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Association between chemokine CXC ligand 12 gene polymorphism (rs1746048) and coronary heart disease

A MOOSE-compliant meta-analysis

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Abstract

Recently a large number of investigations have implicated the association between the chemokine CXC ligand 12 gene polymorphism (rs1746048) and risk of coronary heart disease (CHD), but the results remain debatable. The aim of our study was to provide more compelling evidence for the relationship between rs1746048 and CHD risk. Studies eligible for this meta-analysis were identified through electronic search of PubMed, EMBASE, and CNKI. Two authors performed independent literature review and study quality assessment by using the Newcastle–Ottawa Scale checklist. The odds ratios (ORs) with 95% confidence intervals (CIs) were pooled in a specific genetic model to assess the association. The meta-analysis of 48,852 patients and 64,386 controls from 12 studies showed that patients with rs1746048 had 1.11 times of high risk in developing CHD (OR = 1.11; 95% CI = 1.09–1.14; $P < .005$; $I^2 = 35.8\%$). The increased risk of CHD was also found in both Asian (OR = 1.07; 95%CI = 1.02–1.12; $P < .005$; $I^2 = 40.6\%$) and Caucasian populations (OR = 1.14; 95% CI = 1.10–1.18; $P < .005$; $I^2 = 22.2\%$). The results of our meta-analysis suggested that chemokine CXC ligand 12 gene polymorphism (rs1746048) may be linked with susceptibility to CHD.

Abbreviations: CHD = coronary heart disease, CI = confidence interval, HWE = Hardy–Weinberg equilibrium, NOS = Newcastle–Ottawa Scale, OR = odds ratio, SNP = single nucleotide polymorphisms.

Keywords: CHD, *CXCL12* gene, meta-analysis, polymorphism, rs1746048

1. Introduction

Given extension of life expectancy and promotion of life quality, 3-grade prevention of diseases has become crucial. Coronary heart disease (CHD) is 1 of the leading cause of death and disability in both developed and developing countries.[1] CHD is a complex disease which has a significant genetic component. The promotion of the disease state is resulted from the integrated effect of multiple genetic variants and environmental factors.[2,3] Recent genome-wide association studies been moderately successful in revealing many CHD susceptibility loci.[4–8] However, only less than 5% discovered risky genes contribute to the total heritability of CHD.[9]

As inflammatory responses are involved in the pathophysiology of atherosclerosis, genes that contribute to the inflammation pathways are suitable candidates to be studied in association with CHD. The 10q11.21 is 1 of the proposed loci, which encompasses *CXCL12* gene with an important role in CHD.[10,11]*CXCL12* is highly expressed in atherosclerotic plaques and smooth muscle cells which contributes to the progress of arteriosclerosis.[12–14] Several genome-wide association studies and their replication studies propose a crucial role for the single nucleotide polymorphisms (SNP) rs1746048 of *CXCL12* gene in human atherosclerosis leading to CHD.[10,15]

In order to provide more compelling evidence for the association between rs1746048 and CHD, we therefore performed a systematic meta-analysis of all available data from case–control studies, aiming to better understand the relationship between chemokine CXC ligand 12 gene polymorphism with CHD.

2. Materials and methods

2.1. Literature search strategies

Relevant studies were identified from the following electronic databases: PubMed, Embase, OVID, Cochrane library, Web of Science, CNKI (Chinese National Knowledge Infrastructure),

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MC and Y-FJ have contributed equally to the article.

Authorship: MC and Y-FZ conceived and designed the experiments. MC, Y-FJ, N-NZ, and H-JY performed the literature search, data extraction. L-BX, QR conducted the statistical analysis and drafted the figures. MC and Y-FJ contributed the first draft of the report, and S-JS, J-LY, and Y-FZ helped to wrote the final version. All authors read and met the ICMJE criteria for authorship. All authors agree with the results and conclusions of the report.

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Wanfang Databases up to February 2017, and were systematically identified case–control studies with the use of a standardized protocol. The search was performed using various combinations of keywords including "CXCL12", "SDF-1", "polymorphism", "variant", "mutation", "coronary heart disease" and "myocardial infarction" with language limitation to English and Chinese. Two reviewers (MC and Y-FZ) independently evaluated identified titles and abstracts, and manuscripts were retrieved for any publication that either review considered as potentially relevant. Additional publications were sought using the reference lists of identified papers and published reviews on the topic. As this was a study based on published case–control articles instead of an original research, ethical approval was not needed.

