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The association of the glucokinase rs4607517 polymorphism with gestational diabetes mellitus and its interaction with sweets consumption in Chinese women

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Abstract

Objective: To identify the association of the glucokinase gene (*GCK*) rs4607517 polymorphism with gestational diabetes mellitus (GDM) and determine whether sweets consumption could interact with the polymorphism on GDM in Chinese women.

Design: We conducted a case–control study at a hospital including 1015 participants (562 GDM cases and 453 controls). We collected the data of pre-pregnancy BMI, sweets consumption and performed genotyping of the *GCK* rs4607517 polymorphism. Logistic regression was performed to test the association between the rs4607517 polymorphism and GDM, and the stratified analyses by sweets consumption were conducted, using an additive genetic model.

Setting: A case–control study of women at a hospital in Beijing, China.

Participants One thousand and fifteen Chinese women.

Results: The *GCK* rs4607517 A allele was significantly associated with GDM (OR 1·35, 95 % CI 1·03, 1·77; $P = 0·028$). Furthermore, stratified analyses showed that the A allele increased the risk of GDM only in women who had a habitual consumption of sweet foods (sweets consumption ≥ once per week) (OR 1·61, 95 % CI 1·17, 2·21; $P = 0·003$). Significant interaction on GDM was found between the rs4607517 A allele and sweets consumption ($P = 0·004$).

Conclusions: This study for the first time reported the interaction between the *GCK* rs4607517 polymorphism and sweets consumption on GDM. The results provided novel evidence for risk assessment and personalised prevention of GDM.

Keywords
Gestational diabetes mellitus
Glucokinase
Gene
Sweets
Interaction

Gestational diabetes mellitus (GDM), which refers to carbohydrate intolerance with the onset or first recognition during pregnancy[1,2], may increase the risk of maternal and perinatal complications. In pregnant women, it is associated with hypertension, preeclampsia, increased operative intervention and future diabetes[1,3,4]. The perinatal complications include macrosomia, diabetes, metabolic syndrome and subsequent childhood and adolescent obesity[1,3,4].

The prevalence of GDM ranges from 2 to 20 % worldwide, and it was reported to be up to 19·7 % in Beijing[5]. The wide prevalence of GDM had caused an economic burden of about $5·59 billion in 2015 at Chinese national level[6], which has already become an important public health problem. Determining the risk factors of GDM could help us to diagnose GDM at an early stage, so that we can take preventive measures against GDM to mitigate the GDM burden for individuals, local communities and healthcare systems.

The aetiology of GDM is complicated as it was involved in multiple factors including genetic and environmental factors. Genome-wide association studies and candidate gene profiling have revealed the association between GDM and variants on several genes that are related to insulin secretion, insulin resistance, lipid and glucose metabolism and other pathways[7–10]. Glucokinase gene (*GCK*), one of the candidates for GDM, locates on 7p13 and encodes a glucokinase which is the main glucose-phosphorylating enzyme expressed only in the pancreatic

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beta cell and liver[11,12]. Mutations on *GCK* that altered enzyme activity are associated with HbA_{1c} levels, fasting glucose concentrations and GDM[13]. The *GCK* rs4607517 polymorphism may alter a signalling characteristic of insulin secretion such as pulsatility. This change led to insulin resistance and impaired fasting glucose[14,15]. However, recent investigations showed that the association between rs4607517 and GDM is inconsistent across studies, especially among Chinese population[16,17]. Some confounding factors such as lifestyles may have impacts on the effect of this polymorphism on GDM.

Dietary behaviours, such as high intake of sugar-sweetened beverages, fried foods and animal fat before or/and during pregnancy, had been linked to GDM[18–20]. A high amount of sugar had been directly linked to impaired pancreatic beta cell function in humans[21]. Eventually, the pancreatic beta cell response may fail to produce sufficient insulin to maintain normoglycaemia[22]. The interactions between gene and environmental exposures (such as dietary and physical activity behaviours) may be important in the aetiology of GDM[23]. Both the *GCK* rs4607517 polymorphism and sweets consumption are associated with pancreatic beta cell function. Yet whether the effect of *GCK* polymorphism on GDM is conditional on the consumption of sweet foods (gene–environment interaction) is still unknown.

