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No association of *adiponectin* +45 T/G polymorphism with the risk of gestational diabetes mellitus: Evidence from a meta-analysis

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Abstract

Introduction: Adiponectin (*ADIPOQ*), involved in regulating glucose levels and fatty acid oxidation, plays key roles in metabolic derangements such as gestational diabetes mellitus (GDM). Previously, several studies have been conducted to assess the association between *ADIPOQ* +45 T/G polymorphism and risk of GDM. The results, however, are inconclusive. We aimed to evaluate the effect of the polymorphism on the risk of GDM using a meta-analysis.

Materials and methods: After databases searching, eight records were identified. Pooled odds ratios (ORs) with their corresponding 95% confidence intervals (CIs) were used to evaluate the association between *ADIPOQ* +45 T/G polymorphism and risk of GDM.

Results: No significant association was observed between the *ADIPOQ* +45 T/G polymorphism and the risk of GDM (heterozygote comparison: OR = 1.15, 95% CI, 0.70–1.89; homozygote comparison: OR = 1.21, 95% CI, 0.48–3.03; dominant model: OR = 0.86, 95% CI, 0.50–1.48, recessive model: OR = 1.21, 95% CI, 0.62–2.33, and allele comparison: OR = 1.17, 95% CI, 0.79–1.76, respectively). Apparent heterogeneity was detected. However, no evidence of publication bias was found.

Conclusions: This meta-analysis provides evidence that the *ADIPOQ* +45 T/G polymorphism was not related to the risk of GDM. Further multicenter, prospective studies with larger sample size would be valuable to confirm the result.

Keywords

Gestational diabetes mellitus, adiponectin, polymorphism, meta-analysis, susceptibility

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Introduction

Gestational diabetes mellitus (GDM), characterized as glucose intolerance firstly occurring or recognized during pregnancy, is an important public health problem worldwide.[1,2] In China, the incidence increased during 1999–2013, from 2.4% to 12.1%.[3,4] Women with GDM possess high risks of adverse pregnancy outcomes and several maternal and perinatal complications, including neonatal hypoglycemia and adiposity, metabolic syndrome and future diabetes mellitus.[5–9] Regarding risk factors for GDM, several environmental triggers have been identified so far, such as obesity, poor diet and physical inactivity.[10–12] In addition, genetic components have also been reported to contribute to the development of GDM.[13–15]

Adiponectin (*ADIPOQ*) is a protein hormone involved in regulating glucose levels and fatty acid oxidation.[16,17] The hormone plays a key role in the metabolic derangements that may lead to type 2 diabetes, atherosclerosis, obesity, metabolic syndrome and insulin resistance.[16,18–20] The *ADIPOQ* gene, located on chromosome 3q27 in humans, contains three exons. A single nucleotide polymorphism (SNP) in exon 2 of *ADIPOQ* (+45 T/G,

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rs2241766) may influence the protein expression by affecting RNA splicing and stability.[21] The SNP has been shown to be related to type 2 diabetes and insulin resistance.[22–24]

Given the potential role of the *ADIPOQ* +45 T/G polymorphism in diabetes, several association studies have been conducted to assess the association between the polymorphism and risk of GDM.[25–32] The results, however, are inconsistent and inconclusive. For example, Takhshid et al. reported that the TG/GG genotypes had a 2.55-fold increased risk of GDM compared with the TT genotype,[31] whereas Beltcheva et al. reported that no association with GDM was found for the polymorphism.[25] One reason for the conflicting results is small samples in a single study. Meta-analysis is a useful tool to increase power by pooling all the published data together. In this study, we performed a meta-analysis to clarify whether the *ADIPOQ* +45 T/G polymorphism is associated with the risk of GDM.

Materials and methods

Records selection

PubMed, China National Knowledge Infrastructure, Weipu and Wangfang databases were searched using the following terms: "ADIPOQ or adiponectin" and "polymorphism* or variant" and "gestational diabetes mellitus" or "Gestational diabetes" (last search update October 30, 2015). Forty-one articles were identified after database searching. We selected publications using the following criteria: (a) studies evaluating the association between *ADIPOQ* +45 T/G polymorphism and the risk of GDM; (b) original genotyping data to compute pooled odds ratios (ORs) and 95% confidence interval (CI); (c) language was not restricted. Among them, 18 articles were removed for duplicate publication. After full-text assessment, 12 articles were excluded for these reasons: no *ADIPOQ* +45 T/G polymorphism ($n = 8$), reviews ($n = 3$), and not a study of GDM ($n = 1$). During data collection, we excluded three articles for repeated data. Finally, eight studies were included in this meta-analysis. A flow diagram of studies selection is presented in Figure 1.