2.2. Study selection

The second step of screening was based on full-text review. The references of the selected papers were also checked by hand-search for other potential articles that possibly had been missed in the initial search. To be eligible for inclusion in this meta-analysis, a study must meet the following criteria: The study was a case–control study. Evaluate the association between rs1746048 of *CXCL12* gene with CHD. The control groups were healthy people. Provide the sufficient data for calculating an odds ratio (OR) with its 95% confidence interval (CI). Should be of Hardy–Weinberg equilibrium (HWE) in control ($P > .05$). When duplicate articles were published, the study with the larger sample size and more comprehensive outcome evaluation will be included. Any discordance between reviewers was resolved by consensus.

2.3. Data extraction

Two reviewers conduct all the data extraction independently with standardized data-collection form. Any potential disagreements were resolved by discussion. The following characteristics were extracted from each study: first author's name, year of publication, ethnicity, genotype method, number of genotypes in cases and control subjects, adjusted factors, and the *P* value of HWE in control.

2.4. Quality assessment

The quality of studies was independently evaluated by 2 reviewers using the 9-point Newcastle–Ottawa Scale (NOS).[16] Based on 3 broad perspectives, including selection, comparability, and exposure, the quality of each study was assessed. A total score of 7 or greater indicated that 1 study was of high quality.

2.5. Statistical analyses

All the studies use the allele counting method to determine the allele frequencies. We choose Chi-square interval to assess the HWE, and $P < .05$ was considered to be significant disequilibrium. The combined OR which was reported under an allele model and 95% CI was used to estimate the strength of association between rs1746048 and CHD. We quantified the effect of statistical heterogeneity by I^2 statistic as follows[17]:

$$I^2 = 100\% \times \frac{(Q-df)}{Q}$$

I^2 values of 25%, 50%, and 75% were defined as low, moderate, and high estimates, respectively. If $I^2 > 50\%$ is indicated across studies, a random effect model (DerSimonian–Laird method)[18] was used to calculate pooled effect estimates in the presence of heterogeneity; otherwise, the fixed model (Mantel–Haenszel method)[19] was used.

At last, we performed Begg rank correlation test and Egger linear regression test[20,21] at the $P < .10$ level of significance to evaluate the potential publication bias. For the possible publication bias, a contour-enhanced funnel plot was used to further explore the source of bias. All statistical analyses were performed using Stata version 14.0 (Stata Corporation, College Station, TX).

3. Results

3.1. Study characteristics

Initially, there were 252 papers relevant to the search words through reviewing the potentially relevant genetic association studies (Fig. 1). After screening the titles and abstracts, 233

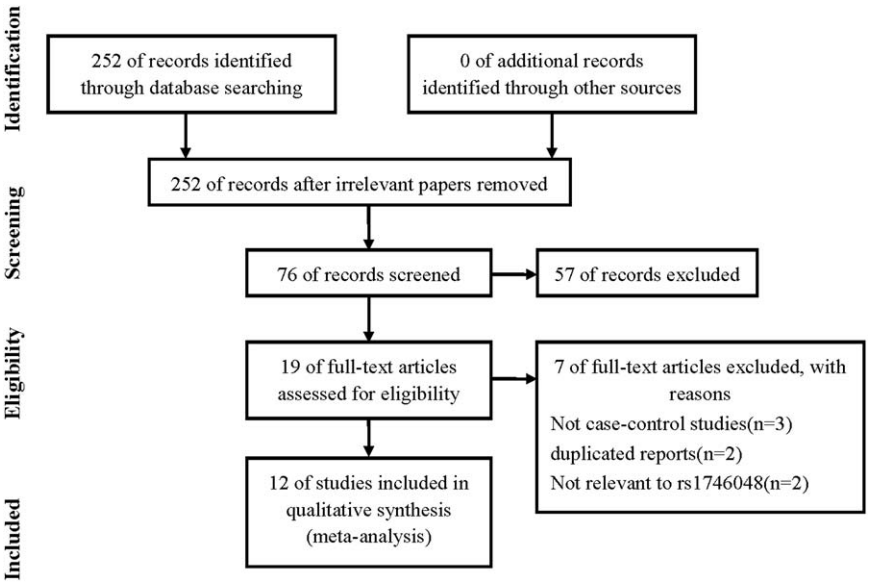

Figure 1. Flowchart of study chart.

Table 1

Characteristics of the studies included for meta-analysis.