Here, we conducted a case–control study among 1015 Chinese pregnant women (562 GDM cases and 453 controls) to identify the association between the *GCK* rs4607517 polymorphism and GDM and to evaluate the interaction between sweets consumption and *GCK* rs4607517 polymorphism on GDM.

Methods

Study design and participants

This case–control study was conducted among 1015 Chinese women, which was described previously[24]. In brief, the pregnant women aged 20–49 years and at 24–28 gestation weeks were recruited consecutively from the Department of Obstetrics and Gynecology of Peking University First Affiliated Hospital in Beijing from May 2012 to November 2013. The exclusion criteria for subjects were as follows: women who had pre-existing diabetes, or abnormal result in a glucose screening test before the 24th week of gestation, or multiple gestations or maternal diseases such as hypertension, endocrine disorders and hepatic diseases; women with incomplete medical information and who had decided to give birth at another hospital; women who were unable or unwilling to get involved in the study[24,25]. Ultimately, 562 cases and 453 controls were enrolled in this study.

All pregnant women were screened for GDM at 24–28 gestation weeks with a 75-g, 2-h oral glucose tolerance test after overnight fast, according to the criteria established by the Ministry of Health of China in 2011[26]. The GDM was diagnosed if one or more plasma glucose levels met or exceeded the thresholds as follows: fasting plasma glucose 5·1 mmol/l, 1-h plasma glucose 10·0 mmol/l or 2-h plasma glucose 8·5 mmol/l. The controls were pregnant women having normal glucose tolerant, which was identified by the oral glucose tolerance test at 24–28 gestation weeks.

Questionnaires

The clinical and biochemical data were collected from the hospital computer database by the trained medical record abstractors, which included self-reported pre-pregnancy weight and height measured at the first prenatal visit. The pre-pregnancy BMI was calculated as pre-pregnancy weight in kilogram divided by height in meter squared.

Pregnant women were recruited into the study as soon as their GDM status was determined. Lifestyle behaviours investigation was performed before the women with GDM participated in exercise and diet intervention. Women completed a lifestyle behaviours questionnaire which was modified for the purposes of our study based on the standardised self-report questionnaire used in the China Chronic Disease and Risk Factor Surveillance[27,28]. The frequencies of lifestyle behaviours during the last 3 weeks before pregnancy were reported. Consumption of sweets (such as ice cream, cakes, pies, chocolate and biscuits) was divided into two categories by average consumption: <once/week and ≥once/week. Consumption of other foods was divided into two categories by the median of average consumption: vegetables and fruits (<3950 g/week and ≥3950 g/week); meat such as beef, pork, chicken and lamb (<700 g/week and ≥700 g/week); staple foods such as noodles, steamed bun and rice (<1400 g/week and ≥1400 g/week); fried foods such as fried potatoes, fried chicken, fried fish, donuts and snack chips (<once/week and ≥once/week). Sedentary behaviour time (total sitting time/d) was also divided into two categories based on the median (50th percentile): <3·5 h/week and ≥ 3·5 h/d.

Genotyping

Genomic DNA was extracted from peripheral blood samples by salting-out procedure. A detailed account on the genotyping procedures has been reported previously[24]. Briefly, genotyping of the rs4607517 polymorphism was carried out with Sequenom's MassARRAY platform (Agena) according to the manufacturer's instructions[29]. The genotyping success rate for the rs4607517 polymorphism on the platform exceeded 98 %. Negative controls and two samples were placed in duplicate on each run, to ensure correct genotyping.

