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Review Article

Association of single nucleotide polymorphisms in *ADIPOQ* gene with risk of hypertension: a systematic review and meta-analysis

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Abstract: Background: Hypertension has been continuing to be a major contributor to the global burden of disease and to the global mortality, leading to over 10 million deaths each year. The purpose of this study was to investigate the association between Adiponectin gene polymorphism with Essential hypertension (EH). Methods: PubMed, EMbase, the Cochrane Library, and China National Knowledge Infrastructure (CNKI) were searched independently by two investigators. Pooled odds ratios and 95% confidence intervals were calculated to estimate the associations of Adiponectin polymorphism with EH. Results: Thirteen studies with 3198 cases and 3076 controls for meta-analysis (MA) were included in present study. Pooled results showed that rs2241766 polymorphism is associated with the risk of EH in the allelic model (G vs. T: OR=1.10; 95% CI, 1.01-1.21). In the <40 years subgroup, rs2241766 polymorphism is associated with the risk of EH in allele model (G vs. T: OR=1.43; 95% CI, 1.06-1.94), recessive model (GG vs. GT + TT: *OR*=5.26, 95% *CI*=1.47-18.76), homozygous model of GG (GG vs.TT: *OR*=5.27, 95% *CI*=1.47-18.95), and rs266729 in recessive model (GG vs. GT + TT: *OR*=2.33, 95% *CI*=1.33-4.08). Conclusions: Our meta-analysis results show that the rs2241766 polymorphism is associated with the risk of hypertension. There still need a larger sample with better design to verify.

Keywords: Adiponectin, polymorphisms, hypertension, meta-analysis

Introduction

Hypertension has been continuing to be a major contributor to the global burden of disease and to the global mortality, leading to over 10 million deaths each year [1, 2]. The etiology of hypertension has not been fully elucidated , however, the interaction between genes and environmental factors is thought to play an important role in the pathological process of hypertension [3]. In recent years, researches have been focusing on the genetic susceptibility and genetic polymorphism of hypertension [4, 5].

Adiponectin (ADIPOQ) is a recently discovered cytokine specifically secreted by adipocytes, with plasma concentrations range from 5 to 30 mg/L and accounting for approximately 0.05% of total plasma protein in healthy adults [6]. Studies have shown that adiponectin plays an vital role in improving insulin sensitivity, anti-inflammation and anti-atherosclerosis [7, 8]. In recent years, there was a study have reported that the polymorphism of *ADIPOQ* gene is associated with plasma levels of adiponectin, and low adiponectin levels predispose essential hypertension [9]. Some studies have investigated the correlation between several polymorphisms in *ADIPOQ* gene and hypertension, including rs2241766 (+45T>G), rs1501299 (+276G>T), and rs266729 (-11377C>G). A study showed [10] that the association between polymorphisms of adiponectin and essential

hypertension and found +45T/G and +276G/T were significantly associated with essential hypertension. Also reported by other scholars [11] that although -11377C>G in the promoter region of *ADIPOQ* gene was not yet suggested to be associated with essential hypertension, they confirmed that -11377C>G was associated with reduced plasma lipids. In addition, it is reported [12] that there was no significant association between rs2241766 and rs15-01299 and hypertension. And other scholars reported [13, 14] found that rs2241766 was associated with the risk of hypertension, but rs1501299 was not associated with the risk of hypertension. Therefore, results of these studies are inconsistent and the association between polymorphisms in *ADIPOQ* gene and hypertension remains to be determined. We performed this meta-analysis aimed at determining the associations of rs2241766, rs15-01299, and rs266729 polymorphisms in the ADIPOQ gene with hypertension susceptibility.

The present meta-analysis aimed to analyze the relationship between three widely evaluated genetic polymorphisms in *ADIPOQ* gene and the risk of hypertension. The *ADIPOQ* gene (OMIM: 605441, Gene ID: 9370) is located in human 3q27 and has a DNA length of approximately 16 kb and contains three exons and two introns. ADIPOQ is a specific hormone protein secreted by fat cells. It is a protective factor and plays a very important role in anti-atherosclerosis, insulin resistance and anti-inflammation [15].

Adamczak et al. [16] first analyzed and reported a negative correlation between plasma levelsof adiponectin and the systolic blood pressure, diastolic blood pressure, and mean arterial pressure and concluded that low levels of adiponectin may play a role in the pathogenesis of essential hypertension. Mangge et al. [17] reported that the polymorphism of *ADPIOQ* gene correlated with adiponectin concentration. Therefore, the polymorphism of *ADPIOQ* gene was considered associating with the risk of hypertension.

Materials and methods

The meta-analysis is conducted in accordance with the guidelines of the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement [18].

