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Original Article

Association of monocyte chemoattractant protein-1-2518A/G polymorphism and risk of coronary artery disease among the Chinese population: a meta-analysis

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Abstract: Background: Numerous studies have evaluated the association between the MCP-1-2518A/G polymorphism and coronary artery disease (CAD) risk; however, the actual association is controversial. To derive a more precise estimation of the relationship in Chinese population, we performed this meta-analysis. Methods: We searched the PubMed, Embase, Web of Science, and CNKI databases to identify studies that examined the association between the MCP-1-2518A/Gpolymorphism and the risk of CAD. We estimated the pooled odds ratio with its 95% confidence interval to assess this association. Results: Seven studies containing 4024 Chinese subjects (2260 patients with CAD and 1764 controls) were included in this meta-analysis. MCP-1-2518A/G polymorphism was not found to be significantly associated with CAD risk in all comparisons (for G vs A: OR=1.10, 95% CI=0.92-1.32; for AG+GG vs AA: OR=1.10, 95% CI=0.79-1.53; for GG vs AA+AG: OR=1.05, 95% CI=0.91-1.21; for GG vs AA: OR=1.12, 95% CI=0.82-1.54; for AG vs AA: OR=1.05, 95% CI=0.76-1.47). Similarly, no associations were found in subgroup analysis based on source of control and endpoint. Conclusions: the MCP-1-2518A/G polymorphism was not associated with the risk of CAD in Chinese population.

Keywords: Coronary artery disease, MCP-1, meta-analysis, polymorphism

Introduction

Coronary artery disease (CAD) is the leading cause of death and disability worldwide [1]. Despite it is well established that a poor diet, advanced age, smoking, hypertension, diabetes, and dyslipidemia are associated with increased risk of CAD, a detailed etiology underlying CAD is still obscure.

Monocyte chemo-attractant protein 1 (MCP-1), also known as CCL-2 (CC chemokine ligand 2), is the key chemokine in the process of atherosclerotic vascular inflammation by being an important chemoattractant for monocytes [2]. The human MCP-1 gene is located on chromosome 17q11.2-q21.1 [3]. A polymorphic G allele at the -2518A/G position at the promoter region of MCP-1 has been shown to increase the gene expression of MCP-1 [4].

Several studies have investigated the relationship between MCP-1-2518A/G polymorphism and CAD risk in various populations worldwide, including American, Tunisian and Indian populations [5-7]. In Chinese population, a variety of molecular epidemiological studies have focused on the relationship between MCP-1-2518A/G polymorphism and CAD susceptibility. However, results in different studies have been inconsistent. We therefore performed a meta-analysis of the published studies to clarify this inconsistency and to establish a comprehensive picture of the relationship between MCP-1-2518A/G polymorphism and CAD risk in Chinese population.

Methods

Publication search

The electronic databases PubMed, Embase, Web of Science, and CNKI were searched using the following terms: "CCL2 or MCP-1 or monocyte chemotactic protein 1" in combination with