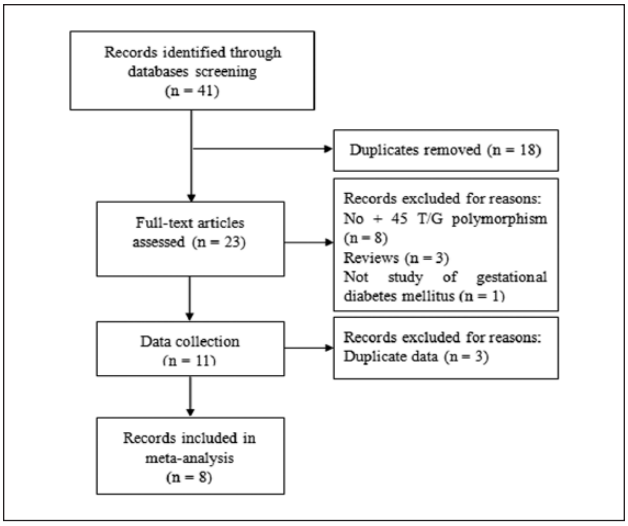

Figure 1. Flow diagram of studies selection.

Data extraction

The following information was extracted by two researchers independently: author, year of publication, country (origin), ethnicity, study design, number of cases and controls, matching criteria, genotyping method, and minor allele frequency in controls. The information was checked by a third researcher to confirm the accuracy.

Statistical analysis

The association between the *ADIPOQ* +45 T/G polymorphism and the risk of GDM was evaluated by pooled ORs and their 95% CI under a heterozygote comparison, homozygote comparison, dominant model, recessive model, and allele comparison. A fixed-effects model was used to estimate summary ORs because p values for heterogeneity test were $\leqslant 0.10$ in all comparison analyses.[33] To identify the sources of heterogeneity, subgroup analyses were performed based on the Hardy-Weinberg equilibrium (HWE) and sample size (>100 vs. $\leqslant$100). Logistic meta-regression was also performed according to ethnicity, genotyping methods, HWE, and sample size. Begg's funnel plot was used to test publication bias.[34] All analyses were conducted using STATA software (version 10.0, STATA Corporation, College Station, TX, USA).

Results

Characteristics of studies

The characteristics of the included studies are shown in Table 1. In total, eight studies were included in this meta-analysis with 875 cases and 884 controls. Among them, seven studies were of Asian descendants[26–32] and one study was of European descendants.[25] The sample sizes were relatively small in all the studies, with the least having 79 participants[30] and the most having 436 participants.[28] Most of the studies (62.5%) reported a matched frequency of controls to cases.[25,27,29,31,32] Several genotyping methods were used, including TaqMan, polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP), and DNA sequencing. However, only two studies reported quality control to ensure the reproducibility of the genotyping assay.[25,31] Most of the studies (75.0%) were consistent with HWE except for one study departing from HWE[27] and one study without available data to assess HWE.[25] Minor allele frequency in controls varied greatly, ranging from 0.10 to 0.49.

Meta-analysis

As shown in Table 2, no significant association was observed between the *ADIPOQ* +45 T/G polymorphism and the risk

Table 1. Characteristics of studies included in this meta-analysis.