Search strategy

To identify studies eligible for the systematic review and meta-analysis, we searched databases of PubMed, EMbase, the Cochrane Library, and China National Knowledge Infrastructure up to December 19, 2019, The following terms: “hypertension”, “adiponectin”, “ADIPOQ”, “intron”, “exon” and “polymorphism” was used for this searching. Additional potential relevant articles were identified by us through screened references of retrieved articles.

Inclusion and exclusion criteria

Inclusion criteria: Studies included must meet the following criteria: (1) Studies were case-control or cohort design; (2) Studies have evaluated the association between single nucleotide polymorphisms in *ADIPOQ* gene and susceptibility of hypertension; (3) Studies evaluated rs2241766, rs1501299, or/and rs266729; (4) Studies provided details of associations between genotypes and phenotypes and sufficient data for estimating odds ratios (ORs) with 95% confidence intervals (CIs).

Exclusion criteria: (1) Conference abstracts, case reports, comments, repeated researches, and systematic reviews were excluded; (2) Studies lacking data for genotype distribution; (3) Studies unable to determine whether the control population meets the Hardy-Weinberg equilibrium (HWE) balance.

Data extraction and quality assessment

Two reviewers independently screened the articles, extracted data, and performed quality evaluations. Data extracted from studies were as follows: first author, country, year of publication, average age, type of study, sample size, ethnicity, genotyping method, genotype distributions, and body mass index (BMI). Disagreements were resolved through discussion or consulting third-party experts. The quality of the included studies was assessed using the Newcastle-Ottawa (NOS) scale, with a rating of 0-9 and a maximum of 9 [19].

Statistical analysis

Stata version 12.0 (Stata Corp, College Station, TX) was used for statistical analyses. A chi-

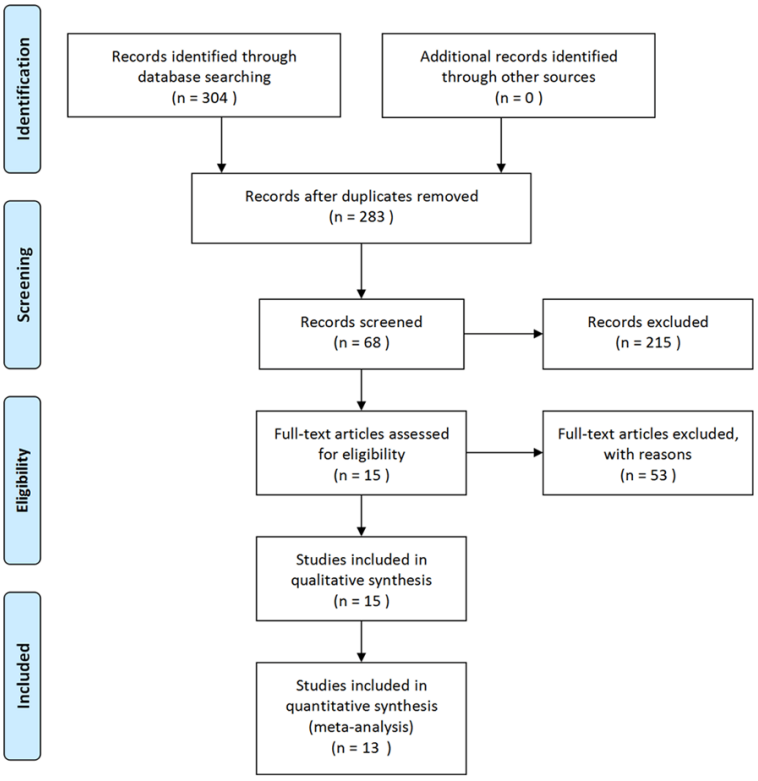

Figure 1. PRISMA flow diagram of studies included in the Meta-analysis.

square test was performed to evaluate the HWE for the control group in each study group. Pooled ORs with corresponding 95% CIs were calculated to evaluate associations between the *ADIPOQ* gene and hypertension for the following genetic models: rs2241766 (allelic model: G vs. T, recessive models: GG vs. GT + TT, dominant models: GG + GT vs. TT, heterozygote model: GT vs. TT, homozygote model: GG vs. TT); rs1501299 (allelic model: T vs. G, recessive models: TT vs. TG + GG, dominant models: TT + TG vs. GG, heterozygote model: TG vs. GG, homozygote model: TT vs. GG); rs266729 (allelic model: G vs. C, recessive models: GG vs. GC + CC, dominant models: GG + GC vs. CC, heterozygote model: GC vs. CC, homozygote model: GG vs. CC). Q tests and I^2 statistics were performed to assess heterogeneity between studies. If P_Q<0.05 or I^2>50%, a significant heterogeneity was existed among studies and then, a random effects model was used to calculate the pooled OR, otherwise (i.e., P_Q>0.05 or I^2<50%), a fixed effects model was performed.