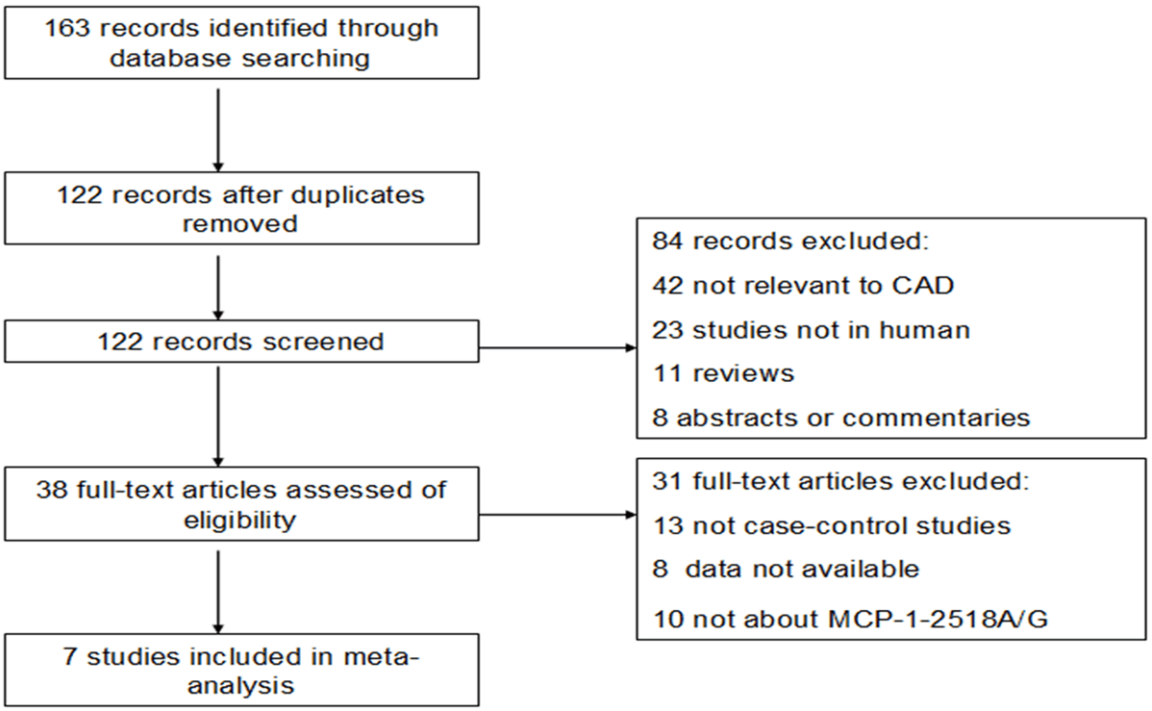

Figure 1. Study flow chart depicting the literature search and study selection.

"acute coronary syndrome or myocardial infarction or acute myocardial infarction or cardiovascular disease or ischemic heart disease or coronary heart disease or coronary artery disease" and "polymorphism or variant or mutation" up to December 2014. Additionally, hand searches for related articles were also performed.

Inclusion criteria

The inclusion criteria for identified articles were as follows: (1) studies on the relationship between MCP-1-2518A/Gpolymorphism and CAD; (2) studies with full text articles; (3) sufficient data for estimating an odds ratio (OR) with 95% confidence interval (CI); (4) not republished data.

Data extraction

Information was carefully extracted from all eligible publications independently by two authors (Zuo S and Wang HL) of this article. Disagreement was resolved by consensus. If these two authors could not reach a consensus, the result was reviewed by a third author (Wang BR). Data were extracted independently and entered into separate databases from each qualified study: the first author, year of publication, region, sample size, mean age of CAD patients and controls, the percentage of male in patients and controls, genotyping method and Hardy-Weinberg equilibrium in controls.

Statistical analysis

ORs with 95% CIs were calculated to assess the strength of the association between MCP-1-2518A/G polymorphism CAD risk. Five genetic models were assessed: homozygote model (GG vs AA), heterozygote model (AG vs AA), recessive model (GG vs AA+AG), dominant model (AG+GG vs AA), and allele model (G vs A). Subgroup analysis based on ethnicity and source of control and endpoint were also performed.

The Hardy-Weinberg equilibrium (HWE) was determined using the chi-square test in the control groups [8]. Heterogeneity assumption was checked by the chi-square-based *Q*-test [9]. In addition, the percentage of total variation due to heterogeneity was quantified by the I^2 value [10]. If $P \geq 0.1$ and $I^2 < 50\%$, we used the fixed-effects model (the Mantel-Haenszel

Table 1. Main characteristics of eligible studies

Study	Year	Region	Source of control	Endpoint	Sample size (case/control)	Mean age in case/control, (years)	Gender component in case/control (% male)	Genotyping method	*HWE*
Zhang	2009	Shenyang	PCC	CAD	502/410	59.3/52.9	77.3/59.0	PCR-RFLP	yes
Zhong	2010	Nanjing	PCC	CAD	132/153	52.1/51.2	48.5/45.1	TaqMan	yes
He	2011	Jiangsu	HCC	MI	330/165	65.63/56.39	69.39/50.91	PCR-RFLP	no
Lin	2012	Taiwan	PCC	CAD	392/216	65.73/66.43	73.7/60.2	PCR-RFLP	yes
Wang	2012	Liaoning	HCC	MI	150/159	63.8/65.9	68/67.9	PCR-RFLP	no
Yang	2012	Chengdu	HCC	CAD	120/60	NA/NA	NA/NA	PCR-RFLP	yes
Xu	2013	Zhejiang	HCC	MI	634/601	63.0/62.0	74.0/71.4	PCR-RFLP	yes

HCC, hospital-based case-control; PCC, population-based case-control; HWE, Hardy-Weinberg equilibrium; CAD, coronary artery disease; MI, myocardial infarction.

method) to pool the results [11]. Otherwise, the random effects model (the DerSimonian Laird method) was used [10]. The Galbraith plot was used to detect the potential sources of heterogeneity, and re-analyses were conducted when the studies possibly causing the heterogeneity were excluded [12]. To access the stability of the meta-analysis, one-way sensitivity analysis was carried out. Publication bias was assessed with funnel plots and Egger regression test [13]. All statistical tests were carried out using STATA 12.0 software (Stata Corporation, College Station, Texas, USA). A *P* value of less than 0.05 was considered significant.