First author[reference]	Year of publication	Country (region)	Ethnicity	Study design	Number of cases	Controls	Matching criteria	Genotyping method	MAF in controls
Beltcheva[25]	2014	Bulgaria (Sofia)	European	Case-control	130	130	Age and degree of obesity	TaqMan	0.10
Han[26]	2015	China (Nantong)	Asian	Cross-section	128	140	–	PCR-RFLP	0.26
Hua[27]	2014	China (Wuxi)	Asian	Case-control	112	150	Age and gestational week	PCR-RFLP	0.49
Li[28]	2013	China (Beijing)	Asian	Case-control	264	172	–	Sequencing	0.24
Liu[29]	2006	China (Wuxi)	Asian	Case-control	52	34	Age and gestational week	PCR-RFLP	0.47
Low[30]	2011	Malaysia (Selangor)	Asian	Case-control	26	53	–	PCR-RFLP	0.18
Takhshid[31]	2015	Iran (Shiraz)	Asian	Case-control	65	70	Age	PCR-RFLP	0.11
Zhang[32]	2014	China (Nanning)	Asian	Case-control	98	135	Age, BMI and gestational week	PCR-RFLP	0.27

MAF: minor allele frequency; PCR-RFLP: polymerase chain reaction-restriction fragment length polymorphism; BMI: body mass index.

Table 2. Meta-analysis of the *ADIPOQ* +45 T/G polymorphism with the risk of gestational diabetes mellitus.

	n	Cases/controls	TG vs. TT		GG vs. TT		Dominant		Recessive		G vs. T	
			OR (95% CI)[a]	*p*[b]	OR (95% CI)[a]	*p*[b]	OR (95% CI)[a]	*p*[b]	OR (95% CI)[a]	*p*[b]	OR (95% CI)[a]	*p*[b]
Total	8	875/884	1.15 (0.70–1.89)	<0.001	1.21 (0.48–3.03)	<0.001	0.86 (0.50–1.48)	<0.001	1.21 (0.62–2.33)	0.01	1.17 (0.79–1.76)	<0.001
HWE	6	763/734	1.35 (0.84–2.17)	0.006	1.54 (0.56–4.11)	0.004	0.72 (0.43–1.19)	0.001	1.49 (0.77v2.88)	0.10	1.33 (0.93–1.90)	0.001
Sample size												
>100	6	797/797	1.29 (0.83–2.01)	0.01	1.46 (0.55–3.83)	0.001	0.76 (0.45–1.28)	<0.001	1.34 (0.64v2.82)	0.01	1.27 (0.86–1.89)	<0.001
⩽100	2	78/87	0.73 (0.07–7.88)	0.001	0.93 (0.03–29.22)	0.01	1.35 (0.11–16.57)	<0.001	1.05 (0.12–9.44)	0.09	0.88 (0.15–5.26)	<0.001

ADIPOQ: adiponectin; OR: odds ratio; CI: confidence interval; HWE: Hardy-Weinberg equilibrium.
[a]Random-effects model was used.
[b]*P* value for heterogeneity test.

