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Associations of maternal diabetes mellitus and adiponectin gene polymorphisms with congenital heart disease in offspring

A case-control study

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Abstract

This study aimed at assessing the association of maternal diabetes mellitus (DM), the adiponectin gene (*APM1*) gene polymorphisms, and their interactions with risk of congenital heart disease (CHD) in offspring.

A case-control study of 464 mothers of CHD patients and 504 mothers of healthy children was conducted.

After adjusting for potential confounding factors, our study suggested that mothers with gestational DM (GDM) during this pregnancy (adjusted odds ratio [aOR = 2.96]), GDM in previous pregnancy experiences (aOR = 3.16), and pregestational DM in the 3 months before this pregnancy (aOR = 4.52) were at a significantly higher risk of CHD in offspring, when compared with those without any diabetes. The polymorphisms of maternal *APM1* gene at rs1501299 (T/T vs G/G: aOR = 3.45; T/G vs G/G: aOR = 1.73) and rs2241766 (G/G vs T/T, aOR = 3.36; G/T vs T/T, aOR = 1.93) were significantly associated with risk of CHD in offspring. In addition, significant interactions between maternal DM and the APM1 genetic variants on the development of CHD were found.

Our findings indicate that maternal DM, *APM1* gene genetic variants, and their interactions are significantly associated with risk of CHD in offspring. However, more studies in different ethnic populations and with a larger sample and prospective design are required to confirm our findings.

Abbreviations: 95%CI = 95% confidence interval, aOR = adjusted odds ratio, APM1 gene = adiponectin gene, CHD = congenital heart disease, DM = diabetes mellitus, GDM = gestational diabetes mellitus, OR = odds ratio, PGDM = pregestational diabetes mellitus, unaOR = unadjusted odds ratio.

Keywords: adiponectin gene, case-control study, congenital heart disease, diabetes mellitus, gene-environment interaction

1. Introduction

Congenital heart disease (CHD) is the most common type of serious birth defects and the leading cause of noninfectious deaths in the first year of life.[1] The global prevalence of CHD ranged from 8‰ to 12‰.[1,2] CHD is a multifactorial disease with complex etiology, and both environmental and genetic factors played an important role in the development of CHD.[3] However, the mechanism was not completely understood. It has been widely identified that maternal exposure to diabetes was significantly associated with an increased risk of CHD in offspring.[4–11] Even there were some studies indicating that women with less severe conditions than DM, such as lesser

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degrees of hyperglycemia, were at a significantly higher risk of poor pregnancy outcomes.[12,13] Epidemiological data from several prospective cohort studies also supported the view that glucose plays a momentous role in the causal pathway for CHD, and confirmed that mothers with pre-gestational diabetes mellitus (PGDM) were more likely to develop CHD in their offspring than those without DM.[5–8] Additionally, some animal experiments showed that diabetic rats can cause abnormal changes in myocardial ultrastructure in offspring, resulting in abnormal cardiovascular development of pregnant embryos.[14,15] However, presently, it remains unclear how DM or its clinical symptoms such as hyperglycemia change the normal development of embryonic heart.

Recent years, adiponectin (*APM1*) gene has been widely studied in type 2 DM (T2DM)[16–19]. The *APM1* gene was located in the chromosomal region at 3q27, and was responsible for encoding adiponectin.[20] Adiponectin is an insulin-sensitizing hormone which can help to increase the sensitivity of insulin and improve islet β-cell dysfunction and fatty acid beta-oxidation.[21–23] A lot of studies indicated that single nucleotide polymorphisms (SNPs) of *APM1* gene were significantly associated with varying level of adiponectin and metabolic diseases. For example, the proximal promoter and intronic region of the *AMP1* gene, rs266729 and rs1501299, were proved to be associated with T2DM, gestational diabetes mellitus (GDM), and insulin resistance.[16,17] Another variants, rs2241766 and rs12495941, were reported to be risk factors for T2DM in Chinese population.[18,19] Subsequent research have showed that maternal disease like diabetes can change the intrauterine environment, which make the fetus more prone to develop disease.[24] Therefore, we hypothesized that polymorphisms of maternal *APM1* gene may affect fetal cardiac development by regulating maternal glucose metabolism. It is possible that both elevations of maternal glucose level and maternal genetic factors related glycolipid metabolism can contribute to development of CHD in offspring. However, no studies have been conducted to assess the association between maternal *APM1* gene SNPs and risk of CHD in offspring.

Given this fact that an improved understanding of this issue may be helpful to provide a new clue for exploring the potential mechanism of maternal DM on CHD, therefore, we conducted a hospital-based case-control study with the following objectives:

(1) to further investigate the association between maternal DM and CHD in offspring;
(2) to evaluate the association between polymorphisms of maternal *APM1* gene and CHD in offspring; and
(3) to explore the interaction between maternal DM and *APM1* gene on CHD in offspring.

2. Materials and methods

2.1. Study design and recruitment of study participants

This study has been registered in the Chinese Clinical Trial Registry Center (registration number: ChiCTR1800016635) and was approved by the Institutional Review Board of Xiangya School of Public Health of Central South University (Ethical Approval Number: XYGW-2018-07). Written informed consent was obtained from all mothers. A hospital-based case–control design was performed in the present study. Recruitment was conducted by the Hunan Children's Hospital from November 2017 to March 2019. Hunan Children's Hospital, as a large specialized hospital for children in China, is responsible for the provincial diagnosis, treatment, and management of CHD patients. Approximately 1000 children with CHD are treated surgically in this hospital each year. Eligible children and their parents were recruited for this study during health counseling or medical examination. The convenience sample, driven mainly by the number of respondents, was used for the study. Children with CHD and their parents were identified as the case group. All CHD patients were diagnosed using ultrasonography and confirmed by surgery. Children without any congenital malformation after medical examination and their parents were identified as the control group. The study participants were recruited at 2 clinics from this hospital. The case group was recruited from Department of Cardiothoracic Surgery which provides diagnosis, treatment, surgery, and management of CHD; and the control group were recruited from Department of Child Healthcare after health counseling or medical examination. The controls were selected from the same hospital during the same study period as the cases.