Results

Study characteristics

Figure 1 shows the results of the study screen. The initial search produced 163 studies from PubMed, Embase, Web of Science and CNKI. After exclusion of duplicates, 122 potentially eligible studies were selected. After detailed evaluations, 7 studies were selected for final meta-analysis [14-20]. The genotype distribution in the controls of all studies was consistent with Hardy-Weinberg equilibrium (HWE) except for two study ($P<0.05$) [16, 18]. Four studies were hospital-based, and three were population-based. The characteristics of the selected studies are summarized in **Table 1**.

Quantitative data synthesis

A summary of the meta-analysis findings on the associations between MCP-1-A2518G polymorphism and susceptibility to CAD is provided in **Table 2**. Overall, this meta-analysis showed that the MCP-1-2518A/G polymorphism was not associated with CAD risk in all genetic models (for G vs A: OR=1.10, 95% CI=0.92-1.32; for AG+GG vs AA: OR=1.10, 95% CI=0.79-1.53; for GG vs AA+AG: OR=1.05, 95% CI=0.91-1.21; for GG vs AA: OR=1.12, 95% CI=0.82-1.54; for AG vs AA: OR=1.05, 95% CI=0.76-1.47) (**Figure 2**). Similarly, no associations were found in subgroup analysis based on source of control and endpoint (**Table 2**).

Heterogeneity analysis

Heterogeneity between studies was observed in most comparisons as well as in subgroup analyses. To explore the potential sources of heterogeneity further, we performed the Galbraith's test and accordingly singled out one study of Wang et al. [18] as the main contributors to heterogeneity (**Figure 3**). When excluding the study, the heterogeneity disappeared in all comparisons (for G *vs* A: OR=0.99, 95% CI=0.90-1.08, I^2=41.6, P=0.128; for AG+GG vs AA: OR=0.92, 95% CI=0.78-1.08, I^2=49.7%, P=0.107; for GG vs AA: OR=0.96, 95% CI=0.79-1.16, I^2=44.6%, P=0.108; for AG vs AA: OR=0.89, 95% CI=0.75-1.06, I^2=36.1%, P=0.166).

Sensitivity analysis

We sequentially excluded the single studies from the overall pooled analysis to check whether the summary ORs were materially changed. The recalculated ORs were found stable, indicating our results are valuable (**Figure 4**).

Publication bias

The shape of funnel plots did not reveal any evidence of obvious asymmetry in the overall meta-analysis (**Figure 5**). Egger's test also displayed no significant statistical evidence of publication bias under any genetic models, suggesting that no publication bias exists.

Table 2. Meta-analysis for the association of MCP-1-2518A/G polymorphism with CAD in Chinese population

Comparison	Study groups	Test of association			Test of heterogeneity			Model[b]
		OR (95% CI)	Z	*P* Value	χ^2	*P*[a]	I^2 (%)	
G vs A	Total studies	1.10 (0.92-1.32)	1.07	0.285	20.42	0.002	70.6	R
	PCC	1.03 (0.83-1.27)	0.24	0.811	4.48	0.107	55.3	R
	HCC	1.20 (0.87-1.66)	1.10	0.271	15.87	0.001	81.1	R
	MI	1.15 (0.79-1.67)	0.71	0.477	13.64	0.001	85.3	R
	Studies in HWE	1.02 (0.87-1.20)	0.28	0.783	8.56	0.073	53.3	R
GG vs AA	Total studies	1.12 (0.82-1.54)	0.69	0.487	14.92	0.021	59.8	R
	PCC	1.06 (0.67-1.69)	0.24	0.809	5.02	0.081	60.2	R
	HCC	1.22 (0.72-2.08)	0.73	0.465	9.86	0.020	69.6	R
	MI	1.10 (0.61-1.99)	0.31	0.756	7.51	0.023	73.4	R
	Studies in HWE	1.05 (0.75-1.45)	0.26	0.792	8.73	0.068	54.2	R
AG vs AA	Total studies	1.05 (0.76-1.47)	0.32	0.751	21.24	0.002	71.7	R
	PCC	1.04 (0.80-1.35)	0.32	0.748	3.58	0.167	44.2	F
	HCC	1.07 (0.60-1.92)	0.24	0.809	17.44	0.001	82.8	R
	MI	1.05 (0.50-2.20)	0.14	0.891	17.15	0.000	88.3	R
	Studies in HWE	0.93 (0.77-1.11)	0.81	0.420	6.22	0.183	35.7	F
AG+GG vs AA	Total studies	1.10 (0.79-1.53)	0.57	0.572	24.42	0.000	75.4	R
	PCC	1.05 (0.70-1.57)	0.23	0.818	4.94	0.085	59.5	R
	HCC	1.15 (0.65-2.04)	0.49	0.624	19.44	0.000	84.6	R
	MI	1.09 (0.53-2.24)	0.24	0.809	18.32	0.000	89.1	R
	Studies in HWE	1.01 (0.76-1.33)	0.04	0.967	8.80	0.066	54.6	R
GG vs AG+AA	Total studies	1.05 (0.91-1.21)	0.71	0.477	5.81	0.445	0.0	F
	PCC	1.01 (0.83-1.23)	0.07	0.944	1.78	0.411	0.0	F
	HCC	1.10 (0.90-1.34)	0.93	0.352	3.68	0.298	18.5	F
	MI	1.06 (0.87-1.30)	0.58	0.561	2.17	0.337	8.0	F
	Studies in HWE	1.01 (0.87-1.18)	0.17	0.865	3.83	0.429	0.0	F

