CCT, GCC, GTC) with frequency >0.03 were analyzed. The results showed that the haplotypes of *SIRT6* rs350846, rs352492, and rs107251 loci gene were not be associated with PDSs in parturients undergoing cesarean section ($p>0.05$, Table 3).

Multivariate Analysis of *SIRT* Polymorphisms and Postpartum Depressive Symptoms

Before establishing the regression model, we first conducted a collinear analysis of all the variables. After assessing correlations between the two variables and the multiple collinearity test, the results showed that rs2873703 and rs4801933 and rs350846 and rs107251 had multiple collinearity. Therefore, rs4801933 and rs107251 were excluded and logistic multivariate analysis was carried out.³¹

Finally, the variables selected were analyzed by logistic analysis, and results are shown in Table 4. Domestic violence (OR 6.59, 95% CI 1.47–29.61; $p=0.014$), stress during pregnancy (OR 1.67, 95% CI 1.09–2.56; $p=0.020$), prenatal depression (OR 5.11, 95% CI 2.73–9.55; $p=0$), and polymorphic rs2873703 genotype TT (OR 3.27, 95% CI 1.46–7.32; $p=0.004$) were risk factors for PDSs. Because of the multicollinearity and weak linkage disequilibrium between rs2873703 and rs4801933, rs4801933 was also associated with PDSs.

Interaction Between *SIRT* and Environment

Identification of gene–environment joint action is one of the most important and challenging topics in human genetics and genetic epidemiology. GMDR software was used to analyze the interaction between *SIRT2* rs2873703 and environmental factors (stress during pregnancy and domestic violence) entering the regression equation. The results showed that there was no significant interaction among the three factors (the model did not pass the 10 +10 cross-validation test; Table 5).

Discussion

The major findings in this study were that *SIRT2* polymorphisms were associated with PDS incidence, compared to parturients carrying a CC or CT genotype, those carrying the the TT genotype in rs2873703 (*SIRT2*) were at

Table 2 General information on parturients and incidence of PDSs, n (%)

	Classification	PDSs	No PDSs	p	OR (95% CI)
Age, years	≥35	13 (21.7%)	47 (78.3%)	0.524	1.247 (0.632,2.462)
	<35	55 (18.2%)	248 (81.8%)		1 (Reference)
Stress during pregnancy	Large	13 (31.7%)	28 (68.3%)	0.001	3.714 (1.660,8.312)
	Medium	34 (24.6%)	104 (75.4%)		2.615 (1.428,4.789)
	Small	20 (11.1%)	160 (88.9%)		1 (Reference)
Domestic violence	Yes	6 (60%)	4 (40%)	0.004 ^a	7.016 (1.923,25.60)
	No	62 (17.6%)	290 (82.4%)		1 (Reference)
Marital relationship	Poor	0	2 (100%)	0.070 ^b	2.516 (1.182,5.352)
	Medium	12 (34.3%)	23 (65.7%)		
	Good	56 (17.2%)	270 (82.8%)		1 (Reference)
Full term	Yes	62 (18.5%)	273 (81.5%)	0.704	0.833 (0.324,2.140)
	No	6 (21.6%)	22 (78.6%)		1 (Reference)
Relationship between mother-in-law and daughter-in-law	Bad	1 (16.7%)	5 (83.3%)	0.056 ^b	1.039 (0.119,9.102)
	Medium	20 (28.2%)	51 (71.8%)		2.038 (1.112,3.734)
	Good	46 (16.1%)	239 (83.9%)		1 (Reference)
Education	High school degree and below	23 (18.4%)	102 (81.6%)	0.084	6.088 (0.786,47.13)
	Bachelor degree	44 (21.1%)	165 (78.9%)		7.200 (0.952,54.46)
	Master degree and above	1 (3.6%)	27 (96.4%)		1 (Reference)
Primipara	No	24 (15.1%)	135 (84.9%)	0.107	0.638 (0.369,1.104)
	Yes	44 (21.8%)	158 (78.2%)		1 (Reference)
Artificial impregnation	Yes	5 (29.4%)	12 (70.6%)	0.334 ^a	1.872 (0.637,5.503)
	No	63 (18.2%)	283 (81.8%)		1 (Reference)
Economic status (CN ¥/month)	<2,500	1 (20%)	4 (80.0%)	0.910 ^a	1.135 (0.122,10.57)
	2,500–10,000	40 (19.7%)	163 (80.3%)		1.114 (0.644,1.926)
	>10,000	26 (18.1%)	118 (81.9%)		1 (Reference)
Depressive prenatal mood	Yes	47 (35.1%)	87 (64.9%)	0 [*]	5.351 (3.020,9.481)
	No	21 (9.2%)	208 (90.8%)		1 (Reference)
Suicidal ideation	Yes	1 (100%)	0	0.187 ^a	
	No	67 (18.5%)	295 (81.5%)		1 (Reference)
Stressful events	Yes	3 (50%)	3 (50%)	0.082 ^a	4.492 (0.887,22.76)
	No	65 (18.2%)	292 (81.8%)		1 (Reference)
Monocytes	>8	9 (25.7%)	26 (74.3%)	0.265	1.578 (0.703,3.543)
	≤8	59 (18%)	269 (82%)		1 (Reference)
Monocyte count (×10 ⁹ /L)	>0.8	7 (19.4%)	29 (80.6%)	0.942	1.033 (0.432,2.468)
	<0.8	61 (18.9%)	261 (81.1%)		1 (Reference)