For studies with significant heterogeneity, stratified analysis for samples may be performed by subgroup analysis to identify potential sources of heterogeneity. Gradually eliminating individual studies or studies deviating from HWE for sensitivity analysis were performed to assess the stability of results. Begg's funnel plot and Egger's test were used to justify potential publication bias.

Results

Literature screening

A total of 308 studies were retrieved in our work. After excluding duplicate publications, case reports, reviews, and studies that could not be combined, thirteen articles with 3198 cases and 3076 controls were included in this study. Studies by Zhang et al. [20], Leu et al. [21], Kang et al. [22], Jiang et al. [23], and Machado et al. [24] contained two studies, which were analyzed separately in the following meta-analysis. A flow chart summarizing the process of literature is depicted in **Figure 1**.

Characteristics and quality evaluations for included studies

Table 1 summarizes characteristics of all included studies. Eleven studies were carried out in China, one in Brazil, and one in Turkey. The rs2241766 polymorphism was analyzed in 12 studies, the rs1501299 polymorphism was in 10, and the rs266729 polymorphism was in 8.

According to the Newcastle-Ottawa quality assessment scale, the quality of the included literature was evaluated. The scores are shown in **Table 1** and 9 studies have a score of no less than 8.

Quantitative synthesis for MA

For a comprehensive evaluation, we calculated Ors with 95% CIs to estimate associations of the three polymorphisms in *ADIPOQ* with the risk of hypertension under the genetic models of alleles, recessive genotypes, dominant geno-