Statistical analyses

The distribution of quantitative or categorical variables in both GDM and control groups is expressed as mean ± SD

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or number (frequency), and the differences between two groups were tested by *t* test or χ^2 test, respectively. The χ^2 test was also used to determine whether the Hardy–Weinberg equilibrium of rs4607517 existed among the controls. Logistic regression was performed under the additive genetic model to evaluate the association between the rs4607517 polymorphism and the risk of GDM. Then, the stratified analyses by sweets consumption (<1/week; ≥1/week) were conducted to test the interaction between rs4607517 and sweets consumption. OR are presented with 95 % CI. A two-sided *P* value <0·05 was considered to be statistically significant. The statistical analyses were performed with SPSS version 18.0 (SPSS Inc.).

Results

General characteristics of the study population

The general characteristics of the GDM patients and controls are shown in Table 1. The women with GDM were older and had greater pre-pregnancy BMI than the controls.

By logistic regression analysis, comparing with less sweets consumption (<1/week), higher sweets consumption before pregnancy (≥1/week) was associated with the increased risk of GDM (OR 2·98, 95 % CI 2·21, 4·03; $P < 0·001$), after adjusting for age and pre-pregnancy BMI. The similar association was also found between GDM and vegetables and fruits consumption, meat consumption, fried food consumption or sedentary behaviour time (Table 2).

Table 1 General characteristics of participants*

	GDM subjects (*n* 562)		Controls (*n* 453)		
Category	Mean	SD	Mean	SD	*P*
Age (years)	30·18	2·64	29·50	2·68	<0·001
Pre-pregnancy BMI (kg/m^2)	22·33	3·25	21·29	2·99	<0·001
	n	%	*n*	%	
Education level					
High school or below	24	4·5	21	4·9	0·069
Bachelor's degree or higher	509	95·5	411	95·1	
Gravidity					
≤2	490	87·3	407	90·6	0·098
>2	71	12·7	42	9·4	
Parity					
Primiparity	520	92·7	424	94·4	0·266
Multiparity	41	7·3	25	5·6	

GDM, gestational diabetes mellitus.
*P values were calculated by *t* tests or χ^2 tests.

Table 2 Food consumption and sedentary behaviour time of participants

	GDM subjects (*n* 562)		Controls (*n* 453)					
Category	*n*	%	*n*	%	*P*	OR	95 % CI	Adjusted *P* value
Sweets consumption								
<1/week	96	17·8	174	39·5		1·00		
≥1/week	443	82·2	267	60·5	<0·001	2·98	2·21, 4·03	<0·001
Vegetables and fruits consumption (g/week)								
<3950	363	71·3	102	23·6		1·00		
≥3950	146	28·7	331	76·4	<0·001	0·12	0·09, 0·17	<0·001
Meat consumption (g/week)								
<700	211	41·6	225	52·9		1·00		
≥700	296	58·4	200	47·1	0·001	1·54	1·18, 2·01	0·001
Staple food consumption (g/week)								
<1400	225	42·0	176	40·4		1·00		
≥1400	311	58·0	260	59·6	<0·001	0·92	0·70, 1·19	0·508
Fried food consumption								
<1/week	156	28·8	213	48·5		1·00		
≥1/week	385	71·2	226	51·5	<0·001	2·46	1·87, 3·24	<0·001
Sedentary behaviour time								
<3·5/d	154	28·9	198	46·9		1·00		
≥3·5/d	378	71·1	224	53·1	<0·001	2·17	1·65, 2·86	<0·001

GDM, gestational diabetes mellitus.
*P values were calculated by χ^2 tests. OR and adjusted P values for food consumption and sedentary behaviour time were calculated by logistic regression adjusted for age and pre-pregnancy BMI.

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Table 3 Genotype frequencies of rs4607517 and its OR for gestational diabetes mellitus (GDM)

	Genotype						Adjusted*		
	GG		GA		AA				
Group	*n*	%	*n*	%	*n*	%	OR	95 % CI	*P*
Controls	283	62·6	154	34·1	15	3·3	1·00		
GDM subjects	316	56·2	200	35·6	46	8·2	1·35	1·03, 1·77	0·028

*Adjusted for age, pre-pregnancy BMI, fruits and vegetables consumption, meat consumption, staple food consumption, fried food consumption and sedentary behaviour time under additive genetic model.