2.2. Inclusion criteria

In our study, the exposures of interest were maternal genetic variants of *APM1* gene and maternal DM including GDM during this pregnancy, GDM in previous pregnancy experiences, and PGDM in the 3 months before this pregnancy. The diagnosis of diabetes was consistent with the World Health Organization criteria. The outcomes of interest were CHD that included the following subtypes: atrial septal defect, ventricular septal defect, atrioventricular septal defect, patent ductus arteriosus, aortopulmonary septal defect, tetralogy of Fallot, and complete transposition of great arteries. Mothers of CHD patients who were diagnosed using ultrasonography and confirmed by surgery were defined as the case group, and mothers of healthy children without any congenital defects defined as the control group. To minimize potential recall bias of exposure by mothers during the pre-pregnancy to the early stage of this pregnancy, all cases and controls were recruited when their children were less than 1 year old. All participants were required to complete the same questionnaire in the same way by some professionally trained investigators. Additionally, eligible mothers need to provide informed consent, belonged to singleton pregnancies for this pregnancy, were of Han Chinese descent, had a complete record of questionnaire, and provided the blood sample. We only concerned nonsyndromic CHDs, and patients with structural malformations involving another organ system or known chromosomal abnormalities were excluded. All the controls were confirmed to have no any malformations. Participants who reported a history of depression or other psychiatric disorders or were diagnosed with depression or a psychiatric illness when they were recruited into the study were also excluded.

2.3. Information collection

Specially trained investigators used a standardized questionnaire to collect information. We collected exposure histories of maternal DM. In this study, we focused on the occurrences of GDM during this pregnancy, GDM in previous pregnancy experiences, and PGDM in the 3 months before this pregnancy as one of main exposures of interest. Exposure histories of maternal DM were mainly provided through the subject's self-report.

Then, we consulted their Maternal and Child Health Manual and medical records to further confirm the corresponding information of maternal DM histories. In China, each pregnant woman will be provided with a Maternal and Child Health Manual, which will record their basic demographic characteristics, behavioral habits, illness, and the results of various medical examinations during pregnancy. In our study, we also examined the SNPs of maternal *APM1* gene at rs1501299, rs12495941, rs2241766, and rs266729 as another major exposure of interest.

When evaluating the association of maternal DM and *APM1* gene polymorphisms with risk of CHD in offspring, we considered other common influencing factors that have been identified by previous studies, so as to control potential confounding factors as much as possible. For mothers, we collected the following information including age at this pregnancy (years), ethnic background, education level, body mass index before this pregnancy, family's annual income in the past 1 year, residence locations (rural or urban areas), family history of birth defects (yes or no), personal history of birth defects (yes or no), family history of consanguineous marriages in the 3 generations (yes or no), folate supplementation status in this pregnancy (yes or no), cold or fever history in the 3 months before this pregnancy (yes or no), active or passive smoking histories in the 3 months before this pregnancy (yes or no), drinking history in the 3 months before this pregnancy (yes or no), history of drinking tea in the 3 months before this pregnancy (yes or no), history of drinking coffee in the 3 months before this pregnancy (yes or no), frequency of cosmetics use in the 3 months before this pregnancy (never, sometime, often, or every day), and dietary habits in the 3 months before this pregnancy (eg, the intake frequency of pickled foods, barbecued or fried foods, fresh meat, fish and shrimp, vegetables, fresh fruits, fresh eggs, soy foods, and milk products).

Additionally, we also investigated the following questions: "Was there a factory near your place of residence that discharges environmentally harmful substances in the 3 months before this pregnancy (ie, environmentally harmful substance exposures)? Was there a traffic road or a noisy factory near where you live in the 3 months before this pregnancy (ie, noise pollution exposures)? Was your house newly renovated in the 3 months before this pregnancy? Did you rear pets in the 3 months before this pregnancy (ie, pet feeding experiences)? Did you often dye or perm your hair in the 3 months before this pregnancy (ie, perming or dying hair experiences)?" For spouses, their age, education level, smoking history, and drinking history were collected. The investigators who were responsible for collecting mentioned-above information underwent rigorous training before the investigation. Additionally, questionnaires were anonymous and confidential and administered by trained investigators.

2.4. Genotyping

Four genetic loci (rs1501299, rs12495941, rs2241766, and rs266729) of *APM1* gene were selected as candidate loci for this study. These loci have been widely studied in the field of DM development by previous studies.[17,19,24–26] When mothers completed the questionnaire, they were requested to provide 3 to 5 milliliters of peripheral venous blood for genotyping. Blood samples were collected in EDTA-treated anticoagulant tubes, then were separated into plasma and blood cells immediately by centrifugation, and finally were stored at −80°C until the genotype analysis was performed. The DNA was extracted from blood cells by using the QIAamp DNA Mini Kit (Qiagen, Valencia, CA) according to the manufacturer's standard protocol and dissolved in sterile TBE buffer. To ensure the DNA was eligible to be used as a template for polymerase chain reaction, ultraviolet spectrophotometer was used to determine the concentration and purity of the DNA solution. The polymorphisms of *APM1* gene at rs1501299, rs12495941, rs2241766, and rs266729 were tested using the matrix-assisted laser desorption and ionization time-of-flight mass spectrometry Mass Array system (Agena iPLEXassay, San Diego, CA, USA). Different cycling conditions were used for optimal amplification of target sequences. The details of polymerase chain reaction primers, cycling conditions, and expected product sizes for this gene have been described by previous studies.[17,19,25,26] The laboratory personnel, who performed the genotyping, were blinded to the cases or controls status. Each sample was retyped and double-checked to ensure the reliability of experiments. The error rate of genotyping was lower than 5%.