Author	Year	Country	Stage	Popolations	Disease	Genotyping Method	Cases	Controls	Adjusted factors	HWE (Y/N)
S.U. Shahid	2017	Pakistan	Pakistani	Asian	CHD	TaqMan and KASPar	405	220	Age, gender, BMI, hypertensive, diabetic status	Y
Y.Q. Wang	2014	China	Chinese	Asian	MI	TaqMan	2365	2678	Age, gender, BMI	Y
Y. Huang	2013	China	Chinese	Asian	CHD	PCR	434	358	NA	Y
A. Angelakopoulou*	2012	England	CBGC	European	CHD	TaqMan and KASPar	5749	25,000	Age, gender, smoking	Y
N. N. Mehta	2011	America	PennCAC	European	CHD	Affymetrix	879	878	Age, gender	Y
M.P. Reilly	2011	America	Stage A3	European	MI	Affymetrix	5078	2311	Age, gender	Y
S. Saade	2011	America	Lebanese	Asian	CHD	Illumina	1524	425	Gender, hypertension, hyperlipdemia, diabetes, smoking family history of CAD	Y
L. Qi	2011	America	Costa Rican	North American	MI	TaqMan	1989	2096	Age, gender, area of residence, waist-to-hip radio, smoking, alcohol consumption, physical activity, total calories, family history of CAD	Y
J.F. Peden-a	2011	England	PROCARDIS	European	CHD	Human1M	5720	4381	NA	Y
J.F. Peden-b	2011	England	HPS	European	CHD	HumanHap	2704	2887	NA	Y
J.F. Peden-c	2011	England	PROMIS	Asian	CHD	HumanHap	4255	4098	NA	Y
J.F. Peden-d	2011	England	LOLIPOP	Asian	CHD	HumanHap	2741	3696	NA	Y
Lu Qi-a	2011	America	NHS	North American	CHD	OpenArray	309	544	Age, gender, glycemic control, HDL, smoking, hypertension and hypercholesterolemia	Y
Lu Qi-b	2011	America	HPFS	North American	CHD	OpenArray	345	451		Y
Lu Qi-c	2011	America	JHS	North American	CHD	OpenArray	435	422		Y
R.W. Davies	2010	Canada	OHGS	North American	CHD	Affymetrix	1542	1455	Gender, hypertension, smoking, total cholesterol, high-density lipoprotein	Y
S. Kathiresan-a	2009	America	Stage1	European	MI	Affymetrix	2967	3075	NA	Y
S. Kathiresan-b	2009	America	Stage2	European	MI	Affymetrix	3942	3942	NA	Y
S. Kathiresan-c	2009	America	Stage3	European and Asian	MI	Affymetrix	5469	5469	NA	Y

BMI = body mass index, CAD = coronary arteryl disease, CHD = coronary heart disease, HPFS = Health Professional Follow-Up Study, HPS = Heart Protection Study, HWE = Hardy–Weinberg equilibrium, JHS = Joslin Heart Study, LOLIPOP = London Life Sciences Prospective Population, MI = myocardial infarction, NA = not available, NHS = Nurses' Health Study, OHGS = Ottawa Heart Genomics Study, PennCAC = Penn coronary artery calcification, PROCARDIS = Precocious Coronary Artery Disease, PROMIS = Pakistan Risk of Myocardial Infarction Study, Stage 1 = MIGen (Myocardial Infarction Genetics Consortium), Stage 2 = WTCCC (Wellcome Trust Case Control Consortium) and GerMIFSI (German MI Family Study I) and PennCATH (PennCATH) and Medstar (MedSTAR), Stage 3 = AMI gene (Acute Myocardial Infarction Gene Study/Dortmund Health Study) and Verona (Verona Heart Study) and MAHI (Mid- America Heart Institute) and IFS (Irish Family Study) and GerMIFSII (German MI Family Study II) and INTERHEART, Stage A3 = Emory Gene Bank, Utah Intermountain Heart Collaborative Study and Verona Heart Study.