[a]*P* value of *Q*-test for heterogeneity. [b]Random-effects model (R) was used when *P* value for heterogeneity test <0.10; otherwise, fixed-effects model (F) was used. HCC, hospital-based case-control; PCC, population-based case-control.

Discussion

CAD is a multi-factorial and polygenic disorder disease which is thought to be the result of interactions between complex gene-gene and gene-environment. MCP-1 is a member of the C-C beta chemokine family that is produced by macrophages, fibroblasts, and endothelial cells to stimulate chemo taxis of monocyte/macrophages and other inflammatory cells. Abundant studies have suggested that MCP-1 is commonly overexpressed in a wide variety of CVD, including atherosclerosis, hypertension and coronary heart disease [21]. The first study associating MCP-1-2518A/G polymorphism with CAD suggested higher frequency of G allele in CAD patients exclusively due to a twofold increase of GG homozygotes in Hungarian patients [22].

Several studies have examined the relationship between MCP-1-2518A/G polymorphism and CAD susceptibility in Chinese population. In addition, the credibility of results from a single case-control study is questionable due to too small sample size of the study populations. As suggested, to generate robust data, a much larger sample size in each group might be required [23]. By increasing the sample size, the meta-analysis has the potential to detect small effects in human genetic association studies. To draw a comprehensive understanding, we pooled the data and performed a meta-analysis in Chinese population. The meta-analysis included 4024 subjects with 2260 cases and 1764 controls. In this meta-analysis, we observed no association between MCP-1-2518A/G and the risk of developing CAD in Chinese population. Similarly, no associations