Table 1. Principle characteristics of the studies included in the meta-analysis

Study	Country	Year	Age		Type of study	Sample size		Ethnicity	Genotyping method	Genotype distributions (case/control)			*P* value of HWE	Quality score	BMI	
			Case	Control		Case	Control								Case	Control
rs2241766										TT	TG	GG				
Yan [12]	China	2006	49.0±9.0	48.0±10.0	Case control	482	497	Asian	PCR	201/222	186/203	95/72	0.024	8	30.80±2.50	22.40±1.80
Jeng [35]	China	2007	51.6±14.7	50.7±12.1	Case control	212	356	Asian	PCR	82/126	99/173	31/57	0.853	7	25.70±3.60	23.80±3.40
Tang [13]	China	2008	63.5±6.5	60.5±7.1	Case control	151	100	Asian	PCR	99/63	32/28	20/9	0.036	8	NR	NR
Wang [14]	China	2008	46.4±14.0	46.8±15.4	Case control	80	160	Asian	PCR	41/87	34/60	5/13	0.561	6	26.82±2.44	22.43±3.99
Youpeng [36]	China	2010	30.9±6.0	30.0±4.5	Case control	107	81	Asian	PCR	74/53	26/27	7/1	0.228	8	22.05±2.65	20.10±1.80
Leu A [21]	China	2011	41.4±0.7	46.7±0.8	Case control	159	446	Asian	PCR	74/233	70/181	15/32	0.696	8	25.40±0.30	23.50±0.10
Leu B [21]	China	2011	41.7±0.6	57.5±1.0	Case control	192	165	Asian	PCR	92/78	81/75	19/12	0.696	8	28.30±0.30	27.10±0.30
Kang B [22]	China	2013	52.3±9.6	49.8±8.7	Case control	153	126	Asian	PCR	63/75	68/40	11/22	0.105	7	22.57±2.27	21.53±2.17
Jiang A [23]	China	2014	68.8±6.7	67.1±7.1	Case control	223	176	Asian	PCR	102/91	86/65	10/14	0.72	9	24.50±4.30	23.10±3.30
Jiang B [23]	China	2014	68.2±6.1	67.1±7.2	Case control	181	176	Asian	PCR	90/91	67/65	12/10	0.72	9	26.00±3.70	23.10±3.30
Machado A [24]	Brazil	2014	26.0±4.5	24.0±4.0	Case control	113	161	Caucasian	PCR	81/139	29/29	3/1	0.697	8	27.53±5.15	22.80±2.70
Machado B [24]	Brazil	2014	27.0±4.5	24.0±5.0	Case control	127	161	Caucasian	PCR	97/139	26/29	4/1	0.697	8	26.28±4.80	22.80±2.70
rs1501299										GG	TG	TT				
Iwashima [9]	Japan	2004	59.4±0.5	57.1±0.6	Case control	446	312	Asian	PCR	225/165	180/124	41/23	0.964	8	24.40±0.10	23.10±0.20
Yan [12]	China	2006	49.0±9.0	48.0±10.0	Case control	482	497	Asian	PCR	259/274	184/187	39/36	0.599	8	30.80±2.50	22.40±1.80
Wang [14]	China	2008	46.4±14.0	46.8±15.4	Case control	80	160	Asian	PCR	41/74	28/73	11/13	0.392	6	26.82±2.44	22.43±3.99
Youpeng [36]	China	2010	30.9±6.0	30.0±4.5	Case control	107	81	Asian	PCR	19/19	60/49	28/13	0.051	8	22.05±2.65	20.10±1.80
Leu A [21]	China	2011	41.4±0.7	46.7±0.8	Case control	159	446	Asian	PCR	85/228	60/178	14/40	0.536	8	25.40±0.30	23.50±0.10
Leu B [21]	China	2011	41.7±0.6	57.5±1.0	Case control	192	165	Asian	PCR	117/93	68/56	7/16	0.089	8	28.30±0.30	27.10±0.30
Kang B [22]	China	2013	52.3±9.6	49.8±8.7	Case control	153	126	Asian	PCR	100/82	46/38	7/6	0.56	7	22.57±2.27	21.53±2.17
Machado A [24]	Brazil	2014	26.0±4.5	24.0±4.0	Case control	113	161	Caucasian	PCR	59/68	46/74	8/19	0.868	8	27.53±5.15	22.80±2.70
Machado B [24]	Brazil	2014	27.0±4.5	24.0±5.0	Case control	127	161	Caucasian	PCR	66/68	47/74	14/19	0.868	8	26.28±4.80	22.80±2.70
Demir [30]	Turkey	2016	63.6±7.1	64.6±7.3	Case control	170	170	Caucasian	PCR	78/92	73/72	19/6	0.071	8	27.30±3.20	26.10±3.20
rs266729										CC	CG	GG				
Jia [37]	China	2008	61.1	57.0	Case control	182	58	Asian	PCR	96/37	77/19	9/2	0.817	8	NR	NR
Zhang A [20]	China	2011	52.4±9.6	49.3±10.8	Case control	112	128	Asian	PCR	72/78	33/46	7/4	0.368	7	NR	NR
Zhang B [20]	China	2011	53.9±10.5	49.8±10.3	Case control	108	140	Asian	PCR	66/85	37/38	5/17	<0.01	7	NR	NR
Leu A [21]	China	2011	41.4±0.7	46.7±0.8	Case control	159	446	Asian	PCR	85/84	90/64	23/11	0.8	8	25.40±0.30	23.50±0.10
Leu B [21]	China	2011	41.7±0.6	57.5±1.0	Case control	192	165	Asian	PCR	93/84	68/64	12/11	0.8	8	28.30±0.30	27.10±0.30
Kang A [22]	China	2013	52.3±9.6	49.8±8.7	Case control	153	126	Asian	PCR	95/70	48/46	10/10	0.532	7	22.57±2.27	21.53±2.17
Machado A [24]	Brazil	2014	26.0±4.5	24.0±4.0	Case control	113	161	Caucasian	PCR	61/93	36/57	16/11	0.577	8	27.53±5.15	22.80±2.70
Machado B [24]	Brazil	2014	27.0±4.5	24.0±5.0	Case control	127	161	Caucasian	PCR	81/93	27/57	19/11	0.577	8	26.28±4.80	22.80±2.70

Abbreviations: PCR: polymerase chain reaction; BMI: body mass index.

Table 2. Pooled ORs and 95%CIs of the associations of ADIPOQ polymorphsims with hypertension

Genotype	s.s	Pooled estimate		Heterogeneity		*P* value for Begg's test
		OR, 95% CI	P_z	I^2	P_Q	
rs2241766						
G vs. T	12	1.10, 1.01-1.21	0.035	0.00%	0.563	0.304
GG vs. GT + TT	12	1.17, 0.96-1.42	0.124	40.20%	0.073	0.537
GG + GT vs. TT	12	1.12, 0.99-1.26	0.073	0.00%	0.567	0.837
GT vs. TT	12	1.09, 0.96-1.23	0.206	25.00%	0.198	0.837
GG vs. TT	12	1.19, 0.97-1.47	0.093	23.30%	0.215	0.537
rs1501299						
T vs. G	10	1.01, 0.92-1.11	0.824	45.90%	0.055	0.592
TT vs. TG + GG	10	1.13, 0.91-1.41	0.257	49.00%	0.039	0.858
TT + TG vs. GG	10	0.98, 0.86-1.11	0.720	15.30%	0.302	0.858
TG vs. GG	10	0.96, 0.84-1.09	0.522	0.00%	0.633	0.474
TT vs. GG	10	1.09, 0.87-1.37	0.455	53.70%	0.022	1.000
rs266729						
G vs. C	8	1.08, 0.94-1.24	0.263	25.90%	0.223	0.711
GG vs. GC + CC	8	1.34, 0.98-1.84	0.063	45.20%	0.078	0.174
GG + GC vs. CC	8	1.03, 0.87-1.22	0.708	17.40%	0.293	1.000
GC vs. CC	8	0.98, 0.82-1.17	0.801	38.20%	0.125	0.902
GG vs. CC	8	0.76, 0.55-1.05	0.095	2.70%	0.409	0.266