* rs1746048-C shows high linkage disequilibrium (LD) ($r^2 = 0.95$) with rs501120-T allele in the CHD study.

papers were excluded. Of these, 19 papers were preliminarily included for further identification of full texts and data. A total of 7 more articles were excluded for the following reasons: 3 were not case–control studies, 2 were duplicated reports, and 2 were not related to CXCL12 mutation. Consequently, a total of 12 studies,[10,22–32] including 48,852 CHD cases and 64,386 controls were subjected to our meta-analysis. Of the 12 articles, there are included 19 study stages. Among them, 6 study stages were conducted in Asian, 7 were in Europe, 5 in North America, and 1 study stage was not limited to ethnic group (including European and Asian). Of the 19 study stages, 17 included both male and female, 1 included only female, and 1 included only male. The mean age of all included subjects ranged from 45 to 75 years. In addition, all except 3 articles provided multivariate-adjusted risk estimates (e.g., age, gender, body mass index, smoking, cholesterol, etc.). The baseline characteristics of all included studies are summarized in Table 1. Genotypic distribution of studied SNP in controls were all in HWE (all $P > .05$). According to the quality criteria, the NOS scores of all studies were all more than 7 (high quality), and the result of NOS scores is shown in Table 2.

3.2. Results of meta-analysis

Overall, a summary of our meta-analysis findings showed a significant positive relation between the chemokine CXC ligand 12 gene polymorphism and risk of CHDs (OR = 1.11; 95% CI = 1.09–1.14; $P < .005$), without heterogeneity among studies ($I^2 = 35.8\%$, $P = .062$) (Fig. 2). Since no evidence of heterogeneity was observed, a fixed-effect method is applied for further analyses.

We performed subgroup analysis of ethnicity and populations in consideration of the potential influence of the confounding

Table 2

NOS scale checklists.

Study	Selection	Comparability	Exposure
S.U. Shahid (2017)	★★★★	★	★★
Y.Q. Wang (2014)	★★★	★★	★★★
Y. Huang (2013)	★★★	★★	★★
A. Angelakopoulou (2012)	★★★★	★	★★★
N.N. Mehta (2011)	★★★★	★★	★★
M.P. Reilly (2011)	★★★	★★	★★★
S. Saade (2011)	★★★	★★	★★
L. Qi (2011)	★★★★	★★	★★
J.F. Peden-a (2011)	★★★★	★	★★★
J.F. Peden-b (2011)	★★★★	★	★★★
J.F. Peden-c (2011)	★★★★	★	★★★
J.F. Peden-d (2011)	★★★★	★	★★★
Lu Qi-a (2011)	★★★★	★	★★
Lu Qi-b (2011)	★★★★	★	★★
Lu Qi-c (2011)	★★★★	★★	★★
R.W. Davies (2011)	★★★	★★	★★★
S. Kathiresan-a (2011)	★★★★	★	★★★
S. Kathiresan-b (2011)	★★★★	★	★★★
S. Kathiresan-c (2011)	★★★★	★	★★★

★ = 'high' quality choice.

