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Gene polymorphism associated with TNF-α (G308A) IL-6 (C174G) and susceptibility to coronary atherosclerotic heart disease

A meta-analysis

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Abstract

To evaluate the association between gene polymorphisms of TNF-α G308A, IL-6 C174G, and coronary atherosclerotic heart disease (CHD) risk.

We used computers to collect related case-control studies. After screening, a meta-analysis was conducted to assess the strength of association by Stata 12.0 software.

Thirty-five articles were included. Among them, 17 studies were related to TNF-α (G308A) gene mutation and CHD, and 18 studies examined IL-6 (C174G) gene mutation. According to the results of subgroup analysis of ethnicity, it suggested that TNF-α (G308A) polymorphism was not significantly associated with CHD risk under all models in Asians ($P > .05$). There were no connected of IL-6 C174G polymorphism with CHD risk under all models in Caucasians after subgroup analysis ($P > .05$).

The present evidence shows that TNF-α (G308A) have no connected with the risk of CHD in Asians; IL-6 (C174G) gene were not associated with the risk of CHD in Caucasians.

Abbreviations: CHD = atherosclerotic heart disease, IL-6 = interleukin-6, OR = odds ratio, TNF-α = tumor necrosis factor-alpha.

Keywords: coronary atherosclerotic heart disease, interleukin-6, meta-analysis, polymorphism, tumor necrosis factor-alpha

1. Introduction

Coronary atherosclerotic heart disease (CHD) characterizes as myocardial ischemia and hypoxia which arises from coronary atherosclerosis.[1] It is a worldwide medical problem and is still one of the leading causes of death in developed and developing countries.[2] At present, the occurrence and development of CHD is generally considered as a chronic inflammatory process characterized by highly specific cytokine response.[3] The regulation network formed by various proinflammatory and anti-inflammatory factors plays an immunomodulatory role in atherosclerosis.[4] Various proteins, cytokines, and adhesion molecules are involved in the development of coronary angiogenesis.[5] Among them, TNF-α and IL-6 have significant effects on the development of coronary heart disease.[6,7] It has been showed that both of them are capable to damage endothelium function and act on the plaque of the vessel wall, accelerating the rupture of the plaque and triggering the clinical coronary events.[8] As a complex disease, CHD results from the interaction between genetic and environmental factors.[9] Recent studies have suggested that the basic level and biological activity of TNF-α and IL-6 can be influenced by gene polymorphism, which may increase the risk of CHD[10,11] C863A of TNF-α and C174G of IL-6 are the mostly investigated but the results remain inconsistent. Asifa et al[12] considered that the TNF-α C863A gene polymorphism was associated with the pathogenesis of CHD through case-control study in Pakistan, while Chu et al[13] research in China drew an opposite conclusion. The studies on IL-6 gene polymorphism and risk of CHD are also inconsistent, similar to that research status of TNF-α.[14,15] This may be due to racial and regional differences, as well as the fact that the sample size is too small to truly reflect the relevance. In order to compare different research results more scientifically and objectively, meta-analysis on this issue coming to be widely carried out also generated conflicting results. Based on it, we carry out a meta-analysis including the genotype data from all eligible investigations in the latest years involving more extensive countries and regions to provide a more precise evaluation of the association between polymorphisms in –308G/A of TNF-α, C174G of IL-6 and CHD susceptibility.

2. Materials and methods

2.1. Search strategy

Our study followed the meta-analysis of Observational Studies in Epidemiology guidelines and the researches were investigated in

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Statement: The ethical approval was not necessary. Because this study is about the Gene polymorphism associated with TNF-α (G308A) IL-6 (C174G) and susceptibility to coronary atherosclerotic heart disease: a meta-analysis. Because this paper is not a clinical trial study, ethical approval and informed consent are not required. All included articles have passed ethical approval and informed consent.

On behalf of all authors, the corresponding author states that there are no conflicts of interest. And manuscript is approved by all authors for publication.

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the following databases since the establishment of the library to April 2018: the China National Knowledge Infrastructure (CNKI), China Wanfang Database, Chinese biomedical literature database and PubMed, EMBASE, Cochrane library, Web of Science, Sciencedirect. The following search words were combined: "G308A" or "TNF-α" or "C174G"or "IL-6" or "coronary atherosclerotic heart disease." In addition, we searched the references in detail for further research. Furthermore all magazines were retrieved from the first issue, and the relevant conference literature was tracked. If necessary, contact the communication author to obtain information not found by the above retrieval strategies.