2.5. Statistical analysis

Categorical variables were described using frequencies and percentages, and continuous variables using means and standard deviations. In univariate analysis, the Pearson Chi-squared test or Fisher exact test were used to compare the differences between the case and control group for nominal variable data; the Wilcoxon rank sum test was used for ordinal categorical variable data. Hardy–Weinberg equilibrium was tested for every group (significance level at $P < .10$). Odds ratios (ORs) and their 95% confidence intervals (CIs) were used to assess the level of association. Univariate logistic regression and multivariable logistic regression were used to calculate the unadjusted ORs (unaORs) and the adjusted ORs (aORs), respectively. We used logistic regression and controlled for the potential confounding factors to examine the main effects and interactive effects of the gene-environment interaction of maternal *APM1* gene and DM for risk of CHDs in offspring. In the logistic regression model, the diagnosis group (case vs control) was set as a dependent variable (binary outcome). The corresponding confounding factors, maternal DM, genotypes of *APM1* gene, and the interaction between maternal *APM1* gene and DM were set as independent variables (covariates). The effects of independent variables were expressed as OR with 95% CI. Models of the gene-environment interactions and their implications were determined according to a method introduced in an article published by Wallace.[28] Whether there is an interaction was determined by using interaction coefficients (γ). The γ values were calculated by regression coefficient (β) from logistic regression analysis (eg, $\gamma 1 = \beta e^{*} g/\beta e$ and $\gamma 2 = \beta e^{*} g/\beta g$ for gene-environment interaction). When all γ values were more than 1, there was a positive interaction; when all γ values were less than 1, there was a negative interaction; and when the γ values were equal to 1, there was no interaction.

Of note, considering the limited sample size in the present study, we only focused on the risk of total CHD, and we did not assess the risk of specific CHD subtypes. Statistical tests were declared significant for a 2-sided *P*-value not exceeding .05, except where otherwise specified. All analyses were performed using SAS version9.1 (SAS Institute Inc., Cary, NC).

2.6. Ethical approval

The study was approved by the Ethics Committee of Xiangya School of Public Health of Central South University.

3. Results

3.1. Recruitment of study participants

From November 2017 to March 2019, 789 mothers of infants with CHDs and 880 mothers of healthy infants were recruited to the case group and control group, respectively. Finally, 464 eligible mothers were included into the case group, 504 into the control group. Among 464 CHD cases, 78 (16.8%) were diagnosed with atrial septal defect, 286 (61.6%) with ventricular septal defect, 50 (10.8%) with atrioventricular septal defect, 130 (28.0%) with patent ductus arteriosus, 6 (1.3%) with aorto-pulmonary septal defect, 26 (5.6%) with tetralogy of Fallot, and 2 (0.4%) with complete transposition of great arteries (of note, some cases have been diagnosed with multiple subtypes of CHD. Therefore, the sum of the various subtypes was not equal to 464). Reasons for not including the remaining participants in the case group were:

(1) non-Han Chinese population (n = 124);
(2) children's age was more than 1 year old (n = 29);
(3) lack of accurate exposure information of maternal DM (n = 13);
(4) multiple pregnancies (n = 26); and
(5) no blood samples were collected (n = 133).

Reasons for not including the remaining participants in the control group were:

(1) non-Han Chinese population (n = 98);
(2) children's age was more than 1 year old (n = 65);
(3) lack of accurate exposure information of maternal DM (n = 27);
(4) multiple pregnancies (n = 19); and
(5) no blood samples were collected (n = 167).

3.2. Baseline characteristics in the case and control groups

The baseline characteristics among 2 groups are summarized Table 1. In the comparisons of baseline characteristics, the following factors were significantly different among 2 groups: maternal age, education level, family annual income, residence location, family history of birth defects, family history of consanguineous marriages, folate supplementation status in this pregnancy, cold and fever history, history of active and passive smoking, drinking history, history of drinking tea, history of drinking coffee, frequency of cosmetics use, environmentally harmful substance and noise pollution exposures, pet feeding experiences, perming or dying hair experiences, and dietary habits (including the intake frequency of barbecued or fried foods, fish and shrimp, fresh eggs, fresh fruits, soy foods, and milk products) as well as spouse's education level, and smoking and drinking histories. Therefore, these factors will be controlled when assessing the association of maternal DM, the *APM1* gene polymorphisms and their interactions with risk of CHD in offspring.

3.3. Maternal DM and risk of CHD

The results of univariable analysis on the association between maternal DM and CHD risk in offspring are summarized in Table 2. Overall, compared with those giving birth to a health child, mothers giving birth to a child with CHD were more likely to report a higher rate of $\chi^2 = 16.018$, $P = .000$), GDM in previous GDM during this pregnancy (11.2% vs 4.4%; $\chi^2 = 14.082$, $P = .000$), and PGDM in the 3 months pregnancy experiences (9.5% vs 3.6%; before this pregnancy; 12.5% vs 4.0%). Additionally, unadjusted logistic regression analysis showed that mothers who reported to have GDM during this pregnancy (unaOR = 2.77; 95% CI: 1.65–4.63), GDM in previous pregnancy experiences (unaOR = 2.83; 95% CI: 1.61–4.97), and PGDM in the 3 months before this pregnancy (unaOR = 3.46; 95% CI: 2.05–5.85) were at a significantly higher risk of CHD in offspring.

We further conducted a multiple logistic regression analysis, the results showed that mothers who reported to have GDM during this pregnancy (aOR = 2.96; 95% CI = 1.57–5.59), GDM in previous pregnancy experiences (aOR = 3.16; 95% CI = 1.59–6.28) and PGDM in the 3 months before this pregnancy (aOR = 4.52; 95% CI = 2.41–8.50) had a significantly increased risk of CHD in offspring, when compared with the reference group.