Table 4 Interaction between the glucokinase gene (GCK) rs4607517 polymorphism and sweets consumption on gestational diabetes mellitus (GDM)

Gene	Sweets consumption	Genotype	GDM subjects	Controls	OR*	95 % CI	*P**	$OR_{G \times E}$†	95 % CI	$P_{G \times E}$†
GCK (rs4607517)	<1/week	GG	64	110	1·00		–	2·84	1·39, 5·81	**0·004**
		GA	28	58						
		AA	4	6	0·58	0·30, 1·12	0·103			
	≥1/week	GG	242	163	1·00		–			
		GA	163	94						
		AA	38	9	1·61	1·17, 2·21	**0·003**			

Bold values were considered to be statistically significant. (1) In the subgroups with different sweets consumption, we only found the A-allele of rs4607517 was associated with GDM in women with sweets consumption ≥1 per week ($P = 0·003$). (2) Sweet consumption and the A-allele of the GCK rs4607517 polymorphism had significant interaction with GDM ($P = 0·003$). (3) In the subgroups with different meat consumption, we only found the A-allele of rs4607517 was associated with GDM in women with meat consumption <700 g/week ($P = 0·011$). However, none of the interactions between other food consumption or sedentary behavior time and the GCK rs4607517 polymorphism on GDM were statistically significant.
*OR with 95 % CI and *P* value of rs4607517 were estimated with logistic regression analysis in each behavioural level under additive genetic model adjusted for age, pre-pregnancy BMI, fruits and vegetables consumption, meat consumption, staple food consumption, fried food consumption and sedentary behaviour time.
†OR with 95 % CI and *P* value of rs4607517 × sweets consumption were estimated with logistic regression analysis under additive genetic model adjusted for age, pre-pregnancy BMI, fruits and vegetables consumption, meat consumption, staple food consumption, fried food consumption and sedentary behaviour time.

Association of rs4607517 with gestational diabetes mellitus

No deviation from Hardy–Weinberg equilibrium was observed for rs4607517 in the control group ($P = 0·796$). The genotype frequencies in the GDM subjects and controls are presented in Table 3. The rs4607517 A allele was significantly associated with GDM after adjusting for age, pre-pregnancy BMI, fruits and vegetables consumption, meat consumption, staple food consumption, fried food consumption and sedentary behaviour time under additive genetic model (OR 1·35, 95 % CI 1·03, 1·77; $P = 0·028$).

Interaction between rs4607517 and sweets consumption on gestational diabetes mellitus

In the subgroups with different sweets consumption, we only found that the A allele of rs4607517 was associated with GDM in women with sweets consumption ≥1/week (OR 1·61, 95 % CI 1·17, 2·21; $P = 0·003$; Table 4). Furthermore, we tested the interaction term between rs4607517 and sweets consumption in the logistic regression model including age, pre-pregnancy BMI, fruits and vegetables consumption, meat consumption, staple food consumption, fried food consumption, sedentary behaviour time, rs4607517, sweet consumption and rs4607517 × sweet consumption as independent variables. Sweet consumption and the A allele of the *GCK* rs4607517 polymorphism had significant interaction with GDM (OR 2·84, 95 % CI 1·39, 5·81; $P = 0·004$). None of the interactions between other food consumption or sedentary behaviour time and the *GCK* rs4607517 polymorphism on GDM was statistically significant ($P_{\text{for interaction}} > 0·05$ for all interaction tests, Table 5).

Discussion

In the current study, we found that the *GCK* rs4607517 polymorphism was associated with the risk of GDM. To the best of our knowledge, this is the first study reporting the interaction between the *GCK* rs4607517 polymorphism and sweets consumption on GDM.