2.2. Inclusion and exclusion criteria

Studies that meet the following criteria will be adopted: the literature must be a case-control study published both at home and abroad, with good balance and comparability. Languages are limited to Chinese or English. The research should involve gene polymorphisms of TNF-α (G308A), IL-6 (C174G), and CHD. The research should meet the diagnostic criteria of coronary heart disease. Each genotype distribution and individual number in the case and control groups should be listed in the literature, or the corresponding number can be calculated by the frequency of each genotype given.

Studies with the following characteristics will be excluded: not associated with TNF-α (G308A), IL-6 (C174G) polymorphism, and CHD; not a case–control study; the data of genotype frequency and allele frequency in the literature are incomplete or unclear.

2.3. Data extraction and quality evaluation

The 2 researchers (Jiang and Zhao) sifted through the title and summary of the studies. Then they read the full text for the secondary screening and eliminated the studies that did not meet the above-mentioned inclusion criteria. For trials that were difficult to determine whether they should be included, consult an expert to discuss the solution. If the information provided in this article was uncertain, contact the original author by phone, email, and other measures to obtain relevant information. We used the 9-star Newcastle-Ottawa scale to evaluate the quality of the studies. It includes 3 aspects: study object selection, group comparability, and exposure factor measurement. In brief, a maximum of 9 points was assigned to each study: 4 for selection, 2 for comparability, and 3 for outcomes. A final score of >6 was regarded as high quality. Then we organized each article included and extracted relevant data: the first author's name, years of publication, country and region, genotype frequencies in the observation group and control group. Hardy–Weinberg equilibrium and quality score of case-control study were showed in Fig. 1.

3. Statistical analysis

All the data were analyzed using Stata 12.0 software and the charts related were drawn below. Based on the odds ratio (OR) with a corresponding 95% confidence interval (CI), we counted the pooled odds which were used to analyze the effect on the association. While crossing these studies, Q test and I^2 were used to test the heterogeneity of the included literature firstly. When I^2 >50%, it was proved that there was heterogeneity between the studies, the random effect model was used, and if not, the fixed effect model was used instead. In order to Search for the sources of heterogeneity, we mainly apply subgroup analysis on the national and regional groups. In order to evaluate the stability of the combined results, a sensitivity analysis was conducted for the meta-analysis results after each removal of a case-control study. The Begg funnel plot was used as a criterion for assessing publication bias.

4. Results

4.1. Characteristics of the included studies

Overall, a total of 35 out of 1158 articles were selected for the final meta-analysis.[16–49] Among the 35 articles, 18 studies[16–33]

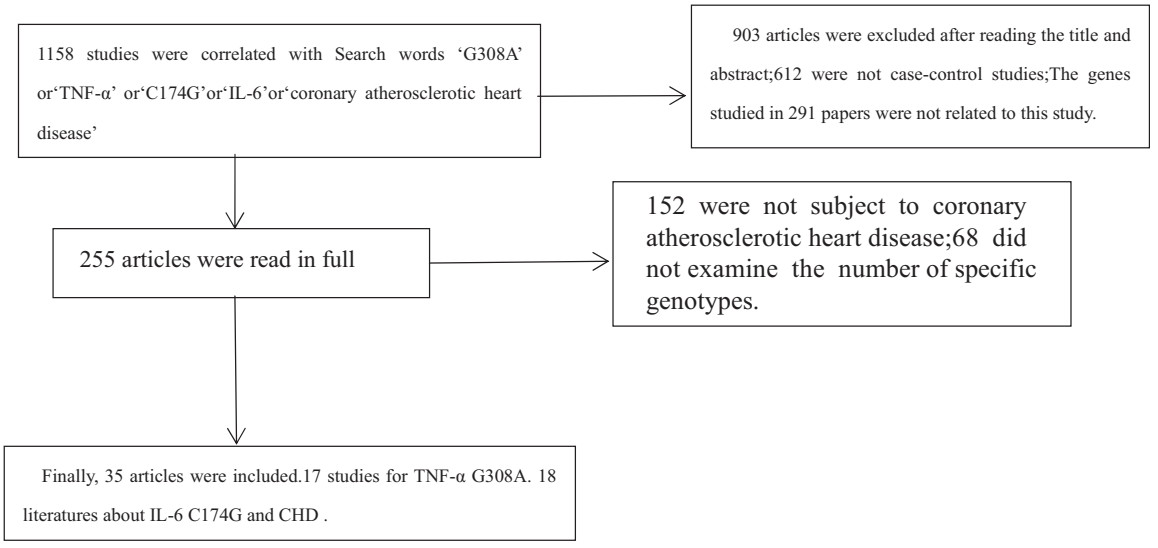


Figure 1. Article screening flowchart.

Table 1

Characteristics of studies on the association between C174G gene polymorphisms of IL-6 and CHD risk.