3.4. Maternal APM1 gene polymorphisms and risk of CHD

The genotype and allele frequencies for each SNP of the *APM1* gene are summarized in Table 3. The genotype distributions of APM1 at rs1501299, rs12495941, rs2241766, and rs266729 were within Hardy–Weinberg equilibrium in the control group. For rs1501299, there were statistically significant 2 = 44.425; χ differences for the genotypes ($\chi^2 = 41.010$; $P = .000$) and the allelic distribution ($P = .000$) between the case and control groups. Overall, mothers with the T/T genotype (unaOR = 3.22, 95% CI = 2.03–5.10) or the T allele (unaOR = 1.98; 95% CI = 1.62–2.42) had a significantly increased risk of CHD in offspring, when compared with those with the G/G genotype or the G allele, respectively. $\chi^2 = 39.109$; $P = .000$) and the allelic distribution for rs2241766, the genotypes ($\chi^2 = 38.564$; $P = .000$) differed significantly between 2 groups. Overall, mothers with the (G/G (unaOR = 3.65; 95% CI = 2.31–5.78) or G/T (unaOR = 1.80; 95% CI = 1.37–2.35) genotype compared with those with the T/T genotype, were at a significantly higher risk of CHD in offspring. Additionally, the risk of CHD in offspring was significantly increased among mothers with the G allele compared with those with the T allele (unaOR = 1.83; 95% CI = 1.51–2.22). However, there were no statistically significant differences for both the genotypes ($\chi^2 = 3.373$ and $P = .185$ for rs12495941; $\chi^2 = 0.772$ and $P = .680$ for rs266729) and the allelic distribution ($\chi^2 = 1.113$ and $P = .291$ for rs12495941; $\chi^2 = 0.473$ and $P = .491$ for rs266729) at rs12495941 and rs266729 between the case and control groups.

The results of multiple logistic regression analysis suggested that polymorphisms of APM1 at rs1501299 and rs2241766 were significantly associated with risk of CHD in offspring. For example, for rs1501299, mothers with the T/G (aOR = 1.73; 95% CI = 1.02–2.92) or T/T (aOR = 3.45; 95% CI = 2.08–5.73) genotype compared with those with the G/G genotype were at a significantly higher risk of CHD in offspring; for rs2241766, mothers with the G/T (aOR = 1.93; 95% CI = 1.42–2.61) or G/G (aOR = 3.36; 95% CI = 2.02–5.60) genotype experienced a significantly increased risk of CHD in offspring, compared with those with T/T genotype. However, our study did not show a significant association between genetic variants at rs12495941 and rs266729 and risk of CHD in offspring.

Table 1

Baseline characteristics in the case and control groups.

Variables	Control group (n = 504)	Case group (n = 464)	Univariable analysis
Maternal age at this pregnancy (yr)	30.91 ± 5.07	29.85 ± 5.76	
<20	2 (0.4%)	14 (3.0%)	$\chi^2 = 10.28$; $P = .006$
20–34	432 (85.7%)	390 (84.1%)	
≥35	70 (13.9%)	60 (12.9%)	
Education level			
Less than primary or primary	6 (1.2%)	66 (14.2%)	$Z = 12.306$; $P = .000$
Junior high school	100 (19.8%)	190 (40.9%)	
Senior middle school	168 (33.3%)	130 (28.0%)	
College or above	230 (45.6%)	78 (16.8%)	
Body mass index before this pregnancy			
<18.5	126 (25.0%)	98 (21.2%)	$\chi^2 = 6.326$; $P = .176$
18.5–23.99	288 (57.1%)	286 (61.6%)	
24–27.99	64 (12.7%)	58 (12.5%)	
≥28	36 (5.2%)	22 (4.7%)	
Family annual income in the past 1 yr (RMB)			
≤50,000	144 (28.6%)	372 (80.2%)	$Z = 15.946$; $P = .000$
60,000–100,000	216 (42.9%)	68 (14.7%)	
110,000–150,000	46 (9.1%)	10 (2.2%)	
≥160,000	98 (19.4%)	14 (3.0%)	
Residence location			
Rural areas	276 (54.8%)	344 (74.1%)	$\chi^2 = 39.390$; $P = .000$
Urban area s	228 (45.2%)	120 (25.9%)	
Family history of births defects			
Yes	4 (0.8%)	28 (6.0%)	$\chi^2 = 20.759$; $P = .000$
Personal history of births defects			
Yes	2 (0.4%)	4 (0.9%)	$P = 0.434$ (Fisher exact test)
Family history of consanguineous marriages			
Yes	4 (0.8%)	28 (6.0%)	$\chi^2 = 20.759$; $P = .000$
Folate supplementation status in this pregnancy			
Yes	470 (93.3%)	386 (83.2%)	$\chi^2 = 23.917$; $P = .000$
Cold and fever history in the 3 mo before this pregnancy			
Yes	58 (11.5%)	98 (21.1%)	$\chi^2 = 16.513$; $P = .000$
History of active smoking in the 3 mo before this pregnancy			
Yes	10 (2.0%)	32 (6.9%)	$\chi^2 = 14.046$; $P = .000$
History of passive smoking in the 3 mo before this pregnancy			
Yes	188 (37.3%)	242 (52.2%)	$\chi^2 = 21.589$; $P = .000$
Drinking history in the 3 mo before this pregnancy			
Yes	36 (7.1%)	60 (12.9%)	$\chi^2 = 9.060$; $P = .003$
History of drinking tea in the 3 mo before this pregnancy			
Yes	102 (20.2%)	60 (12.9%)	$\chi^2 = 9.257$; $P = .002$
History of drinking coffee in the 3 mo before this pregnancy			
Yes	22 (4.4%)	44 (9.5%)	$\chi^2 = 9.959$; $P = .002$
Frequency of cosmetics use in the 3 mo before this pregnancy			
Never	316 (62.7%)	338 (72.8%)	$Z = 2.525$; $P = .002$
Sometime	124 (24.6%)	54 (11.6%)	
Often	28 (5.6%)	30 (6.5%)	
Every day	36 (7.1%)	42 (9.1%)	
Was there a factory near place of residence that discharges environmentally harmful substances?			
Yes	34 (6.7%)	94 (20.3%)	$\chi^2 = 38.443$; $P = .000$
Was there a traffic road or a noisy factory near where you live (noise exposure)?			
Yes	92 (18.3%)	124 (26.7%)	$\chi^2 = 9.999$; $P = .002$
Was your house newly renovated in the 3 mo before this pregnancy?			
Yes	26 (5.2%)	34 (7.3%)	$\chi^2 = 1.955$; $P = .162$
Did you rear pets in the 3 mo before this pregnancy?			
Yes	32 (6.3%)	60 (12.9%)	$\chi^2 = 12.168$; $P = .000$
Did you often dye or perm your hair in the 3 mo before this pregnancy?			
Yes	30 (6.0%)	58 (12.5%)	$\chi^2 = 12.532$; $P = .000$
Dietary habits in the 3 mo before this pregnancy			
The intake frequency of pickled foods			
Never	276 (54.8%)	280 (60.3%)	$Z = -1.515$; $P = .284$
≤2 times/wk	212 (42.1%)	164 (35.3%)	
3–5 times/wk	14 (2.8%)	16 (3.4%)	

(*continued*)

Table 1
(continued).