Notes: ^ap<0.05 vs control. ^aFisher's exact test; ^bMonte Carlo method.

Abbreviation: PDSs, postpartum depressive symptoms.

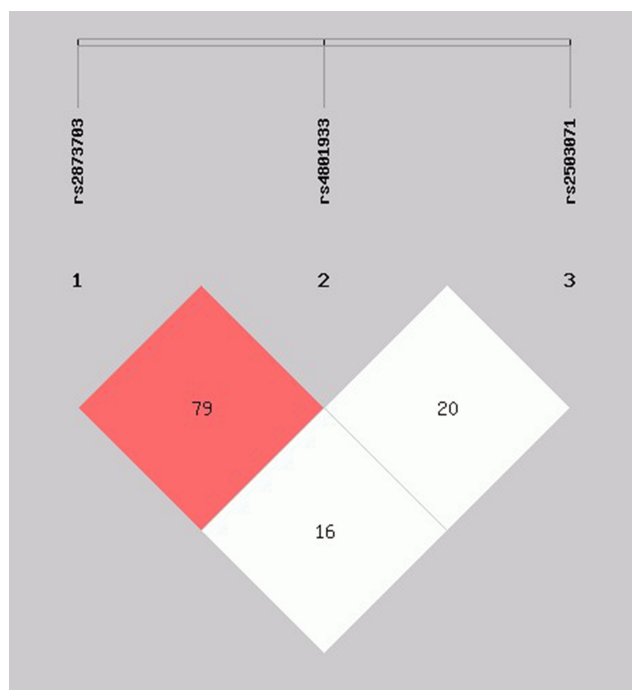


Figure 3 Linkage-disequilibrium test of *SIRT2* loci rs2873703, rs4801933, and rs2503071. The white square represents the weaker linkage disequilibrium between the two loci, and the red square stronger linkage disequilibrium.

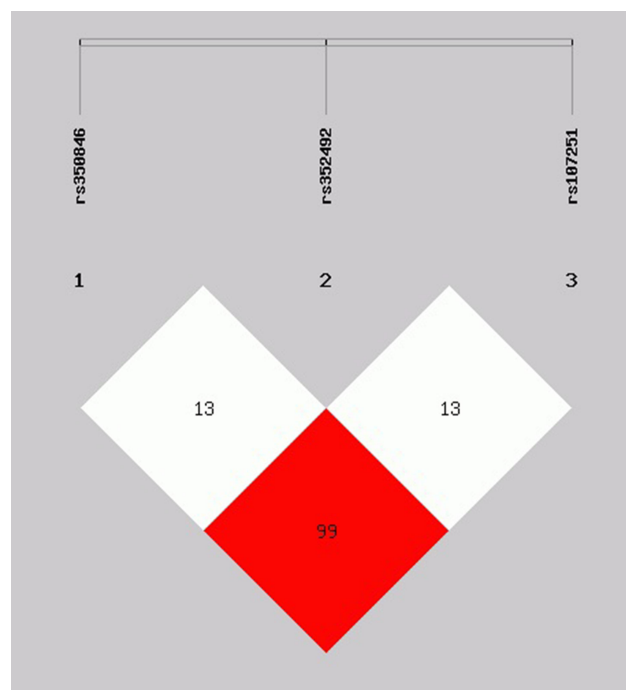


Figure 4 Linkage-disequilibrium test of *SIRT6* loci rs350846, rs352492, and rs107251. The white square represents the weaker linkage disequilibrium between the two loci, and the red square stronger linkage disequilibrium.

higher risk of PDSs, and domestic violence, stress during pregnancy, and prenatal depression were risk factors for PDSs. In addition, we found that overall of PDS incidence based on EPDS score (cutoff ≥ 10) was 18.7%, which was basically consistent with other literature.³²