The *GCK* gene encodes a member of the hexokinase family proteins. Hexokinase phosphorylate glucose produces glucose-6-phosphate, the first step in most glucose metabolism pathways. The use of multiple promoters and alternative splicing of this gene result in distinct protein isoforms that exhibit tissue-specific expression in the pancreas and liver[30]. In pancreas, this enzyme plays a role in glucose-stimulated insulin secretion[31], while in liver, this enzyme is important in glucose uptake and conversion to glycogen. Previous studies have shown that mutations on *GCK* that altered enzyme activity reduced glucose-stimulated insulin secretion and increased the risk of GDM[11,15,16,32]. Accordingly, in the current study, the *GCK* rs4607517 polymorphism was associated with the

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Table 5 Interaction between the glucokinase gene rs4607517 polymorphism and food consumption on gestational diabetes mellitus

Food consumption	OR*	95 % CI	*P**	OR†	95 % CI	*P*†	$OR_{G \times E}$	95 % CI	$P_{G \times E}$ ‡
Vegetables and fruits consumption (g/week)									
<3950	1·00		–	1·00		–	0·95	0·55, 1·64	0·850
	1·12	0·35, 3·58	0·854	1·35	0·89, 2·06	0·160			
≥3950	1·00		–	1·00		–			
	1·30	0·89, 1·91	0·172	1·28	0·89, 1·85	0·183			
Meat consumption (g/week)									
<700	1·00		–	1·00		–	0·61	0·36, 1·05	0·074
	1·80	1·28, 2·52	**0·001**	1·71	1·13, 2·59	**0·011**			
≥700	1·00		–	1·00		–			
	1·15	0·85, 1·56	0·379	1·04	0·73, 1·50	0·816			
Staple food consumption (g/week)									
<1400	1·00		–	1·00		–	0·81	0·47, 1·42	0·463
	1·51	1·06, 2·14	**0·021**	1·50	0·95, 2·36	0·081			
≥1400	1·00		–	1·00		–			
	1·38	1·04, 1·85	**0·028**	1·25	0·88, 1·76	0·213			
Fried food consumption									
<1/week	1·00		–	1·00		–	0·81	0·46, 1·45	0·482
	1·45	1·00, 2·11	0·053	1·54	0·96, 2·46	0·072			
≥1/week	1·00		–	1·00		–			
	1·30	0·98, 1·72	0·068	1·21	0·86, 1·69	0·273			

Bold values were considered to be statistically significant. (1) In the subgroups with different sweets consumption, we only found the A-allele of rs4607517 was associated with GDM in women with sweets consumption ≥1 per week ($P = 0·003$). (2) Sweet consumption and the A-allele of the GCK rs4607517 polymorphism had significant interaction with GDM ($P = 0·003$). (3) In the subgroups with different meat consumption, we only found the A-allele of rs4607517 was associated with GDM in women with meat consumption <700 g/week($P = 0·011$). However, none of the interactions between other food consumption or sedentary behavior time and the GCK rs4607517 polymorphism on GDM were statistically significant.

*OR with 95 % CI and *P* value of rs4607517 were estimated with logistic regression analysis in each behavioural level under additive genetic model adjusted for age and pre-pregnancy BMI.

†OR with 95 % CI and *P* value of rs4607517 were estimated with logistic regression analysis in each behavioural level under additive genetic model adjusted for age, pre-pregnancy BMI, other food consumption and sedentary behaviour time.

‡OR with 95 % CI and *P* value of rs4607517 × food consumption were estimated with logistic regression analysis under additive genetic model adjusted for age, pre-pregnancy BMI, other food consumption and sedentary behaviour time.

increased risk of GDM. However, a previous study showed that the *GCK* rs4607517 polymorphism has not significant association with GDM in pregnant Chinese women after adjusting for age and pre-pregnancy BMI[17]. This was probably due to some confounding factors such as lifestyle factors, other than ethnicity, modify the effect of this polymorphism[33].