Variables	Control group (n = 504)	Case group (n = 464)	Univariable analysis
≥6 times/wk	2 (0.4%)	4 (0.9%)	
The intake frequency of barbecued or fried foods			
Never	306 (60.7%)	358 (77.2%)	Z = –5.431; P = .000
≤2 times/wk	178 (35.3%)	94 (20.3%)	
3–5 times/wk	16 (3.2%)	10 (2.2%)	
≥6 times/wk	4 (0.8%)	2 (0.4%)	
The intake frequency of fresh meat			
Never	14 (2.8%)	14 (3.0%)	Z = –0.193; P = .847
≤2 times/wk	28 (5.6%)	42 (9.1%)	
3–5 times/wk	88 (17.5%)	62 (13.4%)	
≥ 6 times/wk	374 (74.2%)	346 (74.6%)	
The intake frequency of fish or shrimp			
Never	22 (4.4%)	98 (21.1%)	Z = –13.381; P = .000
≤2 times/wk	146 (29.0%)	232 (50.0%)	
3–5 times/wk	136 (27.0%)	94 (20.3%)	
≥6 times/wk	200 (39.7%)	40 (8.6%)	
The intake frequency of fresh eggs			
Never	24 (4.8%)	60 (12.9%)	Z = –8.450; P = .000
≤2 times/wk	56 (11.1%)	126 (27.2%)	
3–5 times/wk	116 (23.0%)	102 (22.0%)	
≥6 times/wk	308 (61.1%)	176 (37.9%)	
The intake frequency of fresh vegetables			
Never	2 (0.4%)	2 (0.4%)	Z = –0.100; P = .920
≤2 times/wk	12 (2.4%)	10 (2.2%)	
3–5 times/wk	22 (4.4%)	22 (4.7%)	
≥6 times/wk	468 (92.9%)	430 (92.7%)	
The intake frequency of fresh fruits			
Never	10 (2.0%)	16 (3.4%)	Z = –3.806; P = .000
≤2 times/wk	26 (5.2%)	52 (11.2%)	
3–5 times/wk	56 (11.1%)	62 (13.4%)	
≥6 times/wk	412 (81.7%)	334 (72.0%)	
The intake frequency of soy foods			
Never	70 (13.9%)	118 (25.4%)	Z = –8.029; P = .000
≤2 times/wk	146 (29.0%)	192 (41.4%)	
3–5 times/wk	128 (25.4%)	94 (20.3%)	
≥6 times/wk	160 (31.7%)	60 (12.9%)	
The intake frequency of milk products			
Never	98 (19.4%)	182 (39.2%)	Z = –6.488; P = .000
≤2 times/wk	104 (20.6%)	102 (22.0%)	
3–5 times/wk	110 (21.8%)	52 (11.2%)	
≥6 times/wk	192 (38.1%)	128 (27.6%)	
Spouse's characteristics before this pregnancy			
Age (yr)			
<35	338 (67.1%)	302 (65.1%)	χ^2 = 0.422; P = .516
≥35	166 (32.9%)	162 (34.9%)	
Education level			
Less than primary or primary	12 (2.4%)	56 (12.1%)	Z = 11.327; P = .000
Junior high school	108 (21.4%)	214 (46.1%)	
Senior middle school	178 (35.3%)	116 (25.0%)	
College or above	206 (40.9%)	78 (16.8%)	
History of smoking			
Yes	288 (57.1%)	314 (67.7%)	χ^2 = 11.391; P = .001
Drinking history			
Yes	234 (46.4%)	260 (56.0%)	χ^2 = 8.921; P = .003

*Statistically significant (a = 0.05).

3.5. Interactions of maternal APM1 gene and maternal DM with risk of CHD in offspring

The gene-environment interactions between the maternal *APM1* gene and maternal DM for the development of CHD in offspring are summarized in Table 4. After controlling for potential confounding factors, for APM1 at rs1501299, there were statistically significant interactions for the risk of CHDs in offspring between the T/T genotype and PGDM in the 3 months before this pregnancy (OR = 20.50; 95% CI = 7.72–54.44), and between the T/G genotype and PGDM in the 3 months before this pregnancy (OR = 5.03; 95% CI = 1.78–14.21); for APM1 at

Table 2

Maternal DM in the case and control groups.

Maternal DM	Control group	Case group	Univariable analysis	Unadjusted OR (95%CI)	Adjusted OR (95%CI)[†]
GDM during this pregnancy					
No	482 (95.6%)	412 (88.8%)	$\chi^2=16.018$; $P=.000$	1	1
Yes	22 (4.4%)	52 (11.2%)		2.77 (1.65–4.63)[*]	2.77 (1.65–4.63)[*]
GDM in previous pregnancy experiences					
No	486 (96.4%)	420 (90.5%)	$\chi^2=14.082$; $P=.000$	1	1
Yes	18 (3.6%)	44 (9.5%)		2.83 (1.61–4.97)[*]	2.77 (1.65–4.63)[*]
PGDM in the 3 mo before this pregnancy					
No	484 (96.0%)	406 (87.5%)	$\chi^2=23.736$; $P=.000$	1	1
Yes	20 (4.0%)	58 (12.5%)		3.46 (2.05–5.85)[*]	2.77 (1.65–4.63)[*]

CHD = congenital heart disease, CI = confidence interval, DM = diabetes mellitus, GDM = gestational diabetes mellitus, OR = odds ratio, PGDM = pregestational diabetes mellitus.