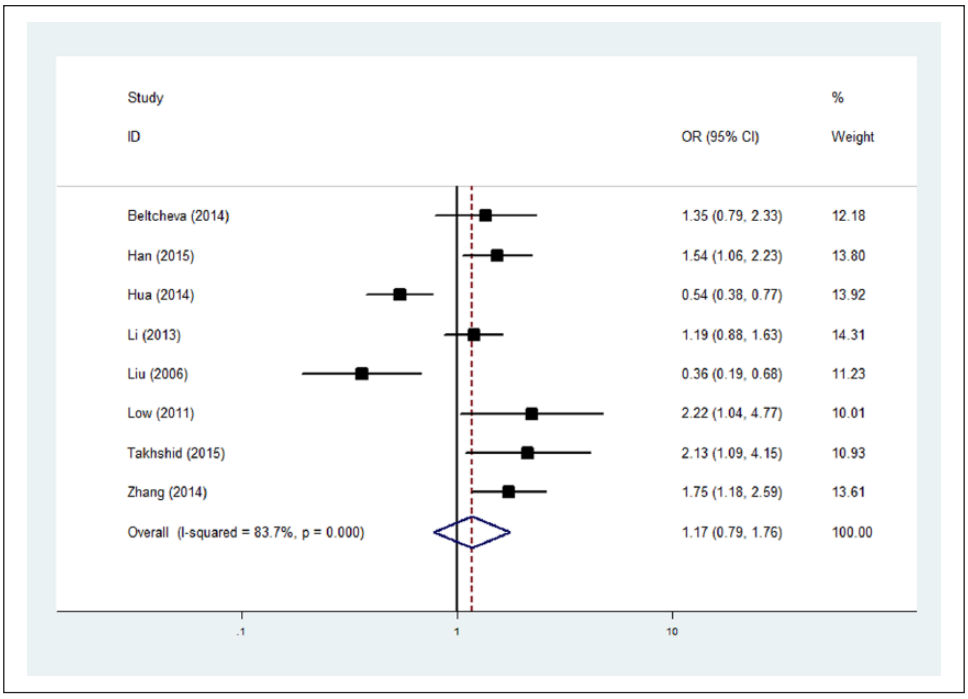

Figure 2. Meta-analysis of the *ADIPOQ* +45 T/G polymorphism with the risk of gestational diabetes mellitus (G vs. T). The random-effects model was used.

of GDM (heterozygote comparison: OR = 1.15, 95% CI, 0.70–1.89; homozygote comparison: OR = 1.21, 95% CI, 0.48–3.03; dominant model: OR = 0.86, 95% CI, 0.50–1.48, recessive model: OR = 1.21, 95% CI, 0.62–2.33, and allele comparison: OR = 1.17, 95% CI, 0.79–1.76, respectively) (Figure 2). After excluding two studies with Hardy-Weinberg disequilibrium, no significant association was found. Additionally, we performed subgroup analysis according to sample size (> 100 and ⩽100); negative results were also observed in both subgroups.

Heterogeneity analysis and publication bias. In overall and subgroup analyses, we detected apparent heterogeneity ($p \leqslant 0.10$). Logistic meta-regression was used to explore the sources of heterogeneity. We took the common variables influencing heterogeneity into consideration: ethnicity, genotyping methods, HWE, and sample size. However, none of these factors affected the heterogeneity among studies.

Begg's funnel plot was used to test publication bias, and no evidence of publication bias was found ($p > 0.05$) in the meta-analysis (Figure 3).

Discussion

To the best of our knowledge, this is the first meta-analysis to investigate the relationship of the *ADIPOQ* +45 T/G polymorphism with GDM. We failed to find any association between the SNP and the risk of GDM, suggesting that the *ADIPOQ* +45 T/G polymorphism may not be a risk factor for the etiology of GDM.

Previously, several SNPs have been performed to evaluate the association with GDM, such as rs2241766 (Gly15Gly, +45 T/G) in exon 2, rs266729 (−11377 C/G) and rs17300539 (−11391G/A) in the promoter region, and rs1501299 (+276 G/T) in intron 2.[25–32] Among them, the *ADIPOQ* +45 T/G polymorphism is the most frequently investigated. Controversial results, however, have been obtained. In this study, we collected all previous publications and performed a meta-analysis to assess the association of the *ADIPOQ* +45 T/G polymorphism with the risk of GDM. Our meta-analysis provided evidence that the polymorphism was not a risk factor for the development of GDM although 75% (six of eight) studies reported a positive result.[26,27,29–32] After subgroup analysis according to HWE and sample size, null results were also observed.

Obvious heterogeneity was detected among studies. We used logistic meta-regression to examine the sources of heterogeneity based on ethnicity, genotyping methods, HWE, and sample size. None of these parameters could explain the heterogeneity, indicating that other unknown reasons may influence the heterogeneity. As most of the studies previously reported a significant association between the *ADIPOQ* +45 T/G polymorphism and susceptibility for GDM, in this meta-analysis we used Begg's funnel plot to test if there is a tendency of prior publication positive results. However, no evidence of publication bias was found.

These are some limitations in this study. Firstly, sample size is very small in each single study as well as in this meta-analysis, which may result in false-negative result due to insufficient power. Secondly, very limited data in the