			Total of cases					Total of controls						
The first author	Publicati-on date	Country/city/ethnicity	GG	GC	CC	G	C	GG	GC	CC	G	C	HWE inspec-tion	Quality score
Ghazouani et al[16]	2011	Tunisia/Caucasian	418	110	10	706	130	406	102	7	696	116	0.96	8
			298					297						
Bennermo et al[17]	2011	Sweden/Caucasian	356	150	87	388	324	378	176	93	394	362	<0.05	9
			119					109						
Fan et al[18]	2011	China/Asian	84	0	0	168	0	130	1	0	259	1	<0.05	6
			84					129						
Chakraborty et al[19]	2012	India/Asian	100	35	8	149	51	120	39	8	185	55	0.43	7
			57					73						
Tuttolomondo et al[20]	2012	Italy/Caucasian	96	46	10	126	66	48	33	1	61	35	0.54	6
			40					14						
Coker et al[21]	2011	Turkey/ Caucasian	167	56	9	260	74	235	81	13	363	107	0.72	8
			102					141						
Chumaeva et al[22]	2014	Finland/Caucasian	978	508	270	908	1048	695	353	201	635	755	0.17	9
			200					141						
Tong[23]	2010	China/Asian	648	0	0	1296	0	648	3	0	1293	3	<0.05	6
			648					645						
Banerjee et al[24]	2009	India/Asian	210	43	8	361	59	232	57	4	399	65	<0.05	7
			159					171						
Sarecka et al[25]	2008	Poland/Caucasian	178	93	42	179	177	202	105	37	225	179	0.55	6
			43					60						
Elsaid et al[26]	2014	Egypt/Asian	104	55	23	107	101	104	49	55	49	159	0.55	8
			26					0						
Li et al[27]	2015	China/Asian	365	113	39	539	191	365	105	15	595	135	<0.05	7
			213					245						
Yang et al[28]	2015	China/Asian	410	163	49	559	261	410	146	25	624	196	0.09	6
			198					239						
Yao et al[29]	2016	China/Asian	275	19	0	531	19	296	14	0	578	14	0.55	7
			256					282						
Carvalho et al[30]	2016	Brazil/Caucasian	200	80	11	298	102	50	23	4	69	31	0.46	9
			109					23						
Gao et al[31]	2016	China/Asian	275	50	42	416	132	286	47	15	495	77	<0.05	6
			183					224						
Tong et al[32]	2013	China/Asian	326	87	38	489	163	341	98	23	538	144	<0.05	7
			201					220						
Mastana et al[33]	2017	India/Asian	138	32	1	242	34	131	39	1	221	41	0.39	7
			105					91						

reported the association between IL-6 (C174G) gene mutation and CHD with 5328 cases and 5077 controls. Seventeen articles[34–49] demonstrated the relationship between TNF-α (G308A) and CHD with 5360 cases and 6197 controls. The baseline characteristics of the studies related to mutation of IL-6 (C174G) and TNF-α (G308A) were respectively shown in Tables 1 and 2. All of the 35 articles were published before January 2018. In addition, 29 manuscripts were published in English, and 6 manuscripts were in Chinese.

4.2. Results of the overall meta-analysis

4.2.1. Meta-analysis of TNF-αG308A polymorphism and CHD risk. Seventeen articles were related to G308A mutation and CHD risk. The results showed that I^2 of all models were >50%, indicating that the included studies had heterogeneity. Subgroup analysis was needed to explore the source of heterogeneity.

4.3. Subgroup analysis

Of the 17 articles included, 10 articles were from Asians, 7 articles were from Caucasians. The results were shown in Table 4. And we conducted subgroup according to different ethnic groups. The I^2 of all models in Asians were <50%, indicating that ethnic differences had an impact on heterogeneity. The results suggested that there was no significantly association between G308A polymorphism and CHD risk under all models from Asians ($P > .05$) (Table 3).

4.4. Meta-analysis of IL-6 C174G polymorphism and CHD risk

Thirteen articles were related to IL-6 C174G polymorphism and CHD emotivity. The results showed that the polymorphism of C174G gene was not significantly associated with CHD risk under heterozygote model (CG vs GG; OR 0.998, 95% CI 0.902–1.103) ($P > .05$). The results were shown in Table 4, Fig. 2. Furthermore, sensitivity analysis revealed that omission of each study made no significant differences on the findings Fig. 3.

4.5. Test for heterogeneity

In the heterogeneity test for the IL-6 C174G genotypes of each model, I^2 of C versus G, CC versus CG+GG, CC versus GG, CC +CG versus GG were >50%, indicating that the included studies had heterogeneity. Subgroup analysis was needed to explore the source of heterogeneity.