[*] Statistically significant ($a=0.05$).

[†] Adjusted for maternal age, education level, family annual income, residence location, family history of birth defects, family history of consanguineous marriages, folate supplementation status in this pregnancy, cold and fever history, history of active and passive smoking, drinking history, history of drinking tea, history of drinking coffee, frequency of cosmetics use, environmentally harmful substance and noise pollution exposures, pet feeding experiences, perming or dying hair experiences and dietary habits (including the intake frequency of barbecued or fried foods, fish and shrimp, fresh eggs, fresh fruits, soy foods, and milk products) as well as spouse's education level, and smoking and drinking histories.

Table 3

Genotype distribution and allele frequencies of APM1 gene in the case and control groups.

APM1 gene	Control group (n = 504)	Case group (n = 464)	Univariate analysis	Unadjusted OR (95%CI)	Adjusted OR (95%CI)[†]
Genotype at rs1501299					
G/G	72 (14.3%)	30 (6.5%)	$\chi^2=41.010$; $P=.000$	1	1
T/G	214 (42.5%)	142 (30.6%)		1.59 (0.99–2.56)	1.73 (1.02–2.92)[*]
T/T	218 (43.3%)	292 (62.9%)		3.22 (2.03–5.10)[*]	3.45 (2.08–5.73)[*]
T/G + TT	432 (85.7%)	434 (93.5%)		2.41 (1.54–3.77)[*]	2.61 (1.59–4.26)[*]
Allele at rs1501299					
G	358 (35.5%)	202 (21.8%)	$\chi^2=44.425$; $P=.000$	1	
T	650 (64.5%)	726 (78.2%)		1.98 (1.62–2.42)[*]	
Genotype at rs12495941					
G/G	170 (33.7%)	154 (33.2%)	$\chi^2=3.373$; $P=.185$	1	1
G/T	266 (52.8%)	228 (49.1%)		0.95 (0.72–1.25)	0.96 (0.70–1.31)
T/T	68 (13.5%)	82 (17.7%)		1.33 (0.90–1.96)	1.37 (0.88–2.11)
G/T + TT	334 (66.3%)	310 (66.8%)		1.03 (0.78–1.34)	1.04 (0.77–1.40)
Allele at rs12495941					
G	606 (60.1%)	536 (57.8%)	$\chi^2=1.113$; $P=.291$	1	1
T	402 (39.9%)	392 (42.2%)		1.10 (0.92–1.32)	
Genotype at rs2241766					
T/T	266 (52.8%)	164 (35.3%)	$\chi^2=39.109$; $P=.000$	1	1
G/T	206 (40.9%)	228 (49.1%)		1.80 (1.37–2.35)[*]	1.93 (1.42–2.61)[*]
G/G	32 (6.3%)	72 (15.5%)		3.65 (2.31–5.78)[*]	3.36 (2.02–5.60)[*]
G/T + G/G	238 (47.2%)	300 (64.7%)		2.04 (1.58–2.65)[*]	2.13 (1.59–2.84)[*]
Allele at rs2241766					
T	738 (73.2%)	556 (59.9%)	$\chi^2=38.564$; $P=.000$	1	
G	270 (26.8%)	372 (40.1%)		1.83 (1.51–2.22)[*]	
Genotype at rs266729					
C/C	266 (52.8%)	252 (54.3%)	$\chi^2=0.772$; $P=.680$	1	1
C/G	208 (41.3%)	190 (40.9%)		0.96 (0.74–1.25)	0.82 (0.61–1.11)
G/G	30 (6.0%)	22 (4.7%)		0.77 (0.44–1.38)	0.75 (0.40–1.43)
C/G + G/G	238 (47.2%)	212 (45.7%)		0.94 (0.73–1.21)	0.81 (0.61–1.08)
Allele at rs266729					
C	740 (73.4%)	694 (74.8%)	$\chi^2=0.473$; $P=.491$	1	
G	268 (26.6%)	234 (25.2%)		0.93 (0.76–1.14)	

CI = confidence interval, OR = odds ratio.

[*] Statistically significant ($a=0.05$).

[†] Adjusted for maternal age, education level, family annual income, residence location, family history of birth defects, family history of consanguineous marriages, folate supplementation status in this pregnancy, cold and fever history, history of active and passive smoking, drinking history, history of drinking tea, history of drinking coffee, frequency of cosmetics use, environmentally harmful substance and noise pollution exposures, pet feeding experiences, perming or dying hair experiences and dietary habits (including the intake frequency of barbecued or fried foods, fish and shrimp, fresh eggs, fresh fruits, soy foods, and milk products) as well as spouse's education level, and smoking and drinking histories.

Table 4

Interactions of maternal APM1 genetic variants and DM experiences associated with CHD in offspring.