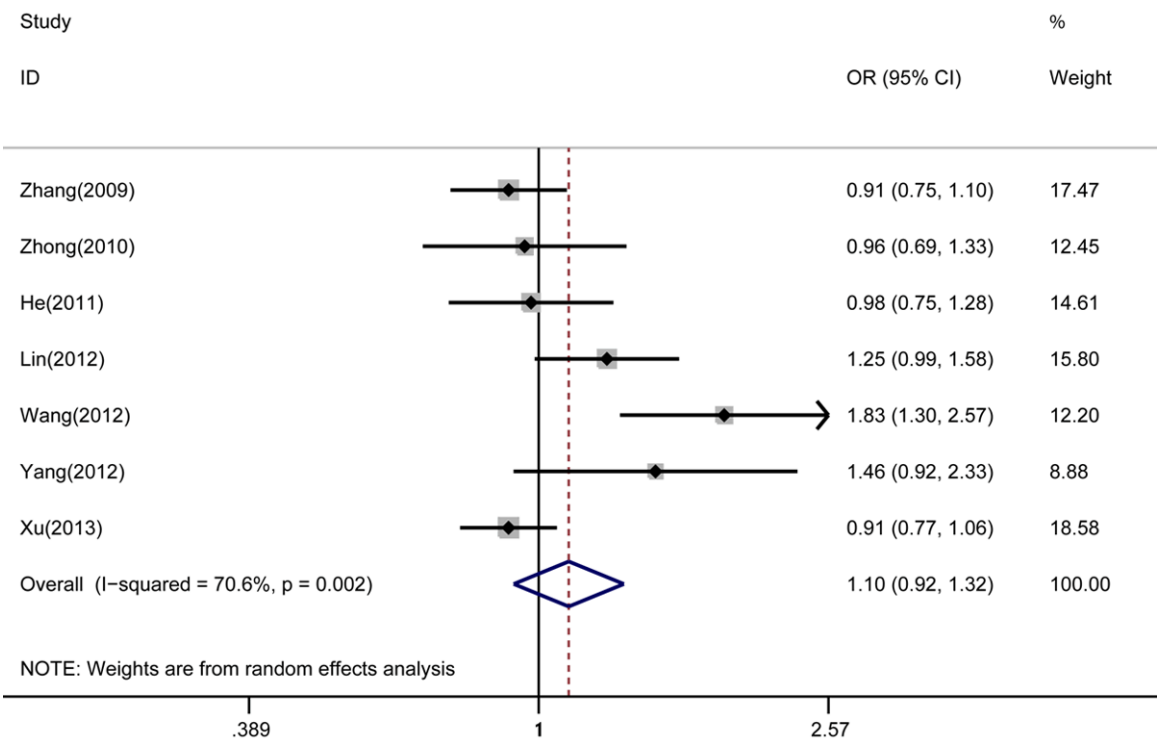

Figure 2. Meta-analysis of the association between the MCP-1-2518A/G polymorphism and CAD risk (G vs A).

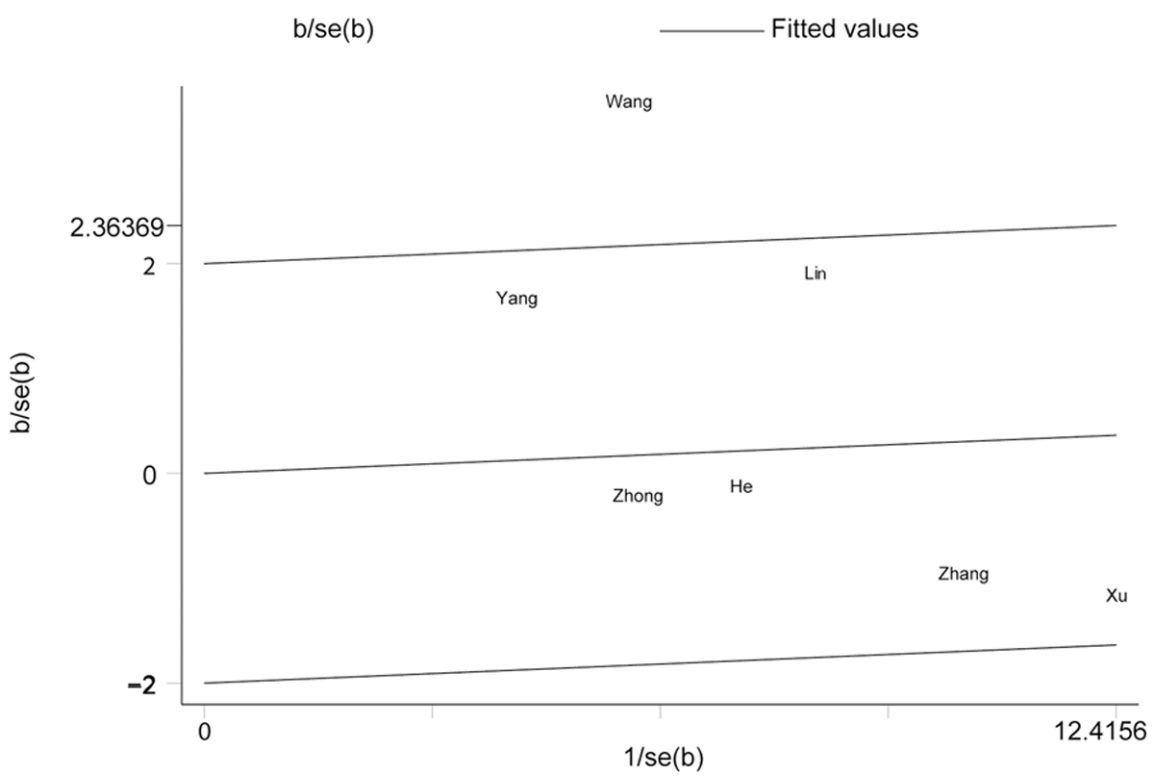

Figure 3. Galbraith's plot of MCP-1-2518A/G polymorphism and CAD risk (G vs A). The study of Wang et al. was spotted as the outlier.