Sirtuins are a family of NAD⁺-dependent enzymes that regulate cellular functions through deacetylation of protein targets. The mammalian sirtuin family consists of seven sirtuins (*SIRT1–7*). *SIRT*s modulate major biological pathways, such as stress response, protein aggregation, and inflammatory processes, which are involved in neurodegenerative

diseases.³³ *SIRT2* is a major deacetylase that has some common substrates in both cytoplasm and nucleus.¹⁷ It has been reported that the rs10410544 polymorphism of *SIRT2* is associated with depression in Alzheimer's disease patients.²³ In the present study, we found that *SIRT2* polymorphism at rs2873703 and rs4801933 was associated with depression. Particularly, both TT genotypes were associated with a higher risk of developing PDSs. Kim et al demonstrated that infusion of the aspecific sirtuin agonist resveratrol promoted depression and anxiety-like behavioral deficits.¹⁵ What is more, Ferland et al suggested that sirtuin inhibition is a therapeutic target for cognitive effects of depression.³⁴

Table 3 Haplotype analysis of *SIRT2* and *SIRT6* loci

	PDSs (frequency)	No PDSs (frequency)	χ^2	<i>p</i>	OR (95% CI)
<i>SIRT2</i>					
CCC	7.99 (0.058)	76.54 (0.132)	5.766	0.016*	0.407 (0.191–0.867)
TTC	45.00 (0.331)	146.44 (0.252)	3.373	0.066	1.460 (0.973–2.191)
TTG	79.99 (0.588)	341.51 (0.587)	0.005	0.941	0.986 (0.670–1.450)
<i>SIRT6</i>					
CCT	41.00 (0.306)	155.99 (0.266)	0.847	0.357	1.212 (0.804–1.828)
GCC	63.00 (0.470)	267.97 (0.457)	0.064	0.800	1.050 (0.721–1.529)
GTC	30.00 (0.224)	161.03 (0.275)	1.476	0.224	0.759 (0.487–1.185)

Notes: Haplotypes with frequency <0.03 not included. **p*<0.05.

Abbreviation: PDSs, postpartum depressive symptoms.

Table 4 Multivariate logistic analysis of risk factors for postpartum depressive symptoms

	β	SE	Wald	p	OR	OR95% CI	
						Lower	Upper
Stress during pregnancy	0.512	0.219	5.448	0.020	1.668	1.085	2.563
Domestic violence	1.885	0.767	5.043	0.014	6.587	1.465	29.609
Depressive prenatal mood	1.631	0.319	26.121	0	5.111	2.734	9.554
<i>SIRT2</i> rs2873703	1.185	0.411	8.311	0.004	3.270	1.461	7.317

Table 5 Interactive analysis of genetic polymorphisms and environmental factors

	Training balance account	Testing balance account	Sign test (p)	CV consistency
Stress during pregnancy	0.6245	0.6169	7 (0.1719)	10/10
Stress during pregnancy: <i>SIRT2</i> rs2873703	0.6506	0.6265	8 (0.0547)	10/10
Stress during pregnancy Domestic violence: <i>SIRT2</i> rs2873703	0.6596	0.6313	8 (0.0547)	10/10

Notes: GMDR software was used to analyze the interaction between SNP (*SIRT2* rs2873703) and environmental factors (stress during pregnancy, domestic violence) entering the regression equation. No model showed 10/10 CV consistency.

Abbreviation: GMDR, generalized multifactor dimensionality reduction.

A previous study showed that the *SIRT2* inhibitor 33i reverted chronic mild stress-induced depressive-like behaviors,²⁴ whereas another study showed that inhibiting *SIRT2* with tenovin D3 resulted in depression-like behavior.¹⁹ As far as we know, rs2873703 is the first *SIRT2* polymorphism found to be related to the incidence of postpartum depression. Because it is located in the noncoding region, we think that rs2873703 may be linked with rs4801933, which may cause changes in *SIRT* expression, then lead to the disease. Another assumption is that the single mutation of rs2873703 may affect gene transcription and translation, then result in disease. However, these conjectures need further confirmation.

SIRT6 plays a key role in sirtuin family, and is highly expressed in nuclei of skeletal muscle, brain, heart, liver, and thyroid. Michishita et al suggested that *SIRT6* may regulate gene transcription by removing acetyl groups of histone H3, transcription factors, and cotranscription factors,³⁵ while Lappas et al and Wu et al reported that *SIRT6* can regulate the expression of many inflammatory factors through NF κ B and alleviate inflammatory injury.^{36,37} Considerable evidence suggests that *SIRT6* is associated with neuropsychiatric diseases. We analyzed the influence of *SIRT* polymorphisms on the occurrence of PDSs, finding that the *SIRT6* polymorphic rs350846 genotype CC and rs107251 genotype TT increased the incidence of postpartum depression ($p < 0.05$). Mao et al

reported that expression of *SIRT6* in the hippocampus was increased in chronically stress rats with depression.³⁸ Iwata et al suggested that the inflammasome is a central mediator by which psychological and physical stressors can contribute to the development of depression.³⁹ Together, these studies have supported the view that *SIRT6* may be involved in the occurrence of PDSs by regulating the expression of many inflammatory factors and inducing nerve-cell injury.