Maternal DM	Genotype	β	*P*-value	Adjusted OR (95%CI)[‡]
GDM during this pregnancy	rs1501299			
No	G/G			1
No	T/G	0.794 (β_{g1})	.005	2.21 (1.26–3.87)
No	T/T	1.527 (β_{g2})	.000	4.61 (2.67–7.96)
Yes[†]	G/G	22.992 (β_{e1})	.999	–
Yes	T/G	1.047 (β_{e1*g1})	.077	2.85 (0.89–9.11)
Yes	T/T	2.391 (β_{e1*g2})	.000	10.92 (4.82–24.76)
GDM in previous pregnancy experiences	rs1501299			
No	G/G			1
No	T/G	0.520 (β_{g1})	.056	1.68 (0.99–2.87)
No	T/T	1.326 (β_{g2})	.000	3.77 (2.25–6.29)
Yes	G/G			
Yes	T/G	1.290 (β_{e1*g1})	.006	3.63 (1.45–9.09)
Yes	T/T	2.467 (β_{e1*g2})	.000	11.78 (4.23–32.81)
PGDM in the 3 mo before this pregnancy	rs1501299			
No	G/G			1
No	T/G	0.705 (β_{g1})	.016	2.02 (1.14–3.58)
No	T/T	1.453 (β_{g2})	.000	4.28 (2.45–7.45)
Yes	G/G	1.559 (β_{e1})	.039	4.76 (1.08–20.87)
Yes	T/G	1.615 (β_{e1*g1})[*]	.002	5.03 (1.78–14.21)
Yes	T/T	3.021 (β_{e1*g2})[*]	.000	20.50 (7.72–54.44)
GDM during this pregnancy	rs2241766			
No	T/T			1
No	G/T	0.662 (β_{g1})	.000	1.94 (1.43–2.63)
No	G/G	1.164 (β_{g2})	.000	3.20 (1.92–5.33)
Yes	T/T	1.191 (β_{e1})	.012	3.29 (1.29–8.36)
Yes	G/T	1.402 (β_{e1*g1})[*]	.000	4.06 (2.01–8.22)
Yes[†]	G/G	21.013 (β_{e1*g2})	.998	–
GDM in previous pregnancy experiences	rs2241766			
No	T/T			1
No	G/T	0.633 (β_{g1})	.000	1.88 (1.39–2.55)
No	G/G	1.042 (β_{g2})	.000	2.83 (1.70–4.74)
Yes	T/T	0.431 (β_{e1})	.357	1.54 (0.62–3.85)
Yes	G/T	1.595 (β_{e1*g1})[*]	.001	4.93 (1.87–12.98)
Yes[†]	G/G	21.350 (β_{e1*g2})	.998	–
PGDM in the 3 mo before this pregnancy	rs2241766			
No	T/T			1
No	G/T	0.704 (β_{g1})	.000	2.02 (1.49–2.75)
No	G/G	1.143 (β_{g2})	.000	3.14 (1.88–5.24)
Yes	T/T	1.476 (β_{e1})	.001	4.37 (1.87–10.23)
Yes	G/T	1.557 (β_{e1*g1})[*]	.000	4.75 (2.20–10.26)
Yes[†]	G/G	21.570 (β_{e1*g2})	.998	

CHD = congenital heart disease, CI = confidence interval, DM = diabetes mellitus, GDM = gestational diabetes mellitus, OR = odds ratio, PGDM = pregestational diabetes mellitus.

[*] The interaction is statistically significant.

[†] Because the sample size is 0, the effective OR value could not be calculated.

[‡] Adjusted for maternal age, education level, family annual income, residence location, family history of birth defects, family history of consanguineous marriages, folate supplementation status in this pregnancy, cold and fever history, history of active and passive smoking, drinking history, history of drinking tea, history of drinking coffee, frequency of cosmetics use, environmentally harmful substance and noise pollution exposures, pet feeding experiences, perming or dying hair experiences and dietary habits (including the intake frequency of barbecued or fried foods, fish and shrimp, fresh eggs, fresh fruits, soy foods, and milk products) as well as spouse's education level, and smoking and drinking histories.

rs2241766, we found statistically significant interactions between the G/T genotype and PGDM in the 3 months before this pregnancy (OR = 4.75; 95% CI = 2.20–10.26), between the G/T genotype and GDM in previous pregnancy experiences (OR = 4.93; 95% CI = 1.87–12.98), and between the G/T genotype and GDM during this pregnancy (OR = 4.06; 95% CI = 2.01–8.22).

4. Discussion

In view of the fact that CHD has these characteristics, including the rising incidence, the great harm to health and the heavy burden of disease, people are becoming more and more interested in its etiology. Although it is generally believed that the development of CHD is multifaceted and involves genetic and environmental factors, the reasons are not completely clear. In this case-control study, we further examined the association between maternal DM and risk of CHD in offspring, assessed the possibility that polymorphisms of maternal *APM1* gene might be associated with risk of CHD in offspring, and finally analyzed the interactions between maternal DM and APM1 genetic variants for CHD in offspring. As far as we know, this is the first time that the association of maternal DM, the APM1 genetic variants, and

their interactions with risk of CHD in offspring has been explored, which could help to provide new insight for the reasons why maternal diabetes were significantly associated with CHD in offspring.

Findings from the present study further indicated that maternal DM was significantly associated with risk of CHD in offspring. In general, the risk of CHD was significantly increased by 196% among women reporting to have GDM during this pregnancy (aOR = 2.96), 216% among mothers reporting to have GDM in previous pregnancy experiences (aOR = 3.16), and 352% among those reporting to have PGDM in the 3 months before this pregnancy (aOR = 4.52). In fact, the association between maternal DM and risk of CHD in offspring has been well confirmed by previous studies. For example, several nationwide cohort studies from USA,[5] Norway,[6] Canada,[7] and Denmark[8] showed that mothers with DM compared with nondiabetic mothers, were at significantly higher risks of CHD and its most phenotypes. Furthermore, our study showed that the risk of CHD in offspring seems to be significantly higher among mothers with PGDM (aOR = 4.52) than those with GDM (aOR = 2.96), which was supported by previous studies.[8] It has been reported that the PGDM was the only relatively prevalent population risk factor for CHD.[10] A common view was that the mechanisms of maternal DM on CHD in offspring were quite different between PGDM and GDM women. We know that the critical stage of fetal heart development is 3 to 7 weeks of gestation.[28] Pregestational diabetes may lead to hyperglycemia conditions in the uterine environment at this stage, resulting in abnormal embryonic heart development.[29,30] However, GDM is usually diagnosed between 24 and 28 weeks of gestation, which has missed the critical stage of embryonic heart development.[31] Therefore, there was a possibility that women with PGDM were at a higher risk of developing CHD in offspring than those with GDM. Of note, both published studies and the present study confirmed maternal DM was an independent risk factor of CHD in offspring, but the exact mechanism involved in the association between maternal DM and CHD remains unknown and warrants further research.