Table 2

Characteristics of studies on the association between G308A gene polymorphisms of TNF-α and CHD risk.

			Total of cases					Total of controls						
The first author	Publicati-on date	Country/city/ethnicity	GG	GA	AA	G	A	GG	GA	AA	G	A	HWE inspec-tion	Quality score
Işik et al[34]	2016	Turkey/Caucasian	41	5	0	77	5	88	15	2	157	19	0.68	8
			36					71						
Zeybek et al[35]	2011	Turkey/Caucasian	143	56	11	208	78	213	33	14	365	61	0.88	9
			76					166						
Ghaderian et al[36]	2011	Iran/Caucasian	996	246	69	1608	384	910	174	19	1608	212	<0.05	7
			681					717						
Vaccarino et al[37]	2013	Italy/Caucasian	60	20	2	96	24	130	17	2	239	21	0.75	8
			38					111						
Szabó GV[38]	2013	Hungary/Caucasian	118	26	2	206	30	384	108	41	578	190	0.94	8
			90					235						
Ghazouani et al[39]	2010	Tunisian/Caucasian	418	142	11	672	164	406	124	15	658	154	0.11	7
			265					267						
Hou et al[40]	2009	China/Asian	300	32	0	568	32	905	101	2	1705	105	0.33	6
			268					802						
Liu et al[41]	2009	China/Asian	286	22	30	490	82	176	11	23	295	57	<0.05	6
			234					142						
Banerjee et al[42]	2009	India/Asian	210	28	1	390	30	232	31	0	433	31	0.94	7
			181					201						
Hussain et al[43]	2015	Pakistan/Asian	150	45	8	239	61	150	26	4	266	34	0.36	8
			97					120						
Cheng et al[44]	2015	China/Asian	493	48	0	938	48	304	21	0	587	21	0.26	6
			445					283						
Chen et al[45]	2014	China/Asian	433	47	2	815	51	477	58	3	890	64	0.67	7
			384					416						
Garg et al[46]	2013	India/Asian	137	20	0	254	20	185	38	1	330	40	0.36	8
			117					146						
Qi et al[47]	2014	China/Asian	206	32	0	380	32	274	33	0	515	33	0.23	6
			174					241						
Cheng et al[44]	2015	China/Asian	246	25	0	467	25	304	21	0	587	21	0.40	7
			221					283						
Zhao et al[48]	2015	China/Asian	783	145	11	1399	167	749	126	6	1360	138	0.43	6
			627					617						
Omer et al[49]	2016	Pakistan/Caucasian	340	65	10	595	85	310	48	3	566	54	<0.05	6
			265					259						

Table 3

Meta-analysis of TNF-αG308A polymorphism and CHD risk.

	I^2	Model	OR		95%CL	P	z
AA vs. GG from Asians	0.00%	FEM	1.089	0.710	1.671	0.696	0.39
AA vs. GG from Caucasians	78.90%	REM	1.632	1.205	2.210	<0.05	3.17
AG vs. GG from Asians	30.30%	FEM	1.134	0.982	1.310	0.087	1.71
AG vs. GG from Caucasians	82.20%	REM	1.395	1.211	1.606	<0.05	4.62
(AA + AG) vs. GG from Asians	40.60%	FEM	1.24	0.978	1.291	0.099	1.65
(AA + AG) vs. GG from Caucasians	86.70%	REM	1.435	1.256	1.640	<0.05	5.3
AA vs. (AG + GG) from Asians	0.00%	REM	1.052	0.686	1.613	0.816	0.23
AA vs. (AG + GG) from Caucasians	77.20%	REM	1.501	1.109	2.032	<0.05	2.63
A vs. G from Asians	46.40%	FEM	1.106	0.974	1.257	0.12	1.55
A vs. G from Caucasians	90.40%	REM	1.371	1.222	1.538	<0.05	5.37

Table 4

Results of IL-6 C174G polymorphism and CHD risk.

	I^2	Model	OR		95% CI	P	z
CG vs. GG	37.40%	FEM	0.998	0.902	1.103	.965	0.04

CI = confidence interval, CHD = atherosclerotic heart disease, OR = odds ratio.