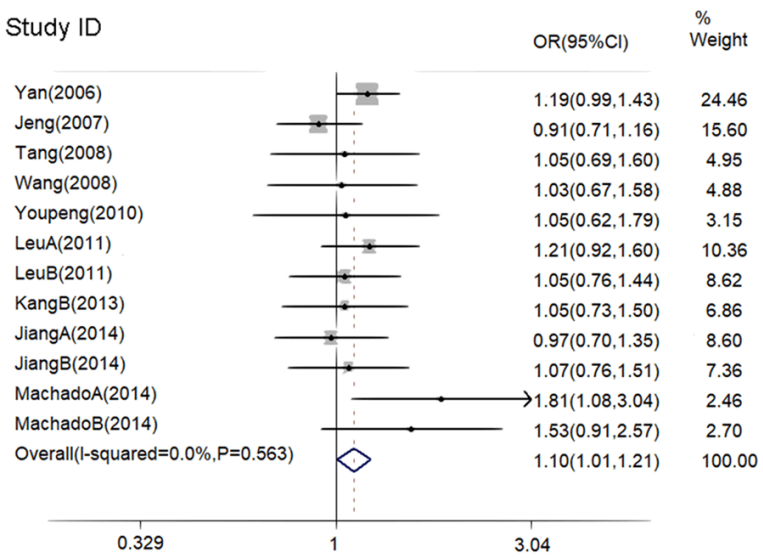

Figure 2. Forest plot for the risk of hypertension with allele model of rs2241766.

types, heterozygote, and homozygote. The genetic polymorphisms of the three loci were not heterogeneous in general, so the combined effect model was used for the combined analysis (as shown in **Table 2**). According to ORs and 95% CIs, there were no statistical significances between the rs1501299 polymorphism and the rs266729 polymorphism and the risk of hypertension in all of the above mentioned genetic models. In the allelic model of the rs2241766 polymorphism, **Figure 2** showed the allele of G was associated with an increased risk of hypertension (G vs. T: OR= 1.10; 95% CI, 1.01-1.21). However, the difference was not statistically significant in the other four genetic models for the rs2241766 polymorphism (**Table 2**).

We then performed analyses for associations of the three single nucleotide polymorphisms in *ADIPOQ* gene with the risk of hypertension in subgroups stratified by age, ethnicity, BMI, and whether the control group met the HWE (Hardy-Weinberg equilibrium) or not. The results of all subgroup analyses were listed in **Table 3**. We found that rs2241766 SNP was significantly associated with the risk of hypertension in individuals no more than 40 years old. Increased risk of hypertension was

Table 3. Hierarchical analysis results for the associations of three locis polymorphsims with hypertension