In the present study, we also assessed the association of the SNPs of maternal *APM1* gene at rs1501299, rs12495941, rs2241766, and rs266729 with risk of CHD in offspring. Our study indicated that genetic variants in the maternal *APM1* gene may play an important role in the development of CHD in offspring. After adjusting for the confounding factors, the results suggested that polymorphisms of APM1 at rs1501299 and rs2241766 were significantly associated with risk of CHD in the homozygote (T/T vs G/G, aOR = 3.45 for rs1501299; G/G vs T/T, aOR = 3.36 for rs2241766) and heterozygote (T/G vs G/G, aOR = 1.73 for rs1501299; G/T vs T/T, aOR = 1.93 for rs2241766) comparisons. The importance of these results lies in the fact that genetic variants of maternal genes related to glycolipid metabolism may be significantly associated with risk of CHD in offspring. It was no doubt that our research will provide a new clue for screening candidate genes of CHD.

As far as we know, so far, there has been no study to focus on the relationship between maternal *APM1* gene and risk of CHD in offspring. In other words, data on the role of maternal *APM1* gene polymorphisms in the pathogenesis of CHD in offspring are not sufficient. As mentioned earlier, maternal DM has been confirmed to be an important risk factor affecting embryonic heart development, which may indicate that these genes related to glycolipid metabolism may become susceptible genes of CHD. In fact, our study supported this hypothesis. The *APM1* gene is responsible for encoding a plasma protein called adiponectin.[20] Adiponectin was shown to stimulate glucose uptake and fatty acid oxidation by the phosphorylation and activation of 5'-AMP-activated protein kinase.[32,33] There were some studies that suggested lower concentrations of adiponectin were significantly associated with T2DM,[34] dyslipidemia,[35] insulin resistance,[36] and cardiovascular disease.[37,38] The presence of genetic variation for some genes such as *APM1* gene, regulating adiponectin metabolism, can bring about a lower level of adiponectin,[39] which in turn may lead to increased glucose levels, insulin resistance, and the risk of cardiovascular disease. The present study is the first to examine the role of maternal *APM1* gene polymorphisms in the etiology of CHD in offspring. Our study suggested that the mutation of maternal *APM1* gene may contribute to the pathogenesis of CHD in offspring.

It has been proposed that CHD occurrence depends on interactions between genetic and environmental factors. Therefore, further analysis was performed for the interactive effect between maternal DM and *APM1* gene polymorphisms at rs1501299, rs12495941, rs2241766, and rs266729 on the occurrence of CHD in offspring. The present study is also the first to demonstrate a gene-environment interaction between maternal *APM1* gene and maternal DM for development of CHD in offspring. Our study found that there were significantly interactive effects between maternal DM and *APM1* gene polymorphisms on the pathogenesis of CHD in offspring. The heart begins to develop in the early stage of embryo and basically completes in the middle stage of embryo. Therefore, the most sensitive period to maternal environment for embryo is in the periconceptional period and the early stage of pregnancy. High glucose status caused by maternal DM may affect the microenvironment for fetal growth and lead to abnormal development of fetal heart. In China, some studies have showed that the *APM1* gene variant may be a risk factor for dyslipidemia that were significantly associated with higher levels of triglycerides, low-density lipoprotein-cholesterol, and total cholesterol as well as lower levels of high-density lipoprotein-cholesterol.[40–42] On the basis of the above studies, *APM1* gene polymorphism may lead to lipid metabolism disorder in pregnant women with diabetes, which may lead to changes in uterine environment. Therefore, maternal diabetes and *APM1* gene may play a combined effect on the occurrence of CHD in offspring by affecting the uterine environment. However, this hypothesis needs to be further confirmed.

Potential limitations of this study should be considered. First, our study was case-control study, so recall bias cannot be excluded. Exposure histories of maternal DM and other factors were mainly provided through the subject's self-report, which bring about a serious concern that mothers did not accurately recall their situation because of memory errors. Recall bias could affect the result in the measurement of maternal DM and other covariates, which can cause the corresponding information bias. However, we further confirmed all information by consulting their Maternal and Child Health Manual and medical records. In China, each pregnant woman will be provided with a Maternal and Child Health Manual, which will record their basic demographic characteristics, behavioral habits, illness and the results of various medical examinations before and during pregnancy. Additionally, to minimize potential recall bias of exposure by mothers during the pre-pregnancy to the early stage of this pregnancy, all cases and controls were recruited when their

children were less than 1 year old. Second, mothers in case group and control group were recruited from different department in a same hospital. Because the cases and controls did not come from the same sample source, the balance of baseline data between the 2 groups is affected. However, we adjusted the baseline data when exploring the association of maternal DM and *APM1* gene with CHD in offspring. Third, it was impossible to select the study participants by random sampling in our study, which may cause the potential selection bias. The convenience sample, driven mainly by the number of respondents, was used for our study. This limitation could lead to subsequent problems, including sample representativeness and generalization of study findings. Fourth, we did not assess the impact of paternal and fetal genotype on the risk of CHD. It is possible that both parental and fetal genotype have independent and/or interactive roles in the development of CHD. Fifth, there are many genes that are also involved in the development of diabetes. However, we only focused on the *APM1* gene. Future studies should extend our current findings to include multiple genes that influence diabetes and to investigate the relationship between CHD and common variants of these genes. Sixth, considering the limited sample size in the present study, we did not assess the association of maternal DM, the *APM1* gene polymorphisms, and their interactions with risk of specific CHD subtypes in offspring, and we only focused on the risk of total CHD. We know that research on different subtypes of CHD will be more instructive for prevention and control of CHD in the future. However, based on the existing sample size, we also cannot carry out relevant research. Last but not least, although we observed a significant interaction between maternal DM and *APM1* gene for risk of CHD, we did not conduct any research for the underlying mechanisms in our study. These limitations highlight the urgent need for large samples, a prospective approach, and different ethnic populations to further confirm our findings.

In conclusion, the present study is the first to explore the association of maternal DM, the APM1 genetic variants, and their interactions with the development of CHD in offspring. Findings from our study show that maternal DM and genetic variants of *APM1* gene at rs1501299 and rs2241766 are significantly associated with risk of CHD in offspring. Additionally, interactions between maternal DM and polymorphisms of the *APM1* gene in development of CHD are observed. Nevertheless, it remains unknown how these factors affect the development of CHD. In the future, more studies in different ethnic populations and with a larger sample and prospective design are required to confirm our findings.

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