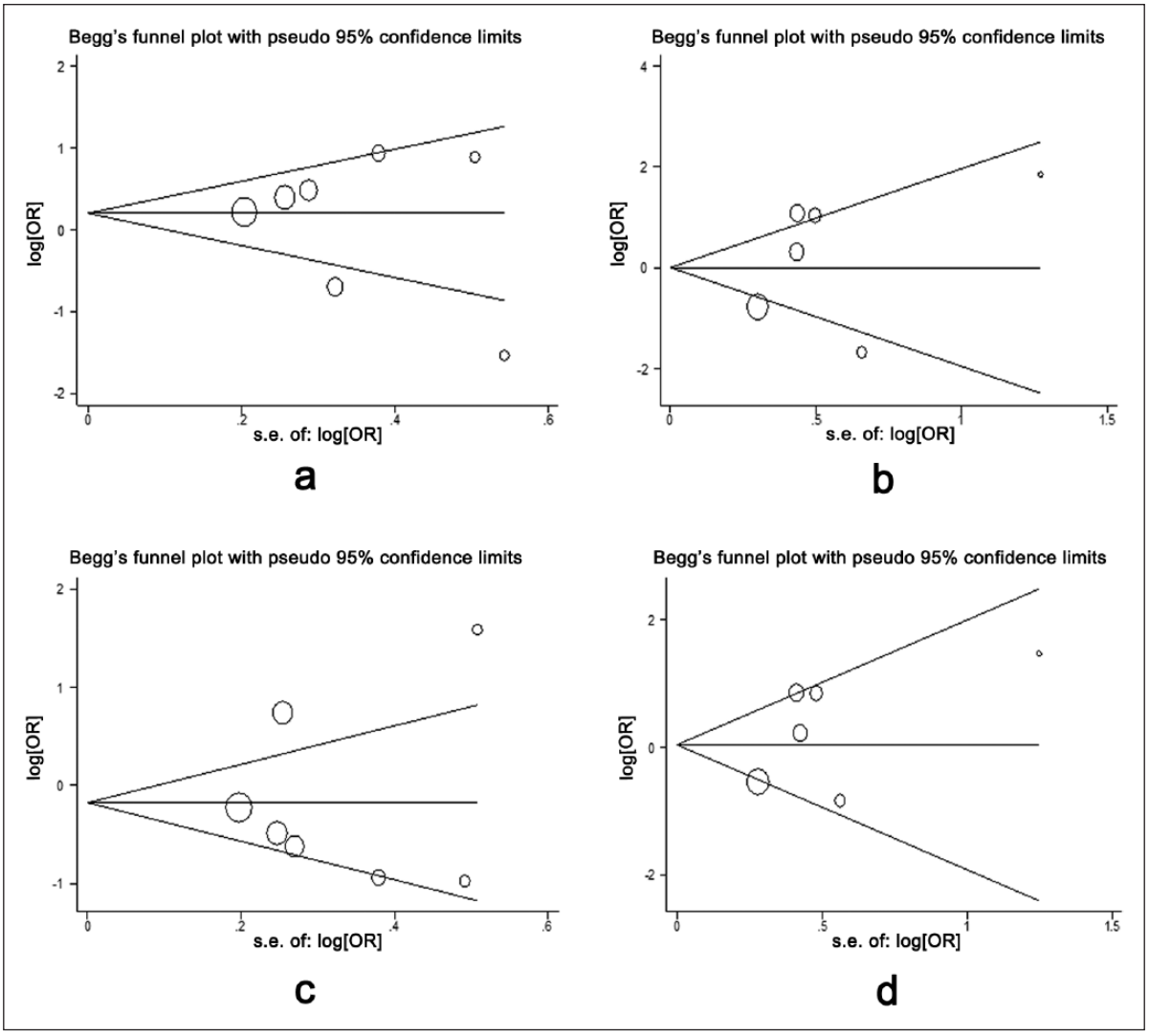

Figure 3. Begg's funnel plot for testing publication bias. Each circle indicates a separate study. (a) TG vs. TT; (b) GG vs. TT; (c) dominant model; (d) recessive model. OR: odds ratio.

literature reported the association between the *ADIPOQ* +45 T/G polymorphism and serum adiponectin level, which prevented further genotype-phenotype analysis. Thirdly, nearly all the studies included in this meta-analysis were of Asian descendants, and thus the results cannot be directly extended to other ethnicities. Further evaluation is warranted, especially in multi-ethnic populations.

In conclusion, this meta-analysis provides evidence that the *ADIPOQ* +45 T/G polymorphism was not related to the risk of GDM. Further multicenter, prospective studies with larger sample size would be of great value to confirm the result. Additionally, gene-gene and genotype-phenotype analysis may help to comprehensively understand the role of the SNP in the etiology of GDM.

Declaration of conflicting interests

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