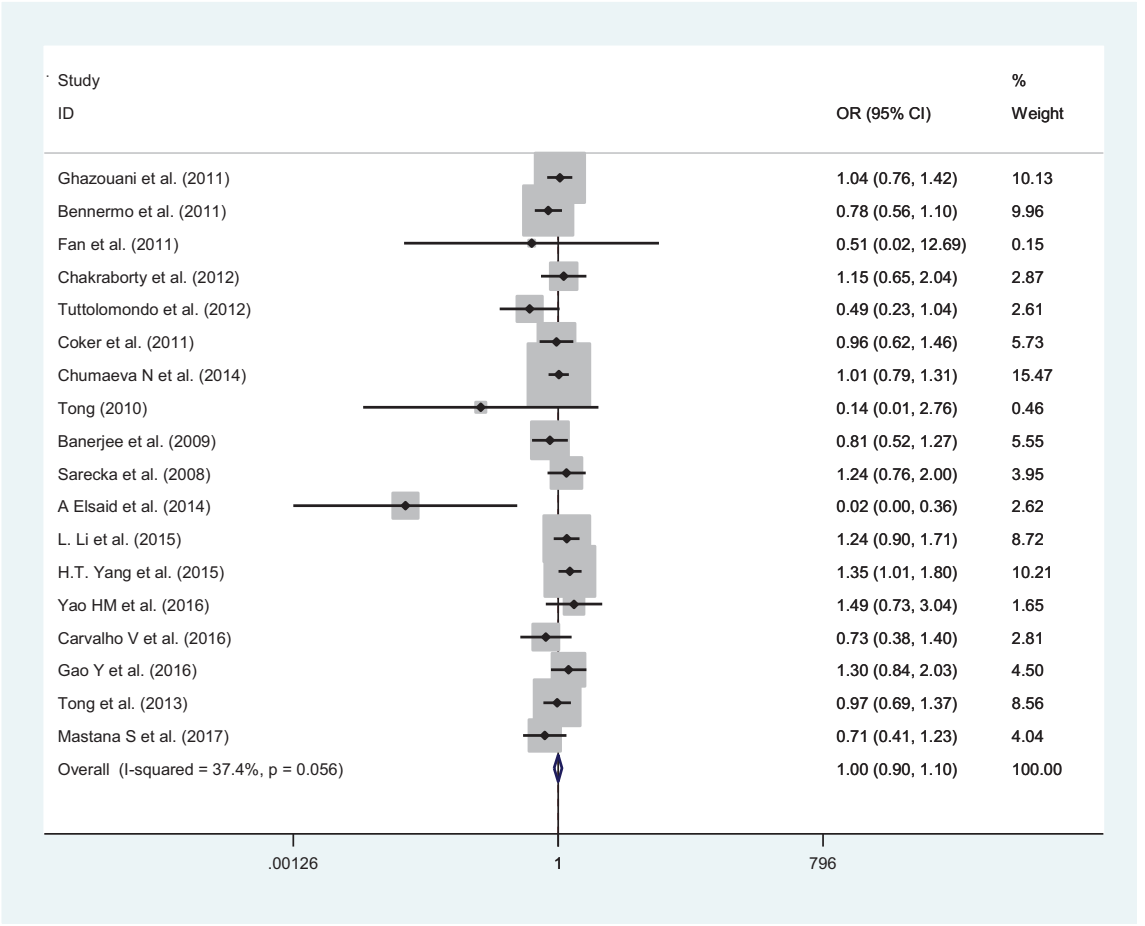


Figure 2. Forest plot of IL-6 C174G polymorphism and CHD risk. CHD = coronary atherosclerotic heart disease, IL-6 = interleukin-6.

4.6. Subgroup analysis

Of the 18 articles included, 11 studies were from Asians and 7 were from Caucasians. We conducted subgroup analysis on CC versus GG, CC+CG versus GG, CC versus CG+GG, C versus G genotype, and CHD risk according to the ethnicity. The I^2 of (CC vs GG, CC+CG vs GG, CC vs CG+GG, C vs G) in Caucasians were <50%, indicating that ethnic differences had an impact on heterogeneity. And there was no significantly