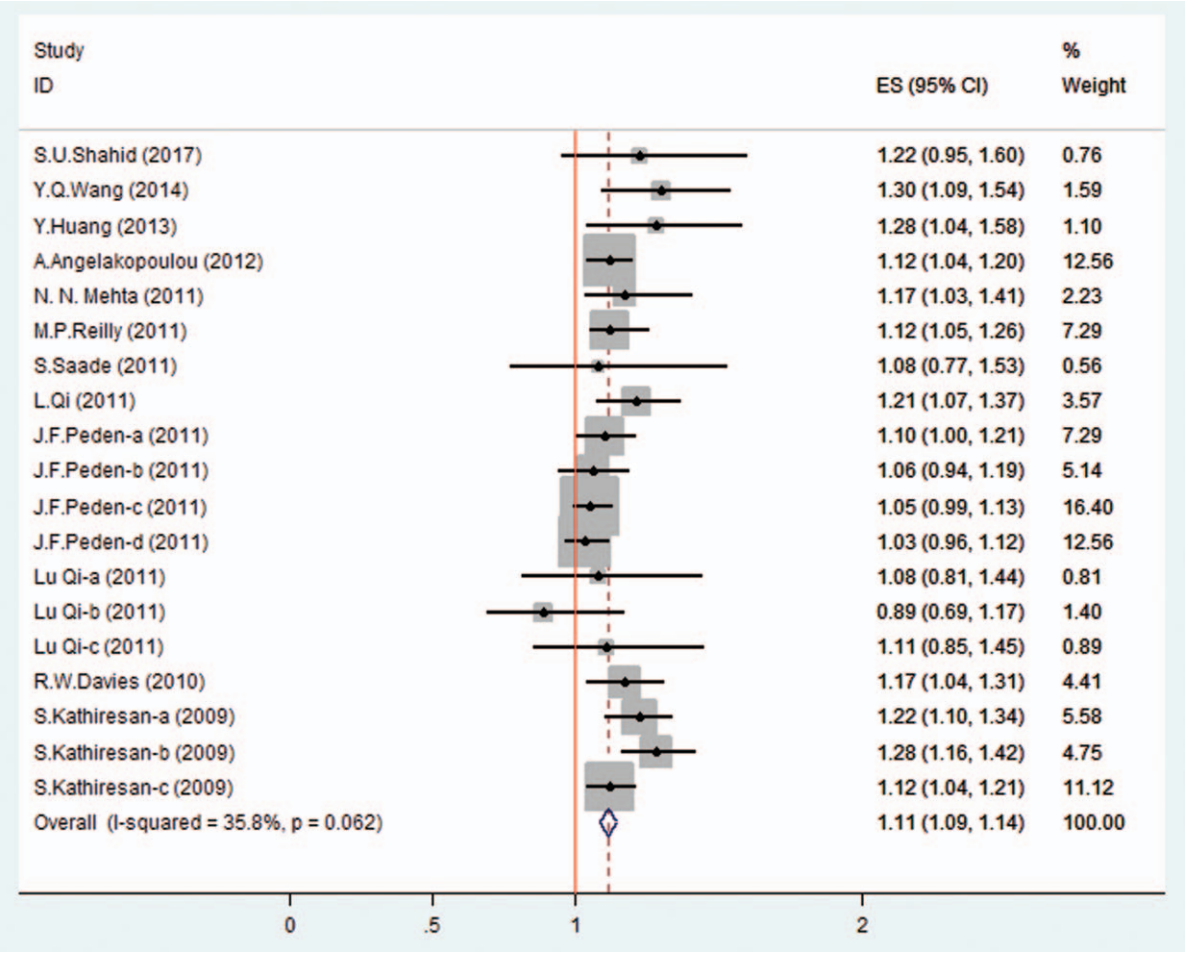

Figure 2. Overall meta-analysis of the relationship between the rs1746048 polymorphism and coronary heart disease risk under an allele model.

factor for the result. As showed in Fig. 3, the similar positive associations between the rs1746048 polymorphism and risk of CHD were found in both Asian (OR = 1.07; 95% CI = 1.02–1.12; $P < .005$; $I^2 = 40.6\%$) and Caucasian populations (OR = 1.14; 95% CI = 1.10–1.18; $P < .005$; $I^2 = 22.2\%$). We further made an analysis of chemokine CXC ligand 12 gene polymorphisms with myocardial infarction (the most serious type of CHD) (OR = 1.18; 95% CI = 1.13–1.23; $P < .005$; $I^2 = 29.6\%$) (Fig. 4).

3.3. Sensitivity analyses

We conducted sensitivity analyses under an allele model to evaluate the stability of the crude results in the association between SNP rs1746048 and CHD by removing 1 study at each round of the analysis (Fig. 5). There was no evidence about quantitative alternation in the ORs. It indicated that our meta-analysis provides more compelling evidence for the association of rs1746048 and CHD susceptibility.

3.4. Publication bias

As we all know, publication bias is a common problem when performing a meta-analysis. Begg funnel plot and Egger test were conducted under an allele model to evaluate the publication bias. As is showed in Fig. 6, the Begg funnel plot did not identify substantial asymmetry. Nevertheless, the results in the Egger test are not optimistic ($P < .05$). Because of this, we use the trim and fill method[33] and found that 2 more unpublished studies were needed to balance the funnel plot (Fig. 7). Inputting the hypothetical studies, the pooled analysis still indicated a statistically positive relationship between rs1746048 and CHD risk (OR = 1.12; 95% CI = 1.09–1.14; $P < .005$).

3.5. Discussion and conclusions

With the rapid development of industrialization and urbanization, the mortality and mobility of CHDs remains only highest worldwide despite all methods.[1] As the 3-grade prevention of diseases has become crucial, the early predictions and diagnosis of CHD need more accurate. The traditional risk prediction algorithms of CHD based on age, gender, blood lipids, hypertension and smoking may overestimate or underestimate the risk.[34,35] Genetic testing may improve the accuracy. On the other hand, gene-targeted therapy may inspire a new thinking about therapy of CHD.