The current study found that the sweets consumption before pregnancy was associated with GDM. Previous studies showed that high amount of sugar had association with impaired pancreatic beta cell function in humans[21,22,34], such that greater consumption of sugar-sweetened product (710 ml non-diet soda and 108 g non-dairy pudding) resulted in the decline of liquid meal tolerance test disposition index, suggesting that the pancreatic beta cell has response (relative to insulin sensitivity) to deteriorated[22]. The detailed molecular mechanism remains unclear and speculative, but may involve in oxidative stress and inflammation which can cause pancreatic beta cell dysfunction[35–37]. Further investigations should be conducted to clarify the relationships among sweet consumption, oxidative stress, inflammation and GDM. Moreover, that sweets consumption before pregnancy contributed to the pancreatic beta cell dysfunction may have a deleterious effect during pregnancy, suggesting that it is a risk factor for GDM[38]. Normal pregnancy is characterised by profound metabolic stresses on glucose homoeostasis including insulin resistance, especially in the late pregnancy (mainly third trimester). In women with sweets consumption (≥once/week) before pregnancy, beta cell dysfunction may worsen further during pregnancy when the insulin resistance of pregnancy is partially additive and this could increase the risk of GDM[38,39].

Both the *GCK* rs4607517 polymorphism and high amount of sugar have been reported to be associated with decreased beta cell function[15,21], suggesting that they may have interactions accounting for the risk of GDM. It should be noticed that we observed strong interaction between the *GCK* rs4607517 polymorphism and habitual intake of sweets before pregnancy on the risk of GDM. The rs4607517 A allele was significantly associated with higher risk of GDM only in women with sweets consumption ≥1/week. This suggested that women with the rs4607517 A allele had a higher risk of GDM if they also had a habitual consumption of sweet foods. There was no significant association between *GCK* rs4607517 and GDM in women with sweets consumption less than once per week. Common variations in *GCK* including rs4607517 are associated with a modest effect on carbohydrate oxidation, fasting glucose and fasting insulin, leading to diabetes[14,40]. These may make an individual with *GCK* rs4607517 A allele more susceptible to the harmful effects of a poor diet such as habitual sweets consumption[41]. According to another study, following up 4106 participants with normal glucose tolerance for 10 years, the *GCK* rs4607517 polymorphism was significantly associated with progression to

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prediabetes leading to beta cell dysfunction in response to progressive decline in insulin sensitivity. The environmental factors including increased energy intake may have important roles in the pronounced decrease in insulin sensitivity soon before development of diabetes among the progressors to diabetes[42]. A large meta-analysis of six discovery and five replication cohorts observed a suggestive interaction between sugar-sweetened beverage intake with *GCK* rs4607517 polymorphism only in women for fasting insulin[40]. However, the mechanism of *GCK*–environment interaction effect is not well understood and awaits future functional studies in liver or pancreatic biopsy tissues.

The study findings suggested that lifestyle interventions introduced before pregnancy have the potential in preventing GDM. Thus, it is important for women with the *GCK* rs4607517 A allele who plan to have a child to consider strict control of sweets consumption before pregnant for preventing GDM.

There were some limitations in the current study. First, assessment with simple FFQ was lack of information such as the portion size. Further investigation should be conducted with more information in dietary intake. Second, the reported interactions may be confounded by other lifestyle factors such as food intake during pregnancy, which was not available in the current study. Third, GDM patients and controls were selected at a third-tier hospital of Beijing which may not be representative of the general population in China[24]. Fourth, case–control study is not as powerful as other types of study in confirming a causal relationship. However, the case–control study design is suitable for clarifying the association.

Conclusions

In conclusion, the case–control study demonstrated that the *GCK* rs4607517 polymorphism was associated with GDM in Chinese women. In particular, we for the first time reported the interaction between the *GCK* rs4607517 polymorphism and sweets consumption on GDM. These results provided novel evidence for risk assessment and personalised prevention of GDM. Future large-scaled population studies are needed to confirm the interaction between the *GCK* polymorphism and sweets consumption on the development of GDM.

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