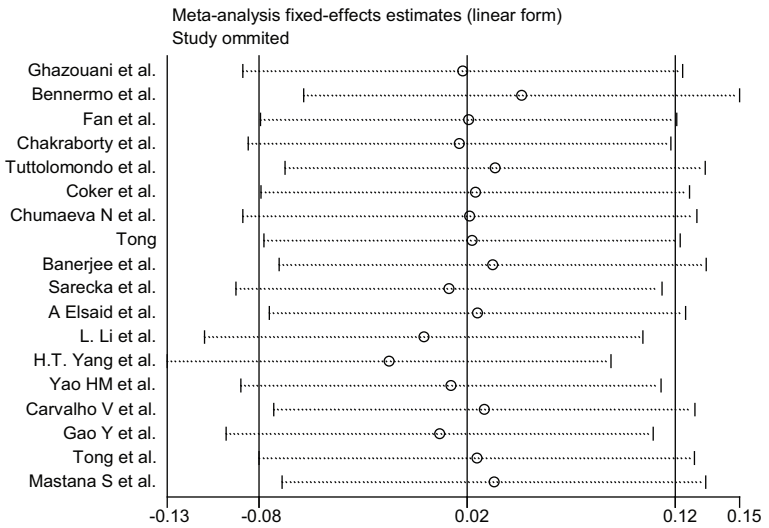
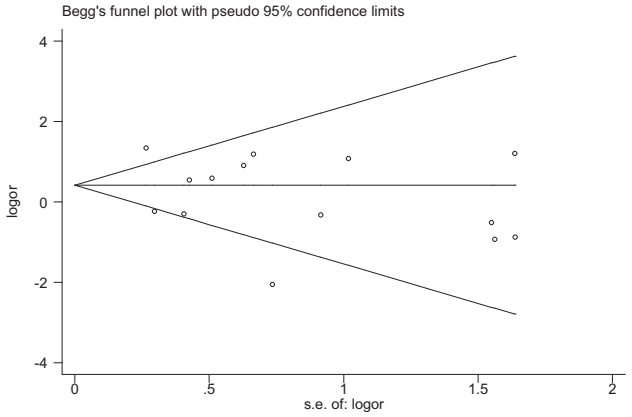


Figure 3. Sensitivity analyses for IL-6 C174G CG versus GG polymorphism and CHD. CHD = coronary atherosclerotic heart disease, IL-6 = interleukin-6.

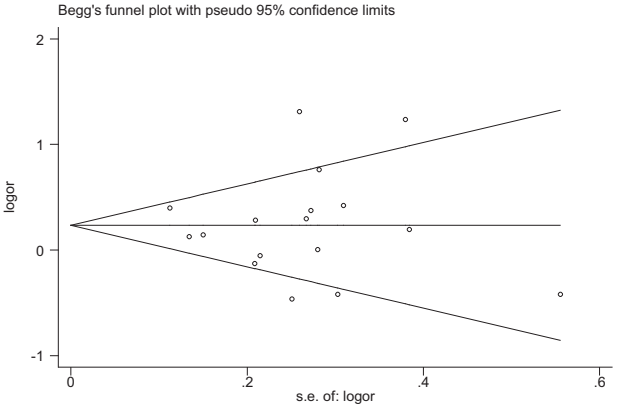
Table 5

results of IL-6 C174G mutation and CHD risk in subgroup analysis.

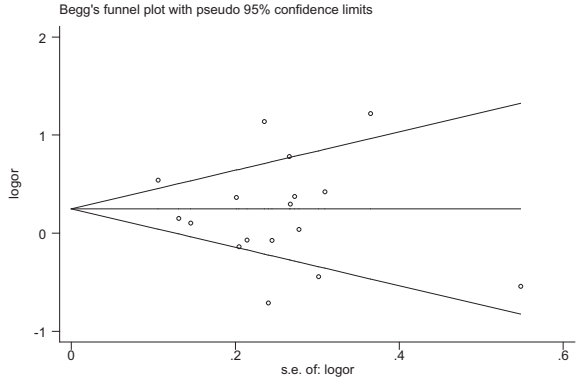
	I^2	Model	OR		95% CI	P	z
CC VS. GG from Asians	70. 50%	REM	1.817	1.419	2.327	<. 05	4. 74
CC vs. GG from Caucasians	0. 00%	FEM	1. 001	0. 821	1. 221	0. 99	0. 01
CC+CG VS. GG from Asians	61. 90%	REM	1. 203	1. 056	1. 371	<0. 05	2. 77
CC+CG VS. GG from Caucasians	4. 50%	FEM	0. 965	0. 841	1. 106	0. 605	0. 52
CC VS. CG+GG from Asians	85. 50%	REM	1. 615	1. 282	2. 035	<0. 05	4. 07
CC VS. CG+GG from Caucasians	0. 00%	FEM	1. 016	0. 863	1. 195	0. 852	0. 19
C VS. G from Asians	85. 60%	REM	1. 089	0. 710	1. 671	<0. 05	3. 95
C VS. G from Caucasians	0. 00%	FEM	1. 632	1. 205	2. 210	0. 739	0. 33