Recently, there is an extensive body of GWAS and literature implicating a locus on chr10q11 in CHD which is marked by rs1746048.[10,15] Its region on chr10q11 at 44.2 Mb is 80 kb downstream proximal to the *CXCL12* gene. CXCL12 is an inflammatory chemokine which is extensively participate in cellular processes about angiogenesis, cell signaling, hematopoiesis, and a direct contribution to the process of atherosclero-

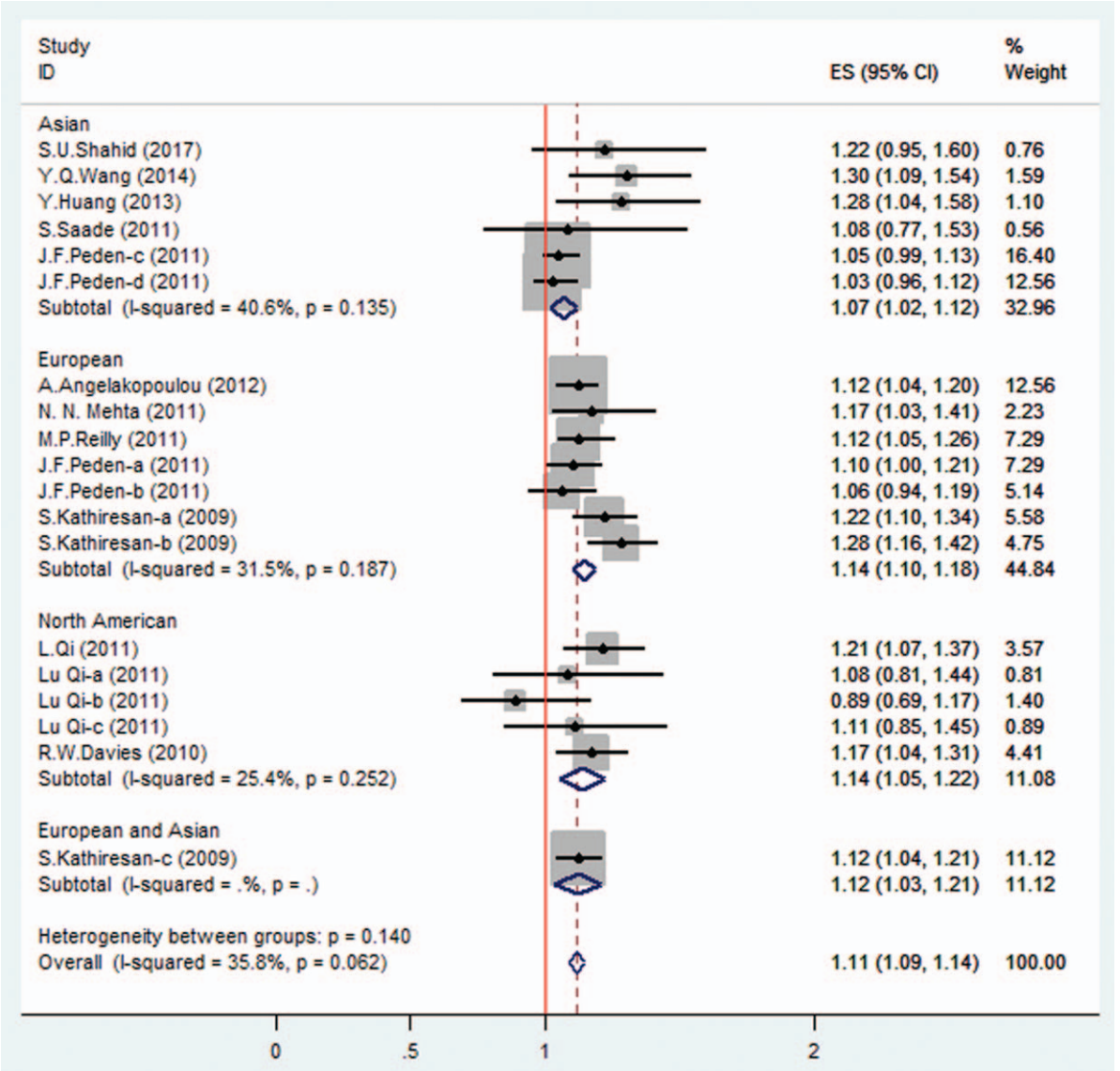

Figure 3. Subgroup meta-analysis by ethnicity of the relationship between the rs1746048 polymorphism and coronary heart disease risk (allele model).