Subgroups (rs2241766)	s.s	G vs. T		GG v GT + TT		GG + GT v TT		GT v TT		GG v TT	
		OR, 95% CI	I^2, P_Q	OR, 95% CI	I^2, P_Q	OR, 95% CI	I^2, P_Q	OR, 95% CI	I^2, P_Q	OR, 95% CI	I^2, P_Q
Age											
≤40 years	3	1.43, 1.06-1.94	7.5%, 0.339	5.26, 1.47-18.76	0.0%, 0.991	1.33, 0.95-1.86	40.8%, 0.185	1.18, 0.84-1.67	53.9%, 0.114	5.27, 1.47-18.95	0.0%, 0.996
>40 years	9	1.07, 0.98-1.18	0.0%, 0.836	1.11, 0.91-1.35	37.6%, 0.118	1.09, 0.96-1.24	0.0%, 0.758	1.07, 0.93-1.23	20.3%, 0.262	1.13, 0.91-1.39	9.4%, 0.356
Ethnicity											
Asian	10	1.07, 0.98-1.18	0.0%, 0.895	1.13, 0.93-1.38	40.2%, 0.090	1.08, 0.95-1.22	0.0%, 0.777	1.05, 0.92-1.20	23.4%, 0.227	1.15, 0.94-1.42	15.9%, 0.297
Caucasian	2	1.67, 1.16-2.40	0.0%, 0.648	5.04, 1.04-24.50	0.0%, 0.913	1.62, 1.08-2.42	0.0%, 0.551	1.49, 0.98-2.25	0.0%, 0.494	5.46, 1.12-26.64	0.0%, 0.947
BMI											
≤25	3	1.01, 0.81-1.26	0.0%, 0.940	0.65, 0.39-1.09	60.4%, 0.080	1.16, 0.88-1.52	15.7%, 0.306	1.26, 0.94-1.68	70.2%, 0.035	0.77, 0.45-1.32	44.1%, 0.167
>25	8	1.13, 1.02-1.26	19.3%, 0.277	1.27, 1.02-1.59	0.0%, 0.474	1.12, 0.98-1.29	0.0%, 0.486	1.07, 0.93-1.24	0.0%, 0.632	1.28, 1.01-1.62	2.1%, 0.413
HWE											
P_H<0.05	2	1.17, 0.99-1.38	0.0%, 0.583	1.46, 1.07-2.00	0.0%, 0.890	1.08, 0.86-1.36	0.0%, 0.435	0.96, 0.74-1.23	0.0%, 0.325	1.45, 1.04-2.02	0.0%, 0.949
P_H>0.05	10	1.08, 0.97-1.20	0.0%, 0.461	1.00, 0.78-1.29	38.8%, 0.100	1.13, 0.98-1.30	0.0%, 0.449	1.14, 0.98-1.32	27.1%, 0.195	1.05, 0.80-1.37	24.3%, 0.219
Subgroups (rs1501299)		T v G		TT v TG + GG		TT + TG v GG		TG v GG		TT v GG	
		OR, 95% CI	I^2, P_Q	OR, 95% CI	I^2, P_Q	OR, 95% CI	I^2, P_Q	OR, 95% CI	I^2, P_Q	OR, 95% CI	I^2, P_Q
Age											
≤40 years	3	0.89, 0.71-1.10	67.9%, 0.044	1.05, 0.68-1.61	54.0%, 0.114	1.03, 0.90-1.17	0.0%, 0.628	0.76, 0.55-1.05	0.0%, 0.369	0.89, 0.55-1.44	63.7%, 0.064
>40 years	7	1.04, 0.94-1.16	30.8%, 0.193	1.16, 0.91-1.50	54.4%, 0.041	0.77, 0.57-1.04	41.8%, 0.179	1.00, 0.87-1.16	0.0%, 0.844	1.16, 0.89-1.50	54.4%, 0.041
Ethnicity											
Asian	7	1.03, 0.92-1.15	2.6%, 0.405	1.13, 0.88-1.44	37.6%, 0.142	1.00, 0.87-1.16	0.0%, 0.795	0.99, 0.85-1.15	0.0%, 0.883	1.10, 0.85-1.43	34.7%, 0.163
Caucasian	3	0.96, 0.79-1.18	80.3%, 0.006	1.16, 0.74-1.83	75.2%, 0.018	0.89, 0.68-1.16	70.9%, 0.032	0.85, 0.65-1.12	46.9%, 0.152	1.06, 0.66-1.69	80.3%, 0.006
BMI											
≤25	3	1.13, 0.95-1.35	0.0%, 0.522	1.38, 0.92-2.06	0.0%, 0.571	1.11, 0.87-1.40	0.0%, 0.715	1.06, 0.83-1.36	0.0%, 0.902	1.40, 0.90-2.15	0.0%, 0.510
>25	7	0.97, 0.86-1.08	54.5%, 0.040	1.04, 0.80-1.35	60.7%, 0.018	0.93, 0.81-1.08	29.5%, 0.203	0.92, 0.79-1.07	0.0%, 0.436	0.99, 0.76-1.29	63.2%, 0.012
Subgroups (rs266729)		G v C		GG v GC + CC		GG + GC v CC		GC v CC		GG v CC	
		OR, 95% CI	I^2, P_Q	OR, 95% CI	I^2, P_Q	OR, 95% CI	I^2, P_Q	OR, 95% CI	I^2, P_Q	OR, 95% CI	I^2, P_Q
Age											
≤40 years	2	1.18, 0.9-1.55	0.0%, 0.414	2.33, 1.33-4.08	0.0%, 0.911	0.95, 0.68-1.33	26.9%, 0.242	0.73, 0.50-1.06	54.0%, 0.140	0.82, 0.46-1.47	0.0%, 0.440
>40 years	6	1.05, 0.89-1.23	38.8%, 0.147	1.04, 0.71-1.53	35.9%, 0.168	1.06, 0.87-1.29	26.4%, 0.236	1.07, 0.87-1.32	19.4%, 0.287	0.73, 0.49-1.08	22.9%, 0.262
Ethnicity											
Asian	6	1.05, 0.89-1.23	38.8%, 0.147	1.04, 0.71-1.53	35.9%, 0.168	1.06, 0.87-1.29	26.4%, 0.236	1.07, 0.87-1.32	19.4%, 0.287	0.73, 0.49-1.08	22.9%, 0.262
Caucasian	2	1.18, 0.9-1.55	0.0%, 0.414	2.33, 1.33-4.08	0.0%, 0.911	0.95, 0.68-1.33	26.9%, 0.242	0.73, 0.50-1.06	54.0%, 0.140	0.82, 0.46-1.47	0.0%, 0.440