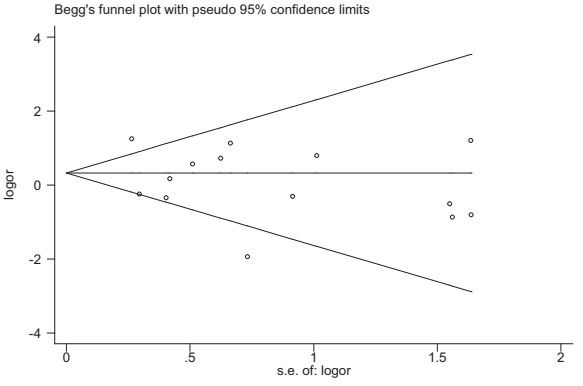
AA vs. GG



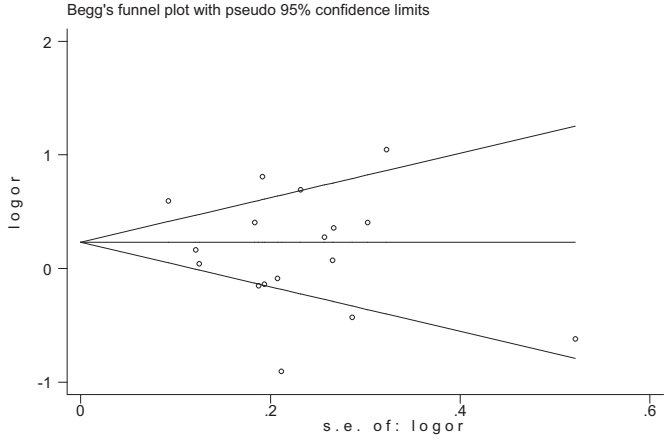
AG vs.GG



(AA + AG) vs.GG



AA vs. (AG + GG)



A vs. G

Figure 4. The publication bias of articles on the relationship between TNF-α G308A and CHD risk was shown in the funnel figure. CHD = coronary atherosclerotic heart disease, TNF-α = tumor necrosis factor-alpha.