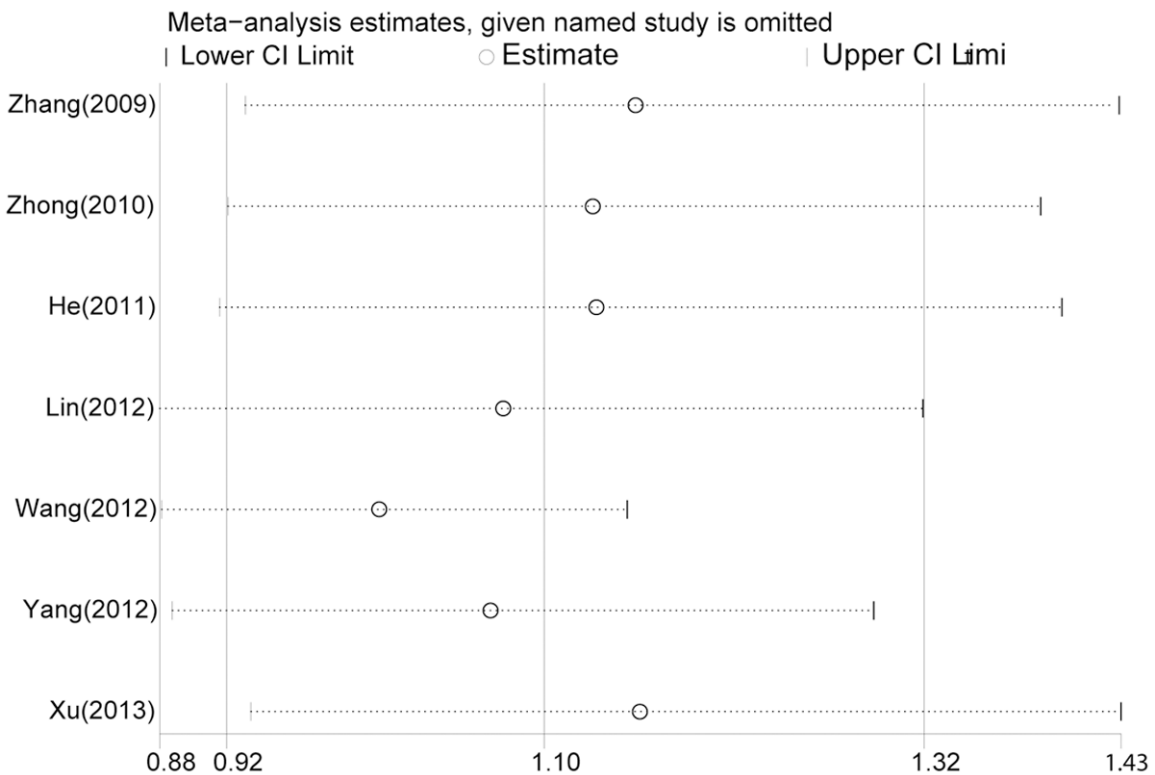

Figure 4. Sensitivity analysis of the correlation between the MCP-1-2518A/G polymorphism and CAD risk (G vs A).

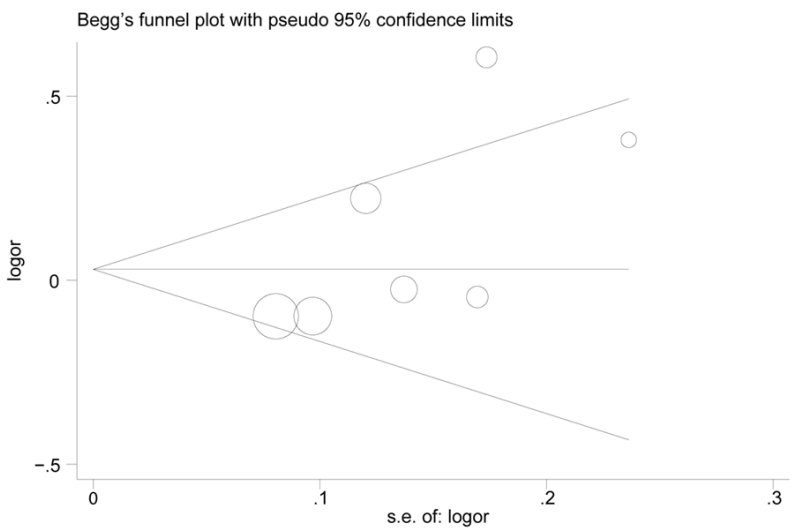

Figure 5. Begg's funnel plot of the meta-analysis of the MCP-1-2518A/G polymorphism and CAD risk (G vs A).

were found in subgroup analysis based on source of control and endpoint.