observed for the allele of G (G vs. T: OR=1.43; 95% CI, 1.06-1.94), for the recessive model (GG v GT + TT: *OR*=5.26, 95% *CI*=1.47-18.76), and for the homozygous model of GG (GG v TT: *OR*=5.27, 95% *CI*=1.47-18.95). In the Caucasian population, the risk of hypertension still increased significantly for the allele of G (G VS T: *OR*=1.67, 95% *CI*=1.16-2.40), for the recessive model (GG v GT + TT: *OR*=5.04, 95% *CI*=1.04-24.50), for the dominant models (GG + GT v TT: *OR*=1.62, 95% *CI*=1.08-2.42), and for the homozygous model of GG (GG v TT: *OR*=5.46, 95% *CI*=1.12-26.64). In the population with BMI of more than25, allele models (G VS T: *OR*=1.13, 95% *CI*=1.02-1.26), recessive models (GG v GT + TT: *OR*=1.27, 95% *CI*=1.02-1.59), and homozygous models (GG vs. TT: OR=1.28; 95% CI, 1.01-1.62) have significant associations with the risk of hypertension. The results of the stratified study showed that the polymorphism of rs1501299 was not associated with the risk of hypertension. Although there was no significant association between the rs266729 polymorphism and the risk of hypertension for the overall group without stratification, it was found that the recessive model of GG in individuals no more than40 years old (GG v GT + TT: *OR*=2.33, 95% *CI*=1.33-4.08) and in the Caucasian population (GG v GT + TT: *OR*=2.33, 95% *CI*=1.33-4.08) was significantly associated with an increased risk for the occurrence of hypertension (**Table 3**).

Sensitivity analysis and publication bias

To rule out the impact of low-quality literature on meta-analysis results, we performed a sensitivity analysis by omitting individual studies one by one. Results showed that no individual studies on the polymorphisms of the three loci affected the value of the combined OR, which proved that the MA has good stability.

The publication bias was analyzed using the Stata 12.0 software. We found that the funnel plot was basically symmetrical with respect to the central axis, and *P* values of Begg's test were all more than 0.05 (**Table 2**), indicating that there was no publication bias in each genetic model.

Discussion

Our results of the present study indicate that there is a significant association between the polymorphism of rs2241766 and the risk of hypertension. The T→G mutation was observed in the allelic model and increased the risk of hypertension by 10% (*OR*=1.10, 95% *CI*=1.01-1.21), meanwhile, no statistical significances were found in other genetic models nor in any genetic models for the polymorphisms of rs1501299 and rs266729. Although no heterogeneity was identified between studies and considering the asymmetry of factors such as race, age, and BMI in the study, we performed analyses for subgroups stratified by these factors. Subgroup analysis showed that significant associations of the rs2241766 polymorphism with the risk of hypertension were observed not only in the allelic model, recessive model, dominant model, and homozygous model in the subgroup of the Caucasian population, but also in the allelic model, recessive model, and homozygous model in individuals with BMI more than 25. In subgroups stratified by age, we found that the allelic model, recessive model, and homozygous models was significantly associated with an increased risk of hypertension in individuals no more than 40 years old. In order to prevent the impact of the HWE study on the analysis, we analyzed the test value based on the control group P, and found that the recessive and homozygous models were significantly associated with the risk of onset in the group at $P<0.05$. The association between the rs2241766 polymorphism in *ADIPOQ* gene and the susceptibility to hypertension has also been discussed by Xi et al. [25] Zhaoet al. [26]. In their study, the rs2241766 was not associated with the hypertension susceptibility, whichis inconsistent with our findings. However, the rs2241766 in *ADIPOQ* gene is associated with risks of obesity, coronary heart disease, and type 2 diabetes. Therefore, no association between the rs2241766 polymorphism and the risk of hypertension that reported by Zhao et al. [26] and Xi et al. [25] may be related to environmental factors such as diet-induced obesity which were not considered in their studies. The level of adiponectin in the plasma of patients with hypertension is low, and low levels of adiponectin are associated with single nucleotide polymorphisms of *ADIPOQ* [27]. Mousavinasab et al. [28] found that the GG genotype of the rs2241766 had a higher prevalence in individuals with hypertension than TT genotype. Tang et al. [5, 28] reported that GG + GT genotype rather than TT genotype was significantly associated with the low level of adiponectin. Therefore, we speculate that the association between