A series of previous studies have shown that environmental factors can modulate PDS occurrence.^{40,41} Our data indicated a role for pregnancy stress, domestic violence, and depressive prenatal mood in PDSs. Consistent with a systematic review,⁴² multivariate analysis showed that depressive prenatal mood was a strong predictor of PDSs, and the risk of PDSs in women with depressive prenatal mood during cesarean section was five times that of women with no prenatal depression. It also suggested that in addition to genetic factors that cannot be interfered with, we need to pay attention not only to the postpartum psychological and emotional state but also to understanding the prenatal psychological and emotional state. Research has found that there is a correlation between pregnancy stress and PDSs.^{43,44} Abnormal stress regulation during pregnancy and changes in the hypothalamic-pituitary-adrenal axis may contribute to the occurrence of PDSs. This study

also supports the view that domestic violence can increase the risk of PDSs.⁴⁵ In view of the composition of family relations in Chinese society, marriage bonds and the relationship between mother-in-law and daughter-in-law are worthy of attention. After calculation, there was a moderate correlation between these ($r=0.501$). The relationship between mother-in-law and daughter-in-law is extremely sensitive in the family. A study also found that compared with those living only with their husbands, women living with their parents-in-law had a higher risk of PDSs.⁴⁶ However, this association was not found in this study. Moreover, a previous study showed that perinatal stress events, suicidal tendencies, and lower socioeconomic status also increased the incidence of PDSs,⁴⁷ but this association was not found in this study. To account for this, it may be that maternal response to stress events and suicidal response are relatively evasive, with few total positive events causing statistical analysis results to be less objective. It is also of note that the socioeconomic evaluation should adopt some domestically and internationally recognized evaluation criteria, rather than just comparison of income levels.

PDSs are a complex multifactorial disease that involves chronic changes in the structure and function of neural circuits. As mentioned, environmental and genetic susceptibility play significant roles in the pathogenesis of depression.⁷ Epigenetics is an important new field in depression research, and provides a mechanism for understanding the link between adverse environmental stimuli and changes in gene expression associated with depression.⁴⁸ This study also analyzed interactions between *SIRT* polymorphisms and the environment. We found that *SIRT* rs2873703 and rs4801933 had no significant interaction with pregnancy stress or domestic violence. Nevertheless, there was insufficient evidence to prove that the interaction between *SIRT* polymorphism and environmental factors was involved in the mechanism of PDSs.

There are some limitations in the present study. First of all, the population consisted of cesarean section patients only and not compared to normal deliveries. Secondly, this was a single-center study, and relevant research parameters should be investigated in future multicenter investigations. In addition, the sample of this study was relatively small, and some clinical observation indicators, such as husband–wife relationship and mother-in-law and daughter-in-law relationship are relatively lacking in objective and recognized evaluation criteria.

In summary, this study explored the related factors of PDSs in women after cesarean section. The results suggest

that rs2873703 and rs4801933 in *SIRT2* are factors in susceptibility to PDSs. This study proposes for the first time that *SIRT2* polymorphisms may play a certain role in the pathogenesis of PDSs, which provides a reference for promoting the genetic mechanism of *SIRT* in the pathogenesis of PDSs. Furthermore, adverse environmental stimulation and negative emotions were also factors in susceptibility to PDSs after cesarean section. It is suggested that more attention be paid to the psychological state and living environment of women during pregnancy, in order to reduce the risk of PDSs and improve their quality of life.

Abbreviations

PDSs, postpartum depressive symptoms; EPDS, Edinburgh Postnatal Depression Scale; SNP, single-nucleotide polymorphism.

Data-Sharing Statement

The data sets used during this study are available from the corresponding author on reasonable request.

Ethics and Consent

The study protocol was registered (Chinese Clinical Registry — CHICTR-ROC-17013357). The study was conducted in accordance with the Declaration of Helsinki (World Medical Association 2013) using procedures that had been approved by the ethics committee of the Third Xiangya Hospital of Central South University (P2014/s155, February 20, 2014). Informed consent was obtained from all participants.

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Author Contributions

All authors contributed to data analysis, drafting or revising the article, have agreed on the journal to which the article will be submitted, gave final approval to the version to be published, and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest for this work. There are no personal, organizational, or financial conflicts of interest.

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