Heterogeneity is a potential problem that may affect the interpretation of the results. Significant heterogeneity existed in this meta-analysis. Galbraith plots were used to find the sources of heterogeneity. We found that I^2 value was decreased after excluding the outliers. The result suggested that the outlying studies may be the major source of the heterogeneity. Moreover, heterogeneity did not influence the results, because the significance of the result was not altered after excluding the outliers. Results from one-way sensitivity analysis suggested stability of these results. Additionally, funnel plots and Egger's tests did not find potential publication bias. All together, these results suggested that results of this meta-analysis were reliable.

Some limitations of this meta-analysis should be considered in interpreting the results. First, the control resources were not from the uni-

formed population, which may cause misclassification bias to some extent. Second, due to lacking of the original data of the eligible studies, we could not perform other subgroup analyses based on age, smoking, and so on. Third, data included in the meta-analysis were obtained from published articles. We could not track unpublished articles, influencing the comprehensiveness of the data. Finallly, our analysis did not consider the possibility of gene-gene or SNP-SNP interactions or the possibility of linkage disequilibrium between polymorphisms.

In conclusion, the MCP-1-2518A/G polymorphism was not associated with the risk of CAD in Chinese population. However, some results of this present meta-analysis are limited by the small number of studies; thus, additional larger well-designed studies are required.

Disclosure of conflict of interest

None.

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References

[1] Salomon JA, Vos T, Hogan DR, Gagnon M, Naghavi M, Mokdad A, Begum N, Shah R, Karyana M, Kosen S, Farje MR, Moncada G, Dutta A, Sazawal S, Dyer A, Seiler J, Aboyans V, Baker L, Baxter A, Benjamin EJ, Bhalla K, Bin Abdulhak A, Blyth F, Bourne R, Braithwaite T, Brooks P, Brugha TS, Bryan-Hancock C, Buchbinder R, Burney P, Calabria B, Chen H, Chugh SS, Cooley R, Criqui MH, Cross M, Dabhadkar KC, Dahodwala N, Davis A, Degenhardt L, Diaz-Torne C, Dorsey ER, Driscoll T, Edmond K, Elbaz A, Ezzati M, Feigin V, Ferri CP, Flaxman AD, Flood L, Fransen M, Fuse K, Gabbe BJ, Gillum RF, Haagsma J, Harrison JE, Havmoeller R, Hay RJ, Hel-Baqui A, Hoek HW, Hoffman H, Hogeland E, Hoy D, Jarvis D, Karthikeyan G, Knowlton LM, Lathlean T, Leasher JL, Lim SS, Lipshultz SE, Lopez AD, Lozano R, Lyons R, Malekzadeh R, Marcenes W, March L, Margolis DJ, McGill N, McGrath J, Mensah GA, Meyer AC, Michaud C, Moran A, Mori R, Murdoch ME, Naldi L, Newton CR, Norman R, Omer SB, Osborne R, Pearce N, Perez-Ruiz F, Perico N, Pesudovs K, Phillips D, Pourmalek F, Prince M, Rehm JT, Remuzzi G, Richardson K, Room R, Saha S, Sampson U, Sanchez-Riera L, Segui-Gomez M, Shahraz S, Shibuya K, Singh D, Sliwa K, Smith E, Soerjomataram I, Steiner T, Stolk WA, Stovner LJ, Sudfeld C, Taylor HR, Tleyjeh IM, van der Werf MJ, Watson WL, Weatherall DJ, Weintraub R, Weisskopf MG, Whiteford H, Wilkinson JD, Woolf AD, Zheng ZJ, Murray CJ, Jonas JB. Common values in assessing health outcomes from disease and injury: disability weights measurement study for the Global Burden of Disease Study 2010. Lancet 2012; 380: 2129-43.

[2] Deshmane SL, Kremlev S, Amini S and Sawaya BE. Monocyte chemoattractant protein-1 (MCP-1): an overview. J Interferon Cytokine Res 2009; 29: 313-26.

[3] Bielinski SJ, Pankow JS, Miller MB, Hopkins PN, Eckfeldt JH, Hixson J, Liu Y, Register T, Myers RH and Arnett DK. Circulating MCP-1 levels shows linkage to chemokine receptor gene cluster on chromosome 3: the NHLBI family heart study follow-up examination. Genes Immun 2007; 8: 684-90.