hypertension susceptibility and rs2241766 polymorphism may be affected by environmental factors such as obesity. The rs2241766 polymorphism in the exon 2 of the *ADIPOQ* gene may affect the expression of *ADIPOQ* genein adipose tissues and thereby associate with a reduced plasma concentration of adiponectin, which may increase the probability of developing hypertension. In the present study, the significance of association identified in the subgroup of the Caucasian may indicate the genetic heterogeneity. We speculate that the linkage disequilibrium structure of human *ADIPOQ* gene may be different in different ethnicities, i.e., the rs2241766 polymorphism is not consistently associated with the risk of hypertension in different races. Further exploration of the genetic structure of *ADIPOQ* gene may improve our understanding of mechanisms by which genetic factors work in hypertension.

We found that the rs266729 polymorphism was not significantly associated with the risk of hypertension risk at an overall level for included subjects. However, after stratification, in individuals no more than 40 years old and those who were Caucasians, the recessive genetic model of GG of the rs266729 were associated with an increased probability of developing hypertension (GG v GT + TT: *OR*=2.33, 95% *CI*=1.33-4.08). Studies on rs266729 and hypertension risk included subjects from different regions. A study of the British population found that the rs266729 polymorphism was associated with the levels of systolic and diastolic blood pressure [29]. The -11377C>G mutation in the proximal promoter region is associated with lower levels ofadiponectin and with an increased risk of hypertension in Hong Kong and the mainland of China. Although our results were also statistically significant, considering the limited number of the included studies, the interpretation of our results needs to be cautious. The association between the rs266729 polymorphism and the risk of hypertension and the underlying mechanism deserve further study.

In our present study, the polymorphism of rs1501299 was not significantly associated with the risk of hypertension in either overall or subgroup analyses. In our included studies, it was reported that the rs1501299 polymorphism is a protective factor for hypertension or a risk factor for hypertension [24, 30], which is inconsistent to our null conclusions. Hara et al. [31] found association between the rs1501299 polymorphism and adiponectin concentration in obese individuals with a BMI of no less than 26.7. We considered that the inconsistency may be due to differences in stratification and assumed that rs1501299 might be less able to regulate adiponectin levels than other polymorphism loci, all of which may be unrelated. Therefore, more research is needed to explore the effect of rs1501299 polymorphism on hypertension.

Nowadays, it has been proved that adiponectin can decrease blood pressure through central and peripheral mechanisms. However, experiments for these findings are performed in environment that were strictly controlled and had well designed controls, which may not directly and accurately reflect the occurrence and development of human hypertension in the real world. Hypertension is affected by a combination of environmental and genetic factors. Adiponectin levels are also affected by both the *ADIPOQ* polymorphism and the environment. Risk factors relating to lifestyle such as obesity may often play a more decisive role than genetic factors. Some studies have shown that after adjustment of some adipokines such as resistin and leptin, adiponectin levels are no longer associated with the risk of hypertension, meanwhile, adipocytokines secreted by perivascular adipose tissue still cause contractions of adjacent small arteries [32, 33]. Under this circumstance, the level of adiponectin may not be sufficient to affect blood pressure, and other fat factors may do. However, a genome-wide association study showed that the *ADIPOQ* polymorphism was identified as an important genetic factor affecting blood pressure, and the *ADIPOQ* gene affects blood pressure by regulating adiponectin levels, rather than by regulating adipokines or other acquired risk factors identified [34].

Our research has some limitations: ① the literature we included is either in Chinese or in English and may have some bias in the results; ② when we conducted subgroup analysis, limited studies were available for certain subgroup analyses and the results need to be treated with caution; ③ there were two control group in the literature that does not meet the HWE bal-

ance, which mightdue to genotyping errors or other biases in the original study; ④ our analysis was based primarily on unadjusted effect estimates, while confounding factors were not controlled and gene-environment interactions with disease were not considered; ⑤ only Asians and Caucasians were included, and the conclusions may not be suitable for all races.

In summary, our meta-analysis results show that the rs2241766 polymorphism is associated with the risk of hypertension. The polymorphism of rs1501299 is not significantly associated with the risk of hypertension. The rs266729 polymorphism is only found to be associated with the risk of hypertension in subgroups of individuals no more than 40 years old and in Caucasian population. Whether these polymorphisms may have a clinical significance in patients with hypertension remains to be determined, and further research is needed to confirm our finding in the future.

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Disclosure of conflict of interest

None.

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