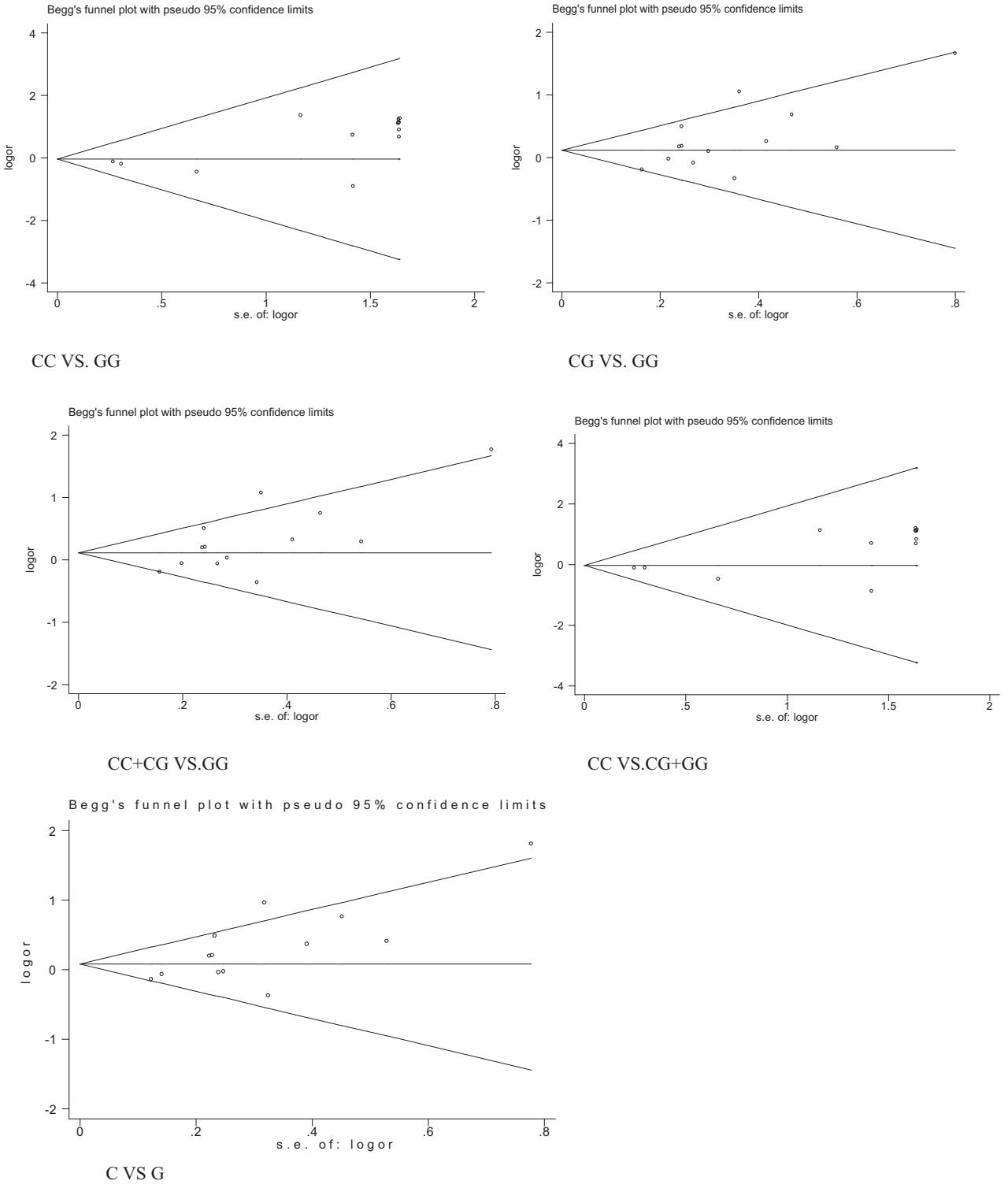


Figure 5. The publication bias of articles on the relationship between IL-6 C174G and CHD risk was shown in the funnel figure. CHD = coronary atherosclerotic heart disease, IL-6 = interleukin-6.

association between CHD risk and IL-6 C174G polymorphism under CC versus GG, CC+CG versus GG, CC versus CG+GG, C versus G in Caucasians ($P > .05$). The results were shown in Table 5.

4.7. Publication bias

We analyzed the publication bias of articles on the relationship between TNF-α (G308A) and IL-6 (C174G) with CHD risk. The 2 groups of gene funnel plot analysis showed asymmetry

indicating the possibility of publication bias. The results were shown in Figures 4 and 5.

5. Discussion

Recently the polymorphisms of TNF-α, IL-6 have aroused great concern among researchers. It has been found that both TNF-α and IL-6 genes have gene polymorphism, which may affect the transcription and expression of genes, and are closely related to the significant increase of CHD risk.[50]

TNF-α is an inflammatory cytokine secreted by macrophages and has multiple biological activities. As a starting factor for endothelial dysfunction and endometrial thickening, it can directly damage the vascular endothelial cells and then increase permeability to make more cholesterol deposited in the vascular wall, forming atherosclerotic plaques.[51] Besides it is also capable of promoting the formation of platelet-derived growth factor, breaking blood coagulation–anticoagulant balance, and contributing to thrombosis.[52] Moreover TNF-α reduces lipoprotein activity, participates in insulin resistance, and affects the synthesis of other inflammatory factors.[53] The concentration of TNF-α in plasma can be influenced by gene polymorphism. Among several common mutation sites, the G-308A was the most studied, which is a single nucleotide conversion from guanine (G) to adenine (A) in the TNF-α promoter at position –308.[54] In our conclusions TNF-α (G308A) polymorphism was not significantly associated with CHD risk under all models in Asians ($P > .05$), which is consistent with the results of Wang et al[55] research. To further identify this association, more high quality studies should be merited.

IL-6 is another important cytokine in the proinflammatory response mainly produced by monocytes and macrophages.[56] In the acute stage of inflammation, IL-6 can induce the production of acute inflammatory reactants such as c-reactive protein and fibrinogen, and interact with cytokine network, involved in the pathogenesis of CHD.[57] A study shows that its mRNA levels in atherosclerotic arteries are 40 to 50 times higher than that in nonatherosclerotic vessels.[58] The plasma level of IL-6 are partly adjusted by the IL-6 C174G polymorphism[59] which is located in the upstream promoter region of IL-6 gene. C174G mutation site transforms from a guanine (G) to cytosine (C) at position –174. A 6-year follow-up study in the UK showed that people with genotype of G/C or C/C were more likely to develop CHD when compared with people carrying G/G genotype (OR = 1.54).[60] In our research, there were no connection between IL-6 C174G polymorphism and CHD risk under all models in Caucasians.

Our meta-analysis also has its own drawbacks. For instance the inspections of the funnel plots suggest that they are not symmetrical. This may be due to the fact that sample sizes of many studies included in our meta-analysis were relatively small, and the number of eligible studies included is also not enough. This requires more relevant case-control studies in the future to make the meta-results more objective and scientific.

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Conceptualization: Yuepeng Jiang, Xiaoxuan Zhao.
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Funding acquisition: Xiaoxuan Zhao, Li Liu.
Investigation: Yuepeng Jiang, Li Liu.
Methodology: Yang Zhao.
Project administration: Yuepeng Jiang, Xiaoxuan Zhao.
Resources: Li Liu.
Software: Yang Zhao.
Validation: Li Liu.
Visualization: Li Liu.
Writing – original draft: Yuepeng Jiang, Xiaoxuan Zhao.
Writing – review & editing: Yuepeng Jiang.

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