[4] Rovin BH, Lu L and Saxena R. A novel polymorphism in the MCP-1 gene regulatory region that influences MCP-1 expression. Biochem Biophys Res Commun 1999; 259: 344-8.

[5] McDermott DH, Yang Q, Kathiresan S, Cupples LA, Massaro JM, Keaney JF Jr, Larson MG, Vasan RS, Hirschhorn JN, O'Donnell CJ, Murphy PM and Benjamin EJ. CCL2 polymorphisms are associated with serum monocyte chemoattractant protein-1 levels and myocardial infarction in the Framingham Heart Study. Circulation 2005; 112: 1113-20.

[6] Jemaa R, Rojbani H, Kallel A, Ben Ali S, Feki M, Chabrak S, Elasmi M, Taieb SH, Sanhaji H, Souheil O, Mechmeche R and Kaabachi N. Association between the -2518G/A polymorphism in the monocyte chemoattractant protein-1 (MCP-1) gene and myocardial infarction in Tunisian patients. Clin Chim Acta 2008; 390: 122-5.

[7] Kaur R, Matharoo K, Arora P and Bhanwer AJ. Association of -2518A>G promoter polymorphism in the monocyte chemoattractant protein-1 (MCP-1) gene with type 2 diabetes and coronary artery disease. Genet Test Mol Biomarkers 2013; 17: 750-5.

[8] Haber M. Exact significance levels of goodness-of-fit tests for the Hardy-Weinberg equilibrium. Hum Hered 1981; 31: 161-6.

[9] Lau J, Ioannidis JP and Schmid CH. Quantitative synthesis in systematic reviews. Ann Intern Med 1997; 127: 820-6.

[10] DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986; 7: 177-88.

[11] Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies

of disease. J Natl Cancer Inst 1959; 22: 719-48.
[12] Galbraith RF. A note on graphical presentation of estimated odds ratios from several clinical trials. Stat Med 1988; 7: 889-94.
[13] Egger M, Davey Smith G, Schneider M and Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997; 315: 629-34.
[14] Zhang X, Han Y, Kang J and Yan C. A monocyte chemoattractant protein-1 gene polymorphism is not associated with coronary artery disease in a Han Chinese population. Clin Chim Acta 2009; 403: 241-3.
[15] Zhong C, Luzhan Z, Genshan M, Jiahong W, Xiaoli Z and Qi Q. Monocyte chemoattractant protein-1-2518 G/A polymorphism, plasma levels, and premature stable coronary artery disease. Mol Biol Rep 2010; 37: 7-12.
[16] He GP, Shi GW, Qi CP, Gao L, Shen DD, Qian ZH and Xu LH. Association between MCP-1 2518G/A polymorphism and the susceptibility of acute myocardial infarction with chinese han population in Sunan district in China. J Pract Med 2012; 28: 85-8.
[17] Lin HL, Ueng KC, Hsieh YS, Chiang WL, Yang SF and Chu SC. Impact of MCP-1 and CCR-2 gene polymorphisms on coronary artery disease susceptibility. Mol Biol Rep 2012; 39: 9023-30.
[18] Wang QB, Zhang YL. Corrrelation of MCP-1-2518A/G Gene Polymorphism with Acute Myocardial Infarction. Chinese General Practice 2012; 15: 1600-2.
[19] Yang LX, Guo RW, Qi F, Shi YK, Wang XM, Ren L and Xu AF. Relationship Between NFAT,MCP-1 With MCP-1-2518G/A Gene Polymorphism and Coronary Artery Disease. Chinese Circulation Journal 2012; 27: 278-81.
[20] Xu X, Wang LH, Xu CF, Zhang P, Yong FD and Shi YP. Association of chemokines and their receptors genes polymorphisms with risk of myocardial infarction. Chin J Med Genet 2013; 30: 601-7.
[21] Wei J, Tang Q, Liu L and Bin J. Combination of peroxisome proliferator-activated receptor alpha/gamma agonists may benefit type 2 diabetes patients with coronary artery disease through inhibition of inflammatory cytokine secretion. Exp Ther Med 2013; 5: 783-8.
[22] Szalai C, Duba J, Prohaszka Z, Kalina A, Szabo T, Nagy B, Horvath L and Csaszar A. Involvement of polymorphisms in the chemokine system in the susceptibility for coronary artery disease (CAD). Coincidence of elevated Lp (a) and MCP-1 -2518 G/G genotype in CAD patients. Atherosclerosis 2001; 158: 233-9.
[23] Munafo MR, Flint J. Meta-analysis of genetic association studies. Trends Genet 2004; 20: 439-44.