sis.[12–14] The CXCL12 protein has been associated with activated platelets and plaque stabilization.[36,37] On 1 hand, platelet-mediated inflammation may make contribution to the process of atherosclerosis.[38] On the other hand, continuous cytokines and matrix proteases secreted by cells within the plaque may also contribute to the thinning of the stability-providing fibrous cap after the formation of plaque.[39] Moreover, CXCL12 also participates in the cell trafficking of monocytes, macrophages, and endothelial progenitor cells, which was the key components in the pathogenesis of atherosclerosis. Thus, the polymorphism of *CXCL12* gene may have relation to the development of CHD. Now more case–control studies attempt to evaluate the association between the SNP rs1746048 and CHDs, but the results have been inconclusive because of small sample size and patchy statistics of individual studies. For this reason, we conducted the present meta-analysis to summarize publications and attempt to clarify the role of the SNP rs1746048 in CHD.

In this set of meta-analyses, we combined 12 studies (including 19 stages) of 48,852 patients and 64,386 controls, and observed that the C allele carriers of SNP rs1746048 was generally correlated with an increased a 11% incidence rate of CHD among various populations (OR = 1.11; 95% CI = 1.09–1.14; $P < .005$). To reduce of difference in genetic backgrounds and the environments, we also performed an ethnicity-specific subgroup analysis and found the similar positive susceptibility to CHD in both Asian and Caucasian. The assessment of the quality of the studies by using NOS indicates all articles is of high quality. Moderate or even low heterogeneity and sensitivity analysis performed across the studies indicated that the association assessed in this meta-analysis is statistically reliable.

There are some limitations to our current meta-analysis. First, the result of Egger test indicated the possibility of publication bias; although the trim and fill sensitivity analysis showed the general results did not change which the strength of the association was even a bit increased. We conducted the further Egger test in Asian ($P < .05$) and Caucasian ($P = .064$), and observed that publication bias mainly exists in articles about Asian. The sample size of Asian was still relatively small which

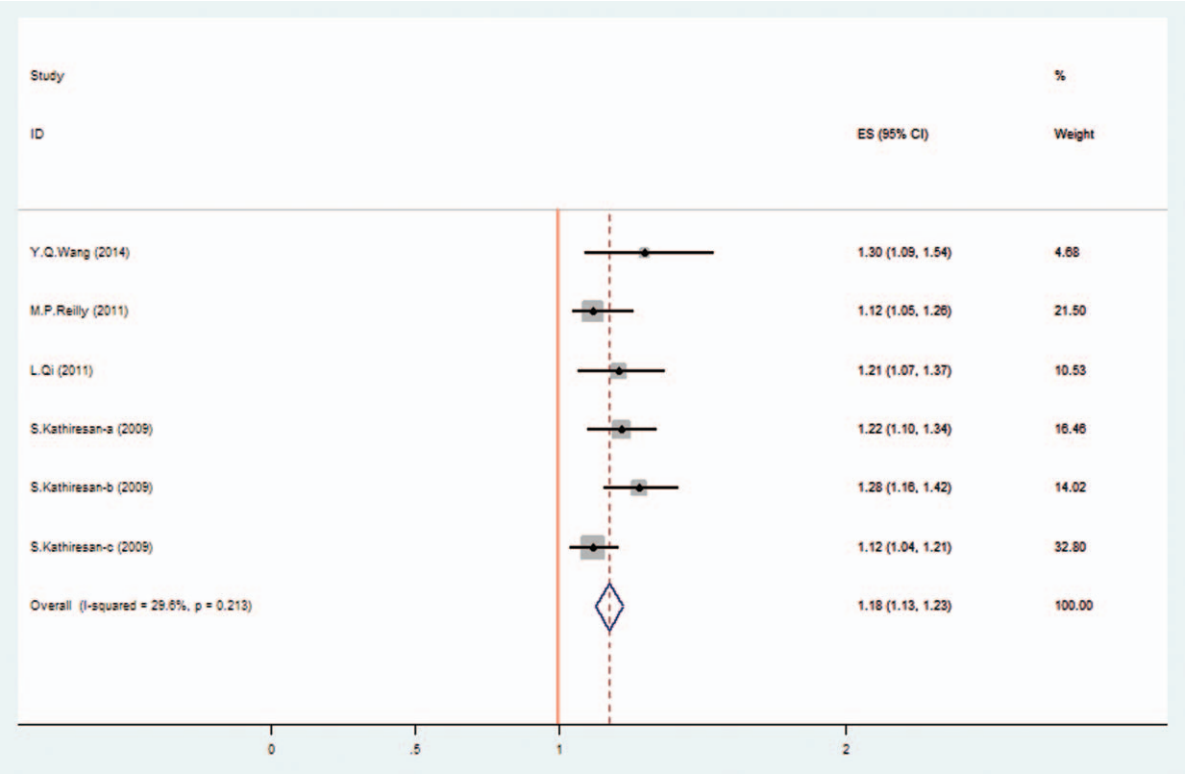

Figure 4. Subgroup analysis between the rs1746048 polymorphism and myocardial infarction risk (allele model).

may be a possible reason. Limitation to English and Chinese may be another reason resulting in the bias. Second, more than half the 12 studies did not give a strict excluding criterion about serious diseases, which may confound the results. Third, due to the lack of relevant specific data and the limited statistical power, we could not conduct subgroup analysis based on gender and age to explore the underlying relationship between rs1746048 and CHD risk. Additional studies are needed to further clarify significance of the subgroup analysis based on gender and age. Finally, although most studies included were based on adjusted OR estimates, a potential confounding bias should be considered.

In conclusion, our meta-analysis indicates that the chemokine *CXCL12* gene polymorphism (rs1746048) is significantly associated with the susceptibility to CHD and suggests that SNP rs1746048 may play an important role in the pathogenesis and progression of CHD. The rs1746048 may be a promising locus for gene-targeted therapy, which inspires a new thinking about clinic treatment of CHD. Considering limitations mentioned above, more and larger sample size of case–control should be performed to provide sufficient power to estimate the association between chemokine *CXCL12* gene polymorphism (rs1746048) and CHDs.

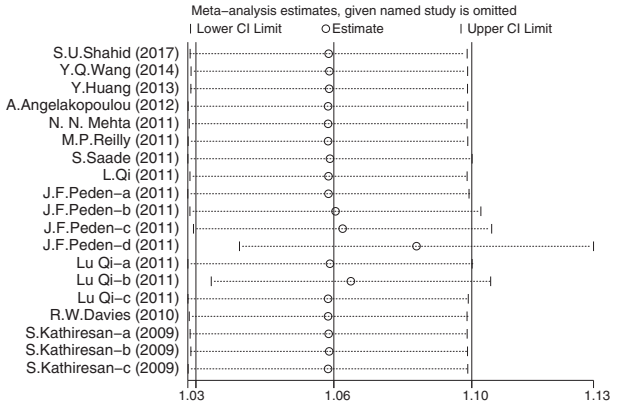

Figure 5. Sensitivity analysis of the pooled odds ratio coefficients on the relationship between rs1746048 and coronary heart disease risk.

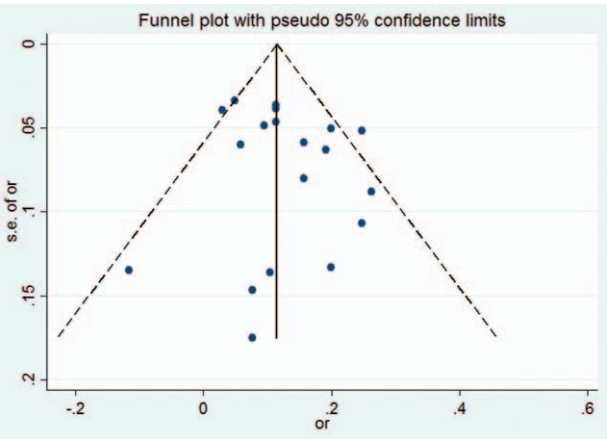

Figure 6. Begg funnel plot with pseudo 95% confidence limits.

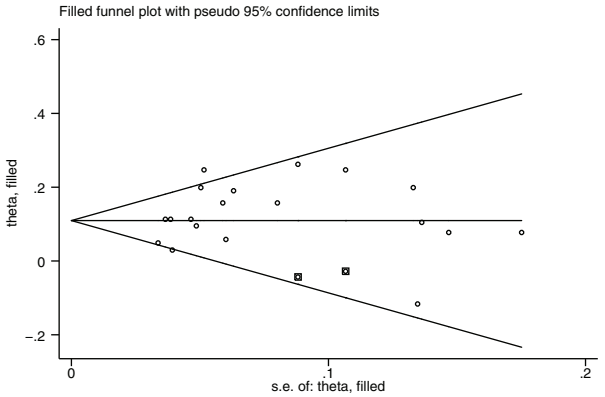

Figure 7. Filled funnel plot with pseudo 95% confidence limits.

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